South African
GASTROENTEROLOGY
Review

Volume 18, Issue 3, 2020

Published by:
inhouse PUBLICATIONS
www.ihpublishing.co.za

The official Journal
of the South African
Gastroenterology Society

ISSN - 1812 - 1659

Their gut protection is in good hands

At Dr. Reddy's, we bring 'Good Health' to people around the world.[1]
We are renowned in the field of Gastroenterology in which we have a broad portfolio of acid suppressive medications to address heartburn, a common symptom of gastro-oesophageal reflux disease.[2]

That's why we believe "Good Health Can't Wait".[1]

S4 OMEZ
OMEPRAZOLE
10 20 40

S4 PENTOZ
pantoprazole 20 mg, 40 mg

Dr.Reddy's
GASTROENTEROLOGY
GOOD HEALTH CAN'T WAIT

CLICK HERE MEDePRO FOR UP TO DATE CPD AND WEBINARS

References: 1. Dr. Reddy's data on file. Dr Reddy's Global Site. Brand. Available at https://www.drreddys.com/our-story/our-brand/ Last accessed 16 June 2020. **2.** Dr. Reddy's data on file. Dr Reddy's Global Site. Therapeutic Focus. Available at https://www.drreddys.com/our-products/therapeutic-focus.aspx Last accessed 16 June 2020. S4 Pentoz 20. Reg. No.: 41/11.4.3/0641. Each film-coated tablet contains pantoprazole sodium sesquihydrate equivalent to pantoprazole 20 mg. S4 Pentoz 40. Reg. No.: 41/11.4.3/0642. Each film-coated tablet contains pantoprazole sodium sesquihydrate equivalent to pantoprazole 40 mg. S4 Omez 10. Each capsule contains omeprazole 10 mg. Reg. No. 34/11.4.3/0299. S4 Omez 20. Each capsule contains omeprazole 20 mg. Reg. No. 34/11.4.3/0300. S4 Omez 40. Each capsule contains omeprazole 40 mg. Reg. No. 34/11.4.3/0301. Dr. Reddy's Laboratories (Pty) Ltd. Reg. No. 2002/014163/07. Block B, 204 Rivonia Road, Morningside, Sandton 2057. Tel: +27 11 324 2100, www.drreddys.co.za. For full prescribing information refer to package insert approved by the medicines regulatory authority. ZA/08/2020-2022/GIT/001. 40231 08/20

Your partner in heartburn management | Dr.Reddy's

Editorial

Wow! A year like none other. COVID-19 has really changed the practice of medicine across the globe and has not left South Africa untouched. Telephonic consults, disruption to endoscopy lists, changes in attendance at outpatients have severely affected our members and many have incurred significant financial losses. The effect of decreasing health care to our patients will have a long lasting effect in particular when we think of cancer treatment and screening. COVID-19 has also enhanced our society's engagement via electronic platforms with numerous electronic webinars. SAGES in conjunction with the Gastro Foundation held a very successful virtual congress this year with over 400 registrations including international attendees. A big thank you to Karin Fenton and Eastern Sun and all the speakers in hosting such an amazing event.

The current edition highlights the treatment of HCC with 2 case reports showing the variability in treatment protocols and a comprehensive review article is provided. Treatment modalities are increasing in the field of HCC and with newer agents becoming accessible the options for patients in Southern Africa will hopefully increase. The case report by Dr Lee from Kimberly highlights a rare but serious complication of gastro cutaneous fistula and she provides a good review on this topic. A case report on achalasia reminds us of possible other co-existing medical conditions or associations and that these complications can complicate our gastroenterology treatment protocols.

I would like to thank Prof Watermeyer and her fellow authors on the amazing effort to get the IBD position statement published. Hard copies are available as a supplement to this journal and the electronic copies will be distributed to SAGES members and placed on the SAGES website. The position paper is a practical guide on the treatment and management of IBD and is highly recommended. The SAGES council is having ongoing discussion with key stakeholders regarding increasing access to best care for IBD, both in state and private. Ongoing discussions in conjunction with many other surgical societies is occurring with key stakeholders to make endoscopy accessible and affordable, but a note of caution to our members that we need to regulate our treatment according to best standards and protocols that are recognized. We do have a responsibility to assist in driving costs down.

Lastly a warm welcome to all our recently qualified gastroenterologists (medical, surgical and paediatric). I wish all our members a prosperous and uneventful 2021 and hope we get the COVID vaccine sooner than later.

Adam Mahomed
Editor

CONGRATULATIONS TO THESE FELLOWS, WELL DONE CONSIDERING THE YEAR WE HAVE HAD :

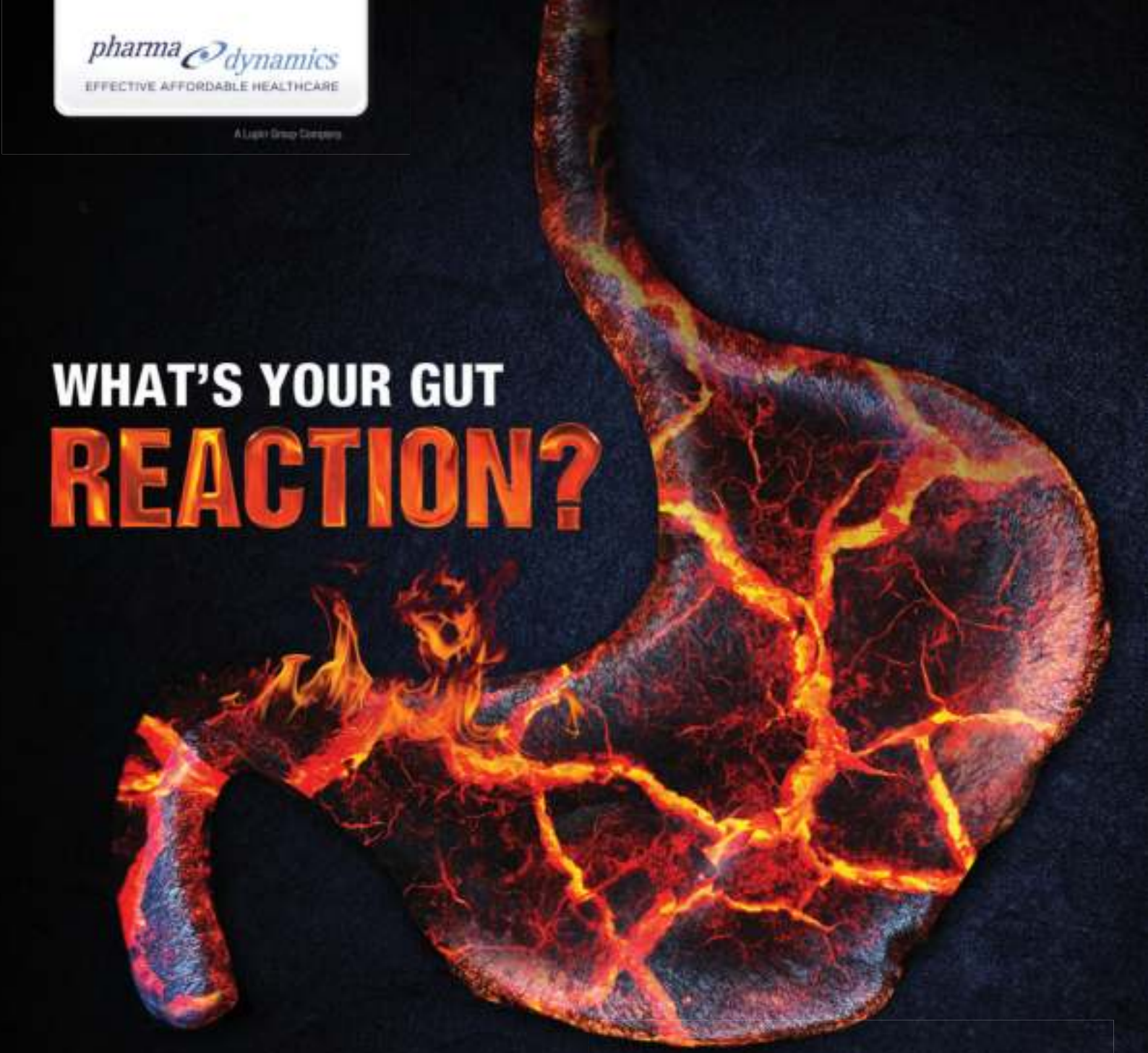
Cert Gastroenterology (Paed)
Utpol Chowdhury
Zeenat Gaibee
Yahya Sheikh Mohamud

Cert Gastroenterology (Phys)
Ahmad Abdelsalem
Cathrine Gounden
Vikash Lala
Portia Ngwata
Chikezie Nwankwo
Dinen Parbhoo

Cert Gastroenterology (Surg)
Karan Gandhi
Nadir Hilal
Fusi Madela
Hendrik Pretorius
Mazwi Pungutche
Kiyasha Singh

pharma dynamics
EFFECTIVE AFFORDABLE HEALTHCARE
A Lupin Group Company

WHAT'S YOUR GUT REACTION?



Lancap

15 mg | 30 mg

LANSOPRAZOLE

For further product information contact **PHARMA DYNAMICS** P O Box 30958 Tokai Cape Town 7966 **Tel** 021 707 7000 **Fax** 021 701 5898
Email info@pharmadynamics.co.za **CUSTOMER CARE LINE** 0860 PHARMA (742 762)/+27 707 7000 **www.pharmadynamics.co.za**

LANCAP 15, 30 mg. Each capsule contains 15, 30 mg lansoprazole respectively. S4 Reg No.: A40/11.4.3/0247,0248 NAM NS2 07/11.4.3/0098,0099. For full prescribing information, refer to the professional information approved by SAHPRA, January 2009. **LPG461/07/2018.**

The South African Gastroenterology Review is published by In House Publications, P.O. Box 412748, Craighall, 2024. Johannesburg, South Africa

Email: inhouse@iafrica.com
Website: www.ihpublishing.co.za

PUBLISHER: In House Publications
PRODUCTION: Andrew Thomas
ADVERTISING: Andrew Thomas
082 604 5038
REPRODUCTION: Rachel du Plessis
rachel@prycision.com
Prycision
prycision.com

THE SOUTH AFRICAN GASTROENTEROLOGY REVIEW is written by specialists in the field. Its aim is to publish articles pertinent to the practicing Gastroenterologist in South Africa. The South African Gastroenterology Review is distributed to a broad spectrum of clinicians who have an interest in clinical gastroenterology and hepatology.

South African
GASTROENTEROLOGY
Review

CONTENTS

Volume 18 | Issue 3 | 2020

EDITORIAL

REVIEW

CASE REPORTS

GASTROENTEROLOGY FOUNDATION

DIFFERENT PEOPLE, DIFFERENT CHOICES.

PENTASA® SACHETS

Ulcerative Colitis & Crohn's Disease

PENTASA® 500 mg TABLETS

Ulcerative Colitis

PENTASA® 1 g SUPPOSITORIES

Ulcerative Proctitis

PENTASA® 1 g ENEMA

Ulcerative Proctosigmoiditis & Left-sided Colitis

BENEFITS OF PENTASA® ORAL FORMULATIONS	PENTASA® prolonged release granules
Mesalazine is released throughout the GI tract?	✓ YES[1,2]
Release of mesalazine at all pH values in the GI tract?	✓ YES[1]
Does diarrhoea affect the release of mesalazine?	✓*YES[3]
Any peak plasma concentrations of mesalazine?	✗ NO[4]
May be taken with or without food?	✓ YES[1,2]

*Although the disposition from Pentasa® is impaired in case of diarrhoea, the changes were not substantial, and the disposition remains rather favourable.

PENTASA's different dosage forms & strengths allow you to choose the best fit for your patient.

PENTASA®
MESALAZINE
To remission and beyond.

Be GUTsi
Be GUTsi Take Control

The Be GUTsi campaign & IBD Health Diary are the latest innovations by Ferring.
A NEW approach in empowering patients!
Improving outcomes in the palm of your hands.

Apple QR code

Google QR code

References: 1. Hardy JG, Harvey WJ, Sparrow RA, *et al.* Localization of drug release sites from an oral sustained-release formulation of 5-ASA (Pentasa®) in the gastrointestinal tract using gamma scintigraphy. *J Clin Pharmacol.* 1993;33:712-718. **2.** Wilding IR. A scintigraphic study to evaluate what happens to Pentasa® and Asacol® in the human gut. *Practical Gastroenterology.* Suppl to November 1999:1-8. **3.** Rijk MCM, van Schaik A, Van Tongeren JHM. Disposition of mesalazine from mesalazine-delivering drugs in patients with inflammatory bowel disease, with and without diarrhoea. *Scand J Gastroenterol* 1992;27(10):863-868. **4.** Christensen LA, Fallingborg J, Abildgaard K, *et al.* Topical and systemic availability of 5-aminosalicylate: comparisons of three controlled release preparations in man. *Aliment Pharmacol Ther.* 1990;4:523-533.

S3 PENTASA® SACHETS 2 g. Each sachet contains 2 g mesalazine. **Reg. No.:** 43/11/0014. S3 PENTASA® 1 g Suppositories. Each suppository contains 1 g mesalazine. **Reg. No.:** A40/11/0374. S3 PENTASA® 500 mg Tablet. Each tablet contains 500 mg mesalazine. **Reg. No.:** 33/11/0088. S3 PENTASA® 1 g ENEMA. Each 100 ml rectal suspension contains 1 g mesalazine. **Reg. No.:** 44/11/0888.

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION: FERRING (Pty.) Ltd. Route 21 Corporate Park, 6 Regency Drive, Irene Ext 30. Pretoria, South Africa. Tel: +27 12 345 6358 Fax: +27 12 345 1156. www.ferring.co.za. PENTASA, FERRING, and the FERRING logo are registered trademarks of Ferring B.V. For full prescribing information please refer to the package insert approved by the medicines regulatory authority. 2020/019 Date of preparation: March 2020.

FERRING
PHARMACEUTICALS

SBRT in portal tumour thrombosis in hepatocellular carcinoma: a review of the literature

C de la Pinta Alonso
Radiation Oncology, Ramón y Cajal Hospital, Madrid, Spain

ABSTRACT
Locally advanced hepatocellular carcinoma includes the presence of portal tumor thrombosis. The prognosis and treatment options for these patients are limited. Radiation therapy allows portal recanalization and the combination of other treatments such as TACE or even surgery. There are different modalities of radiotherapy including conventional radiotherapy, 3DRT, IMRT or VMAT. SBRT allows high doses of radiation to be delivered to the tumor while limiting the dose to the nearby healthy tissues. This allows high doses of radiation to be delivered to the tumor in a few sessions with low side effects. This study aims to review the role of radiation therapy in hepatocellular carcinoma with portal tumour thrombosis, specifically the role of SBRT.

KEYWORDS: HCC, PVTT, radiotherapy, SBRT

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver tumor in adults, constituting 75% of liver tumors, and representing 6% of all cancers. It is the third leading cause of death in the world. It is more common in men and the age at initial diagnosis is between 40 and 60 years. Most patients with HCC are asymptomatic until advanced stages of the disease, even in advanced stages they may continue to be asymptomatic, but it is common for analytical alterations to appear. The main prognostic factors for HCC are the possibility of tumor resection or liver transplantation, general condition, liver function, alpha-fetoprotein levels and the existence of distant disease.[1]

The incidence of portal vein tumour thrombosis (PVTT) occurs in 30-40% of cases according to series1. This confers a poor prognosis, with a survival of 2-4 months.[2] PVTT causes portal hypertension, tumour spread and compromises liver function limiting treatments.[3] Poor prognostic factors in HCC with PVTT include large, diffuse tumors, poor general condition, and PVTT involvement of the bilateral branch or main trunk. Effective treatment is needed to manage these patients as current treatments have minimal benefit.

Correspondence
Carolina de la Pinta Alonso
email: cdelapinta88@gmail.com

HCC PVTT treatments according to clinical practice guidelines

According to European and American guidelines, portal tumour thrombosis in HCC is classified as stage C by BCLC (Barcelona Clinic Liver Cancer) and sorafenib is recommended for treatment.[4] Jeong et al evaluated 143 patients with unresectable HCC treated with sorafenib in monotherapy, 30 patients with PVTT.[5] Survival was 3.1 months and median progression-free survival was 2 months. However, in Asian countries, patients with PVTT are treated with surgery, radiation therapy, TACE, and/or sorafenib.[6,7] Surgical treatment is recommended in HCC with PVTT type I/II.[8] However, PVTT with involvement of the main portal vein or contralateral venous trunk have no survival benefit from surgical treatment.[9] TACE is contraindicated in portal tumour invasion of the main trunk and/or first branch of the portal vein because of the risk of liver infarction and liver failure due to ischaemia.[10] The management of HCC with portal tumour thrombosis is complicated and controversial.

SBRT can be considered as an alternative to local treatment in inoperable, unresectable patients who refuse surgery or as a bridge to transplantation. In addition, it is a treatment used in advanced stages such as patients with PVTT in which surgery, TACE and radioembolization are contraindicated or as a complementary treatment along with other therapeutic modalities.[11,12] Several studies have demonstrated the efficacy of conventional radiotherapy in HCC with PVTT, however, the use of SBRT has been less studied. SBRT is a radiotherapy treatment that allows high doses of radiation to be administered directly to the

tumour, destroying the tumour cells without affecting normal tissue. SBRT represents a therapeutic alternative in these patients, being possible the vascular recanalization. The use of radiation therapy in PVTT may allow the subsequent combination of other treatments such as TACE improving the results of these patients.

Modalities of radiotherapy

The different radiotherapy modalities include conventional radiotherapy, 3D radiotherapy and IMRT or VMAT. SBRT can be applied with 3D radiotherapy, IMRT or VMAT. The characteristics of SBRT compared to other radiotherapy techniques include the possibility of focusing high doses of radiation on the tumor, limiting the doses received by the surrounding healthy tissue, in a small number of sessions. For this purpose, immobilization or respiratory control systems are used, allowing the maximum reduction of the tissue to be irradiated, and image-guided radiotherapy is used to guarantee that the planned treatment is the one given. Thanks to advances in radiotherapy, SBRT has become a local treatment option with a 75-100% response at 1-2 years of survival.[13]

Dowstaging at advanced HCC

In many centres, research is being developed on the role of dowstaging, i.e. the use of a pre-treatment to enable the criteria of other treatments initially contraindicated to be met. Soin et al analysed patients subjected to HCC dowstaging with PVTT with SBRT, TACE or TARE. Patients who received sorafenib with TARE/SBRT had an overall survival (OS) at 2 years of 17%.[14] Kishi et al in their study analyzed HCC patients with PVTT treated with SBRT followed by surgery and hepatic arterial infusion chemotherapy (HAIC), 8 patients received 48 Gy in 4 fractions, 6 of them were operated, presenting 50% complete pathological response. There were no major toxicities to grade 2.[15]

SBRT in PVTT used for dowstaging is a promising option to achieve less invasive hepatectomies. However, a high rate of recurrence has been observed in the remaining liver. In patients with preserved liver function and with lesions confined to the hemilobule, SBRT may be effective as a preoperative treatment in curative liver resection.

Radiation therapy and malignant thrombosis

The first data on the efficacy of radiotherapy in portal tumour thrombosis are from 1994[16], starting the use of SBRT treatment in 2002.[17]

Conventional radiotherapy and HCC with PVTT

The overall response after conventional 3DRT is 25.2-62.3%, and the OS at 1 year is 25-57.6%, with a median survival of 3.8-13.9 months.[10,18-23] Articles published prior to 3DRT include few patients. Chen et al, in 1994 treated 10 patients with unilateral PVTT with conventional radiotherapy. The prescription dose was 30-50 Gy. Five patients had a complete response and five patients had a partial response.[16] Leung et al reported a case of HCC with PVTT treated with 3DRT, with a dose of 55 Gy, demonstrating the efficacy of treatment for small tumour volumes with high doses of radiation.[24] Huang et al, treated 41 patients with conventional radiotherapy followed by TACE. The prescription dose was 36-66 Gy, with complete response in 39% of patients and partial response in 41% of patients. Survival was related to response.[25] Zeng et al analysed 158 patients. 44 patients were treated with conventional radiotherapy for portal tumour thrombosis, 9 with radiotherapy and surgery, 25 with radiotherapy and TACE, and 10 with radiotherapy alone. Thirty-four percent of patients had complete responses and 11.4% had partial responses. The median survival was 8 and 4 months for radiotherapy. With a median survival of 15 and 5 months for patients with complete and partial response versus patients with stable or progressive disease. Multivariate analysis showed that radiotherapy was an independent factor in survival[26]. Yamada et al treated 8 patients with TACE and conventional radiotherapy in a pilot study. The response was 37.5%.[27] In a second study they used 3DRT in 19 patients obtaining a 57.9% response. The average dose was 57 Gy in the two studies.[28] Kamiyana et al reported the use of conventional 3DRT followed by surgery significantly improved survival.[29] Yeh et al reported HCC with PVTT treated with 3DRT but median survival of 7 months.[30]

SBRT and HCC with PVTT

Very few studies have investigated the role of SBRT for PVTT and inferior vena cava thrombosis (IVCTT) in patients with HCC. The use of SBRT as a bridge to transplantation provides between 27-63% of pathological complete responses.[31] Data on the efficacy of SBRT for PVTT are limited, with a median OS of 6-8 months in less than 10 patients.[32,33] Until 2013 there were no data in the literature on the efficacy of SBRT in portal tumour thrombosis. In 2013 Xi et al reported the efficacy and toxicity of SBRT for the treatment of PVTT and/or IVCTT in patients with advanced HCC. They included 41 patients using SBRT with VMAT. Thirty-three patients had PVTT and eight patients had IVCTT. The median dose was 36 Gy (30-48 Gy) in 6 fractions over 2 weeks. Median follow-up was 10 months. At the time of analysis 36.6% of patients had complete responses, 39% partial responses, 17.1% stable disease and 7.3% progression. OS at one year was 50.3% with a median of 13 months. The factor related to better survival was response to radiation therapy. The study by Yoon et al included 412 patients with PVTT.[18] Patients were treated with 40 Gy (21-60Gy) in daily sessions of 2-5 Gy. The response was 39.6%. Median survival was 10.6 months, and OS at 1 year was 42.5%. Rim et al[20] analysed the treatment of 45 patients with PVTT with complete responses of 6.7% and partial responses of 55.6%. Tse et al reported good results in unresectable HCC treated with SBRT with 6 fractions in two weeks.[34] SBRT is a promising treatment, however, the survival of these patients remains limited by the high frequency of intra- and extrahepatic recurrences.

Comparison in radiotherapy modalities

In 2006, Lin et al analysed the rate of vascular recanalisation after radiotherapy in HCC with PVTT.[32] They included 43 patients, 22 treated with SBRT and 21 with 3DRT. 3 Gy per fraction was administered 3 days per week up to 45 Gy in SBRT and 1.8Gy per fraction 5 days per week up to 45Gy in 3DRT. 16 of the 43 patients completed treatment, with 14 recanalizations observed, 8 in the SBRT group and 6 in patients treated with 3DRT. In all patients the response was 26%. For the 16 patients who completed the treatment the response was 79%. Seventy-five percent of the responses were in the SBRT group and 83% in the 3DRT group, with a median survival of 6 and 6.7 months in the SBRT and 3DRT groups, respectively. Rim et al in 2018 published a meta-analysis and systematic review for the study of radiation therapy treatment modalities in HCC with PVTT.[35] They analyzed 37 studies with 2513 patients. The OS at 1 year of non-SBRT 3DRT, selective internal RT (SIRT) and SBRT was 43.8%, 46.5% and 48.5%, with no statistically significant difference between groups (p=0.635). Response rates were 51.3%, 33.3% and 70.7% for non-SBRT 3DRT, SIRT and SBRT respectively, p=0.001 and 0.031 for non-SBRT 3DRT vs SBRT.

Most major complications at grade 3 were lymphocytopenia and bilirubin disturbances in 3DRT non-SBRT and SIRT respectively. Toxicity greater than or equal to grade 3 was rare in the SBRT group.

Matsuo et al compared the efficacy of SBRT with 3DRT in the management of PVTT, with a one-year OS of 49.3% in the SBRT group and 29.3% in 3DRT.[36] Tumor response was 67%, 70%, 62% and 46% after SBRT, Cyberknife® (CK), True Beam® and 3DRT respectively (p=0.04, 0.04, 0.25). The 1-year OS was 49.3%, 56.7%, 38.1%, and 29.3% respectively (p=0.02, 0.02, 0.2), and the 1-year local progression was 20.4%, 21.9%, 18.8%, and 43.6% respectively (p=0.01, 0.04, 0.1). It improves local control and survival in the CK group and in the entire SBRT group. It is a potential treatment in PVTT and vena cava. Xi et al reported response to high doses as prognostic factors.[37]

Theoretical advantages of SBRT over conventional radiotherapy

Some of the theoretical advantages of SBRT include that it allows higher doses of radiation to be delivered than conventional radiotherapy. In the available studies, it appears that for recanalization of the portal vein with SBRT or conventional 3DRT, a dose of 45Gy may be sufficient. However, dose escalation above 45Gy may help improve the recanalization rate.[38]

SBRT is given in a limited number of sessions, however, conventional radiotherapy requires more than five weeks to deliver adequate doses and can be fatal for non-responders.

Combined treatments with SBRT

SBRT and TACE

The theoretical advantages of the combination of SBRT and TACE include increased tumor cell death or inhibition after TACE[39,40]; in addition to the sensitivity of PVTT to radiation therapy.[18,41] Shui et al in 2018, included 70 patients with a median follow-up of 9.5 months (1-21 months)[42]. The median survival for the group was 10 months with 6- and 12-month survival of 67.3% and 40%. Patients receiving SBRT and TACE had better survival. Patients with good response to SBRT had better survival. Objective responses were at 1, 3, and 6 months of 77.4%, 79.1%, and 83.8% respectively. Within one month after SBRT, five cases achieved almost complete response. Complete response increased over time, from 9.7% at 3 months to 32.2% at 6 months after SBRT. Of the 16 patients with imaging evaluation at 9 months after treatment, more than half had complete response. Progression after SBRT was found in 17.1% of cases, with most progression occurring within the first 3 months. In our series, 4 patients had progression of PVTT within 1 month, 6 between 1-3 months, and only 2 patients at 6 months. Most of the portal venous flow was restored, giving the opportunity to receive other treatments such as surgery or TACE. The median survival from the start of SBRT for these patients was 10 months, with the respective OS at 6 and 12 months of 67.3% and 40%. Published data are scarce and the median survival is 8 and 13 months, with an OS at 1 year of 43.2% to 50.3%.[38,41,43] In a prospective phase I and II study, Bujold et al[12], included 56 patients with thrombosis showing an OS at 1 year of 44% after SBRT. With a median survival of 12 months, patients who received TACE after SBRT had a long survival.[40] 40Gy or more appear to have long OS. Choi et al in 2020 analysed 24 patients with HCC with PVTT with 45 Gy in 3 fractions in 17 (70.8%) patients, modified in 7 patients (29.2%), with a dose range of 39-42Gy in 3-4 fractions. After SBRT, TACE was administered in 16 patients (66.7%). Of the 24 patients, 2 (8.3%) showed complete response, and 11 (45.8%) showed partial response. After a follow-up of 8.4 months (2.6-56.5 months), OS at 1 year and median survival were 67.5% and 20.8 months, respectively. Grade 3 liver toxicity was higher in the combination treatment.[44]

SBRT and sorafenib

Evidence shows that sorafenib in monotherapy is inferior to other therapies or combination therapies. Theoretically, sorafenib mediates the blockade of RAF/MAPK and the VEGF receptor by increasing the effectiveness of radiotherapy. Radiation therapy combined with sorafenib may be associated with increased tumor growth retardation.

Brade et al[45] reported on a phase I study that combined sorafenib and SBRT within two weeks of SBRT in 6 fractions in patients with locally advanced HCC with unacceptable Child Pugh A toxicity. We do not recommend this combination especially in patients with large liver volumes. A phase II study by Chen et al, analysed 40 patients with unresectable HCC and 24 patients with PVTT who were treated with radiotherapy and sorafenib.[46] The radiotherapy dose ranged from 40-60 Gy, with a two-year progression-free survival of 39%. The multi-centre study by Im et al included 985 patients with PVTT in the main and/or first branch treated with radiotherapy[47]. A 51.8% response was observed with a median OS of 10.2 months. When sorafenib was administered after SBRT, the median survival increased to 12.5 months, a 1- and 2-year OS of 55.6% and 17.7%. The median progression-free survival was 3 months longer than for patients treated with SBRT alone. Progression-free survival at 1 and 2 years was long with patients receiving SBRT alone was not statistically significant. Acute toxicity was higher in the combination of SBRT and sorafenib. That et al included 54 patients, 18 patients combined SBRT and sorafenib, and 36 patients received SBRT alone.[48] The dose administered was 36-45 Gy (median 40 Gy) in 3-5 fractions. There was no statistically significant difference between groups in response to treatment with 77.77% for the combination of SBRT and sorafenib, and 75% for treatment with SBRT alone. The benefits of combining the treatments remain undetermined.

Other combinations

Li et al reviewed the three treatment modalities studied in PVTT: SBRT combined with TACE, 3D radiotherapy with hepatic arterial infusion chemotherapy (HAIC) or TACE, TACE and sorafenib and SBRT, HAIC, sorafenib and TACE alone. After analyzing 15 studies from 2010 to 2016 with 2359 patients the study showed that HAIC radiation therapy was most effective, followed by radiation therapy and TACE. Grade 3 and 4 side effects were less frequent in SBRT treatment.[49]

Only the meta-analysis by Zhao et al was similar to the study by Li et al including patients with advanced HCC with portal vein invasion.[50] The combination of 3DRT or SBRT therapies with HAIC or TACE and TACE combined with sorafenib to treat PVTT was superior to any single treatment option.[51]

Side effects after SBRT in HCC with PVTT

Acute side effects have been described in liver SBRT, including asthenia, nausea, loss of appetite, dyspepsia, gastritis, ascites, hepatomegaly and increased transaminases, most of which are grade 1-2 toxicities according to CTCAE V4.3.

Bujold and Bae et al reported toxicity greater than or equal to grade 3 of 14-30%.[12, 52] The liver is a radiosensitive

organ and patients with HCC often have liver cirrhosis and liver dysfunction. The more volume is radiated, the greater the probability of side effects, so it is important to develop techniques that allow volumes to be reduced[53], in addition to reducing the risk in surrounding organs such as the stomach by preventing bleeding, ulcers or stenosis.[54,55] In 2013 Xi et al there were no major grade 4 toxicities within three months of treatment. One patient had elevated grade 3 bilirubin. Toxicities were lower than with 3DRT.[10,19,24]

Limitations of the study

The nature of the studies is retrospective with few patients. In addition, most studies perform re-evaluation after SBRT with CT or MRI, however because of the characteristics of HCC with PVTT it is sometimes not complete without an echo-Doppler as portal flow changes after SBRT.

Conclusiones

Radiotherapy and specifically the development of SBRT could be a single local treatment alternative or combined with other therapies in HCC with PVTT or IVCTT. More studies are needed to evaluate its efficacy, dose and fractionation and side effect profile.

Main points

SBRT is a therapeutic option in patients with portal thrombosis with no other options.

SBRT enables safe and effective delivery of high-dose radiation in hepatocellular carcinoma.

SBRT allows revascularization in patients with tumoral vascular thrombosis facilitating the administration of other contraindicated treatments.

However, more studies are needed to establish the use of this therapy in these patients.

REFERENCES

1. *Zhang ZM, Lai EC, Zhang C, et al. The strategies for treating primary hepatocellular carcinoma with portal vein tumor thrombus. Int J Surg. 2015; 20:8–16.*
2. *Nakazawa T, Adachi S, Kitano M, Isobe Y, Kokubu S, et al. Potential prognostic benefits of radiotherapy as an initial treatment for patients with unresectable advanced hepatocellular carcinoma with invasion to intrahepatic large vessels. Oncology. 2007; 73:90–97.*
3. *Kim JH, Yoon HK, Kim SY, Kim KM, Ko GY, et al. Transcatheter arterial chemoembolization vs. chemoinfusion for unresectable hepatocellular carcinoma in patients with major portal vein thrombosis. Aliment Pharmacol Ther. 2009; 29:1291–1298.*
4. *Toya R, Murakami R, Baba Y, Nishimura R, Morishita S, et al. Conformal radiation therapy for portal vein tumor thrombosis of hepatocellular carcinoma. Radiother Oncol. 2007; 84:266–271.*
5. *Jeong, Y. et al. Stereotactic body radiation therapy using a respiratory-gated volumetric-modulated arc therapy technique for small hepatocellular carcinoma. BMC Cancer. 2018; 18, 416.*
6. *Huang YJ, Hsu HC, Wang CY, Wang CJ, Chen HC, et al. The treatment responses in cases of radiation therapy to portal vein thrombosis in advanced hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2009; 73:1155–1163.*
7. *Han KH, Seong J, Kim JK, Ahn SH, Lee do Y, et al. Pilot clinical trial of localized concurrent chemoradiation therapy for locally advanced hepatocellular carcinoma with portal vein thrombosis. Cancer. 2008; 113:995–1003*
8. *Chok KS, Cheung TT, Chan SC, Poon RT, Fan ST, Lo CM. Surgical outcomes in hepatocellular carcinoma patients with portal vein tumor thrombosis. World J Surg. 2014;38(2):490–6.*
9. *Katagiri S, Yamamoto M. Multidisciplinary treatments for hepatocellular carcinoma with major portal vein tumor thrombus. Surg Today. 2014;44(2): 219–26.*
10. *Kim JY, Chung SM, Choi BO, Kay CS. Hepatocellular carcinoma with portal vein tumor thrombosis: improved treatment outcomes with external beam radiation therapy. Hepatol Res. 2011; 41:813–824.*
11. *Jacob R, Turley F, Redden DT et al. Adyuvant stereotactic body radiotherapy following transarterial chemoembolization in patients with non resectable hepatocellular carcinoma tumors of > 3 cm. Int Hepato-Pancreato-Biliary. 2015; 17 (2): 140-49.*
12. *Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol. 2013; 31(13):1631-1639.*
13. *Cammà C, Cabibbo G, Petta S, et al. Cost-effectiveness of sorafenib treatment in field practice for patient with hepatocellular carcinoma. Hepatology. 2013;57 (3):1046–1054.*
14. *Soin AS, Bhangui P, Kataria T , Baijal SS , Piplani T , Gautam D, Chaudhary N, Thiagarajan S , Rastogi A , Saraf N , Saigal S. Experience With LDLT in Patients with Hepatocellular Carcinoma and Portal Vein Tumor Thrombosis Postdownstaging. Transplantation. 2020; 6.*
15. *Kishi N, Kanayama N, Hirata T, Ohira S, Wada K, Kawaguchi Y, Konishi K, Nagata S, et al. Preoperative stereotactic body radiotherapy to portal vein tumour thrombus in hepatocellular carcinoma: Clinical and pathological analysis. Scientific Reports. 2020; 10:4105*
16. *Chen SC, Lian SL, Chang WY. The effect of external radiotherapy in treatment of portal vein invasion in hepatocellular carcinoma. Cancer Chemother Pharmacol. 1994; 33:S124–S127.*
17. *Zeng ZC, Fan J, Tang ZY, Zhou J, Qin LX, Wang JH, et al. A comparison of treatment combinations with and without radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombus. Int J Radiat Oncol Biol Phys. 2005; 61:432–443.*
18. *Yoon SM, Lim YS, Won HJ, Kim JH, Kim KM, et al. Radiotherapy plus transarterial chemoembolization for hepatocellular carcinoma invading the portal vein: long-term patient outcomes. Int J Radiat Oncol Biol Phys. 2012; 82:2004–2011.*
19. *Koo JE, Kim JH, Lim YS, Park SJ, Won HJ, et al. Combination of transarterial chemoembolization and three-dimensional conformal radiotherapy for hepatocellular carcinoma with inferior vena cava tumor thrombus. Int J Radiat Oncol Biol Phys. 2010; 78:180–187.*
20. *Rim CH, Yang DS, Park YJ, Yoon WS, Lee JA, et al. Effectiveness of high-dose three-dimensional conformal radiotherapy in hepatocellular carcinoma with portal vein thrombosis. Jpn J Clin Oncol. 2012; 42:721–729.*
21. *Toya R, Murakami R, Baba Y, Nishimura R, Morishita S, et al. Conformal radiation therapy for portal vein tumor thrombosis of hepatocellular carcinoma. Radiother Oncol. 2007; 84:266–271.*
22. *Huang YJ, Hsu HC, Wang CY, Wang CJ, Chen HC, et al. The treatment responses in cases of radiation therapy to portal vein thrombosis in advanced hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2009; 73:1155– 1163.*
23. *Han KH, Seong J, Kim JK, Ahn SH, Lee do Y, et al. Pilot clinical trial of localized concurrent chemoradiation therapy for locally advanced hepatocellular carcinoma with portal vein thrombosis. Cancer. 2008; 113:995–1003.*

24. Leung SW, Huang EY, Cheng YF, Lu SN. Conformal radiation therapy for hepatoma with portal vein thrombosis. Br J Radiol. 2000; 73:550–552.
25. Huang CJ, Lian SL, Chen SC, Wu DK, Wei SY, Huang MY, et al. External beam radiation therapy for inoperable hepatocellular carcinoma with portal vein thrombosis. Kaohsiung J Med Sci. 2001;17:610–614.
26. Zeng ZC, Fan J, Tang ZY, Zhou J, Qin LX, Wang JH, et al. A comparison of treatment combinations with and without radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombus. Int J Radiat Oncol Biol Phys. 2005; 61:432–443.
27. Yamada K, Soejima T, Sugimoto K, Mayahara H, Izaki K, Sasaki R, et al. Pilot study of local radiotherapy for portal vein tumor thrombus in patients with unresectable hepatocellular carcinoma. Jpn J Clin Oncol. 2001; 31:147–152.
28. Yamada K, Izaki K, Sugimoto K, Mayahara H, Morita Y, Yoden E, et al. Prospective trial of combined transcatheter arterial chemoembolization and three-dimensional conformal radiotherapy for portal vein tumor thrombus in patients with unresectable hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2003; 57:113–119.
29. Kamiyana T et al. Efficacy of preoperative radiotherapy to portal vein tumor thrombus in the main trunk or first branch in patients with hepatocellular carcinoma. Int J Clin Oncol. 12, 363-368 (2007).
30. Yeh, S. A., Chen, Y. S. & Perng, D. S. The role of radiotherapy in the treatment of hepatocellular carcinoma with portal vein tumor thrombus. J. Radiat. Res. 2015; 56, 325–331.
31. Uemura, T. et al. Stereotactic Body Radiation Therapy: A New Strategy for Loco-Regional Treatment for Hepatocellular Carcinoma While Awaiting Liver Transplantation. World. J. Surg. 2019; 43, 886–893.
32. Lin CS, Jen YM, Chiu SY, Hwang JM, Chao HL, et al. Treatment of portal vein tumor thrombosis of hepatoma patients with either stereotactic radiotherapy or three-dimensional conformal radiotherapy. Jpn J Clin Oncol. 2006; 36:212–217.
33. Choi BO, Choi IB, Jang HS, Kang YN, Jang JS, et al. Stereotactic body radiation therapy with or without transarterial chemoembolization for patients with primary hepatocellular carcinoma: preliminary analysis. BMC Cancer. 2008; 8:351.
34. Tse RV, Hawkins M, Lockwood G, Kim JJ, Cummings B, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol. 2008; 26:657–664.
35. Rim CH, Kim CY, Yang DS , Yoon WS. Comparison of radiation therapy modalities for hepatocellular carcinoma with portal vein thrombosis: A meta-analysis and systematic review. Radiother Oncol. 2018 Oct;129(1):112-122.
36. Matsuo Y, Yoshida K, Nishimura H, et al. Efficacy of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein tumor thrombosis/inferior vena cava tumor thrombosis: evaluation by comparison with conventional three-dimensional conformal radiotherapy. J Radiat Res. 2016;57(5):512–23.
37. Xi M, Zhang L, Zhao L, et al. Effectiveness of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombosis. PLoS One. 2013;8(5): e63864.
38. Kong XG, Dong YP, Wu JX, et al. High-biologically effective dose palliative radiotherapy for a tumor thrombus might improve the long term prognosis of hepatocellular carcinoma: a retrospective study. Radiat Oncol. 2017;12:92
39. Lu DH, Fei ZL, Zhou JP,Hu ZT, Hao WS. A comparison between three-dimensional conformal radiotherapy combined with interventional treatment and interventional treatment alone for hepatocellular carcinoma with portal vein tumour thrombosis. J Med Imaging Radiat Oncol. 2015;59(1):109–114.
40. Kang J, Nie Q, DU R, et al. Stereotactic body radiotherapy combined with transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis. Mol Clin Oncol.2014;2(1):43–50.
41. Kim TH, Kim DY, Park JW, et al. Three-dimensional conformal radiotherapy of unresectable hepatocellular carcinoma patients for whom transcatheter arterial chemoembolization was ineffective or unsuitable. Am J Clin Oncol.2006;29(6):568–575
42. Shui Y, Yu W, Ren X, Guo Y, Xu J, Ma T, Zhang B, Wu J, Li Q, Hu Q, Shen L, Bai X, Liang T and Wei Q. Stereotectic body radiotherapy based treatment for hepatocellular carcinoma with extensive portal vein tumor thrombosis. Radiation Oncology. 2018; 13:188
43. Lee SU, Park JW, Kim TH, et al. Effectiveness and safety of proton beam therapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Strahlenther Onkol. 2014;190(9):806–14.
44. Choi HS, Kang KM, Jeong BK, Jeong H, Lee YH, Ha IB, Song JH. Effectiveness of stereotactic body radiotherapy for portal vein tumor thrombosis in patients with hepatocellular carcinoma and underlying chronic liver disease. Asia Pac J Clin Oncol. 2020; 5.
45. Brade et al. Brade A, Ng S, Brierley J, et al. Phase1 trial of sorafenib and stereotactic body radiation therapy for hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2016; 94:580–7.
46. Chen SW, Lin LC, Kuo YC, et al. Phase 2 study of combined sorafenib and radiation therapy in patients with advanced hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2014; 88:1041–7.
47. Im et al Im JH, Yoon SM, Park HC, et al. Radiotherapeutic strategies for hepatocellular carcinoma with portal vein tumor thrombosis in a hepatitis B endemic area. Liver Int. 2017; 37:90–100
48. Que J, Wu HC, Lin CH, Huanf CI, Li LC, Ho CH. Comparison of stereotactic body radiation therapy with and without sorafenib as treatment for hepatocellular carcinoma with portal vein tumor Thrombosis. Medicine. 2020; 99:13.
49. Li Q, Hu Y, Xi M, et al. Sorafenib modulates the radio sensitivity of hepatocellular carcinoma cells in vitro in a schedule-dependent manner. BMC Cancer. 2012; 12:485.
50. Zhao Q, Zhu K, Yue J, et al. Comparison of intra-arterial chemoembolization with and without radiotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: a meta-analysis. Ther Clin Risk Manag. 2016; 13:21–31.
51. Huo YR, Eslick GD. Transcatheter arterial chemoembolization plus radiotherapy compared with chemoembolization alone for hepatocellular carcinoma: a systematic review and meta-analysis. JAMA Oncol. 2015;1(6):756–765.
52. Bae, S. H. et al. Feasibility and efficacy of stereotactic ablative radiotherapy for Barcelona Clinic Liver Cancer-C stage hepatocellular carcinoma. J. Korean. Med. Sci. 2013; 28, 213–219.
53. Doi, H. et al. Validation of the liver mean dose in terms of the biological effective dose for the prevention of radiation-induced liver damage. Rep. Pract. Oncol. Radiother. 2017; 22, 303–309.
54. Wang, P. M. et al. Feasibility of stereotactic body radiation therapy with volumetric modulated arc therapy and high intensity photon beams for hepatocellular carcinoma patients. Radiat. Oncol. 2014; 9, 18.
55. Scorsetti, M. et al. Stereotactic body radiation therapy for abdominal targets using volumetric intensity modulated arc therapy with RapidArc: feasibility and clinical preliminary results. Acta. Oncol. 2011; 50, 528–538.

AMGEN®

WHAT'S BEHIND AMGEVITA™ MAKES THE DIFFERENCE

A company that has served patients with chronic inflammatory conditions for over 20 years[1] and a proven leader with four decades of experience in biologics[2,3]

Introducing the adalimumab biosimilar[4]

AMGEVITA™ (adalimumab)

Amgevita™

- is approved across all key adalimumab indications[5]
- has similar safety, efficacy and immunogenicity as the originator biologic[6,7,8,9]

References: 1. AMGEN Therapeutic Area Heritage. C2019. Accessed 25/3/2020. Available from https://www.amgenbiosimilars.com/heritage/therapeutic-area-heritage/ **2.** AMGEN Fact Sheet. C2020. Accessed 25/3/2020. Available from https://www.amgen.com/about/quick-facts/ **3.** AMGEN Biotech. C2017. Accessed 25/3/2020. Available from https://www.amgenbiotech.com/manufacturing-innovation.html **4.** Kozlowski S. US FDA perspectives on biosimilar biological products. c2014. Accessed 25/3/2020. Biotechnology Technology Summit. IBBR University of Maryland, Rockville, MD. Available from https://www.ibbr.umd.edu/sites/default/files/public_page/Kozlowski%20-%20Biomanufacturing%20Summit.pdf **5.** AMGEVITA™ package insert. 18 Feb. 2020. **6.** Kaur P, Chow V, Zhang N, *et al.* A randomised, single-blind, single-dose, three-arm, parallel-group study in healthy subjects to demonstrate pharmacokinetic equivalence of ABP 501 and adalimumab. *Ann Rheum Dis* 2017;76:526-533. **7.** Cohen S, Genovese MC, Choy E, *et al.* Efficacy and safety of the biosimilar ABP 501 compared with adalimumab in patients with moderate to severe rheumatoid arthritis: a randomised, double-blind, phase III equivalence study. *Ann Rheum Dis* 2017;76:1679-1687. **8.** Cohen S, Pablos JL, Pavelka K, *et al.* An open-label extension study to demonstrate long-term safety and efficacy of ABP 501 in patients with rheumatoid arthritis. *Arth Res & Ther* 2019;21:84. **9.** Papp K, Bachelez H, Costanzo A, *et al.* Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: A randomized, double-blind, multicentre, phase III study. *J Am Acad Dermatol* 2017;76:1093-1102.

S4 **AMGEVITA** 40 mg solution for injection in pre-filled syringe. Each single dose pre-filled syringe contains 40 mg of adalimumab in 0.8 ml (50 mg/ml) solution. Reg. No. 51/30.1/0678. S4 **AMGEVITA** 40 mg solution for injection in pre-filled pen. Each single dose pre-filled pen contains 40 mg of adalimumab in 0.8 ml (50 mg/ml) solution. Reg. No. 51/30.1/0678. For full prescribing information refer to the package insert approved by the medicines regulatory authority.

Amgen South Africa (Pty) Ltd., Co. Reg. No.: 2011/112148/07. Building D, Ballyoaks Office Park, 35 Ballyclare Drive, Bryanston Ext. 7, 2021. Tel: 011 100 5300 Fax: 011 100 5301. Adverse Event Reporting Fax: 0800 166 513. PR-AMV-ZAF-000018.

AMGEN 40 YEARS

HCC with PVT. Complete pathologic response following transarterial radioembolization: A case report

M. Tunmer[1], C. Sanyika[2], A. Mahomed[3]

[1] WITS Donald Gordon Medical Centre, Department of Radiation Sciences, Radiation Oncology, University of the Witwatersrand, Johannesburg South Africa

[2] WITS Donald Gordon Medical Centre, Department of Radiology, University of the Witwatersrand, Johannesburg, South Africa

[3] Charlotte Maxeke Johannesburg Academic Hospital, Division of Gastroenterology and Hepatology and WITS Donald Gordon Medical Centre, Transplant Hepatology unit and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

ABSTRACT

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide and management of this disease remains challenging in many cases. For patients with Barcelona Clinic Liver Cancer (BCLC) advanced stage (C) disease, systemic therapy with Sorafenib has been the standard of care with median overall survival (OS) rates of less than one year. Patients presenting with portal vein tumour thrombosis (PVT) are considered to have a particularly dismal survival. For select patients, various loco-regional therapies may improve outcomes and even aid in downstaging to surgical resection or liver transplant. We present a case report of an adult male patient with a unilobar HCC with lobar portal vein invasion who underwent transarterial radioembolization (TARE) as a downstaging procedure. The patient had complete radiological response and then underwent a liver transplant. Complete pathological response was confirmed in the liver explant. At time of writing, almost 4 years following diagnosis, this patient was still alive with no evidence of recurrence. Patient selection is key when deciding on the optimal management of HCC and multidisciplinary team (MDT) involvement is encouraged.

Introduction

HCC is predicted to be the third to fourth most common cause of cancer-related mortality in the world[1,2]. The main risk factors for this disease are related to chronic inflammatory conditions of the liver, most commonly hepatitis B, hepatitis C, excessive alcoholic use, non-alcoholic fatty liver disease and aflatoxin exposure[3]. Successful management of this disease is challenging with many patients succumbing to their disease within months to years of diagnosis.

For patients with very early (0) or early (A) stage disease according to the BCLC guidelines[1], the disease is potentially curable by surgical resection or transplantation. Patients who are non-surgical candidates may be cured by various ablative procedures – thermal (radiofrequency and microwave), chemical (acetic acid or percutaneous ethanol injection) or cryoablation.[4] However, these stages represent the minority of cases of patients diagnosed with HCC. Furthermore, some patients who are potentially transplantable at diagnosis will upstage due to waiting times on transplant lists.

Unfortunately, most patients present with intermediate stage (B) or advanced stage (C) disease. The standard of care for these patients according to the BCLC treatment algorithm are transarterial chemoembolization (TACE) and systemic therapy, respectively.[1,5]

Correspondence
M Tunmer
email: mariza@radonc.co.za

Across the stages and in well-selected patients, loco-regional therapies may aid in downstaging disease to surgery or as a bridging therapy while awaiting transplant. These include the ablative procedures listed above, transarterial approaches including TACE, transarterial embolisation (TAE), drug-eluting bead chemoembolization (DEB-TACE) and TARE as well as contemporary external beam radiotherapy techniques such as volumetric modulated radiotherapy (VMAT) and stereotactic body radiotherapy (SBRT).[1,4,21,26]

For appropriate disease stages the therapies which have demonstrated a survival benefit include surgery (resection and transplant), ablation, TACE, sorafenib, lenvatinib and regorafenib and more recently the combination of atezolizumab with bevacizumab.[22]

Other ablative procedures, embolisation without chemotherapy and radiotherapy have shown tumouricidal effects but no proven survival benefit. Hence, selection of the most appropriate modality should be individualized, and given the plethora of treatment options available as well as the variable and often controversial benefits of the available modalities, discussion and management within a multidisciplinary team is advised.[1]

We present a case of a male patient with advanced stage (C) disease at presentation (with portal invasion) who underwent TARE as a downstaging procedure to liver transplant.

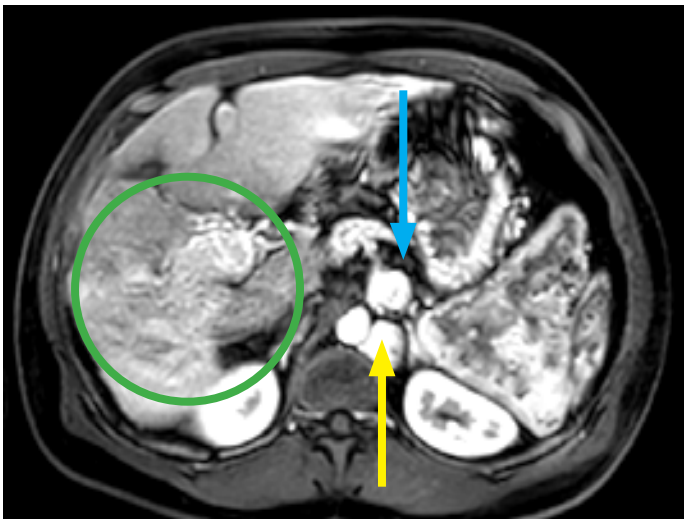
Case Description

Mr. PC was a 43-year-old male, PS 0, who presented in early 2017 with abdominal pain and bleeding oesophageal varices.

He had a history of long-standing hepatitis C which had been diagnosed in the early 1990s and was virally suppressed on serum HCV RNA quantitation PCR. He had showed sustained viral suppression post treatment with direct acting antivirals. Following work-up the patient was diagnosed with an advanced stage HCC with portal vein involvement. A liver biopsy in January 2017 revealed features of chronic active hepatitis with features suggestive of autoimmune hepatitis (AIH) and incipient cirrhosis. The AIH was considered to be related to his Hepatitis C.

An MRI study using liver specific contrast (Gadoxetate disodium, Primovist®, Bayer) was performed. The MRI of the liver revealed an infiltrative hypervascular tumour within the atrophic right lobe with invasion into the right portal vein (figure 1). The restricted diffusion signal of the infiltrative lobar tumour and the right portal vein tumour thrombus is shown in figure 2. The right portal vein tumour thrombus did not extend into the left portal vein or main portal vein (figure 3). A staging CT scan also done in January 2017 did not reveal any extrahepatic metastases. The MRI (figure 1) and CT scan showed an incidental 2.3cm splenic artery aneurysm and a left sided IVC. The patient's Child-Pugh score was A6 and the ALBI score was -1.89 (Grade 2). His AFP was elevated at 31.4µg/L (normal range 0-7). Of note his platelet count was low (83 x 10^9/L) due to hypersplenism because of portal hypertension. Liver and renal function laboratory studies were within normal limits.

Figure 1. Arterial phase T1 MRI study showing hypervascular infiltrative tumour of the atrophic right lobe with right portal vein invasion (green circle). Incidental splenic artery aneurysm noted (blue arrow) and left side IVC (yellow arrow) noted.



The patient was considered irresectable and was outside criteria for liver transplant. Following a multidisciplinary team discussion, it was decided to offer him an attempt at downstaging of the disease by TARE.

A planning hepatic arteriogram for the TARE demonstrated the tumour supply to be predominantly from the right hepatic artery with minimal supply from the segment 4 artery (fig 4). Coil embolization of the segment 4 artery was performed to promote redistribution of flow into the tumour to be entirely from the right hepatic artery (fig 5). The gastroduodenal artery was not embolised. A splenic artery angiogram confirmed the splenic artery aneurysm (fig 6). Technetium-99 labelled MacroAggregated Albumin (MAA) was injected into the right hepatic artery and a whole-body planar isotope study

Figure 2. DWI MRI showing restricted diffusion in the right lobe and right portal vein tumour (circle).

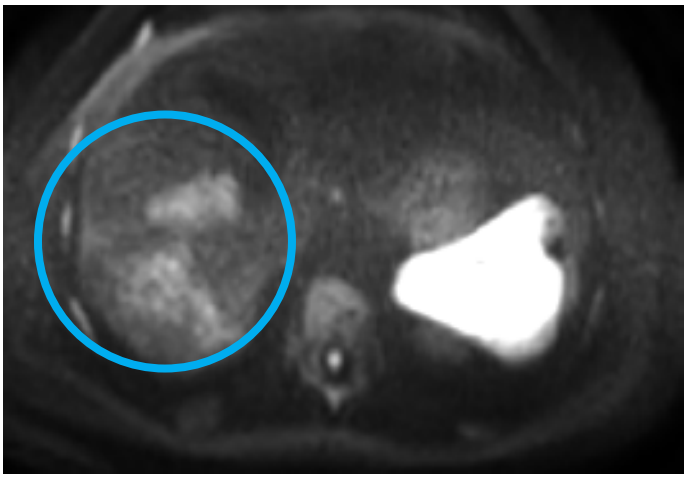


Figure 3. Venous phase T1 MRI showing normal enhancement of uninvolved left portal vein (arrow).

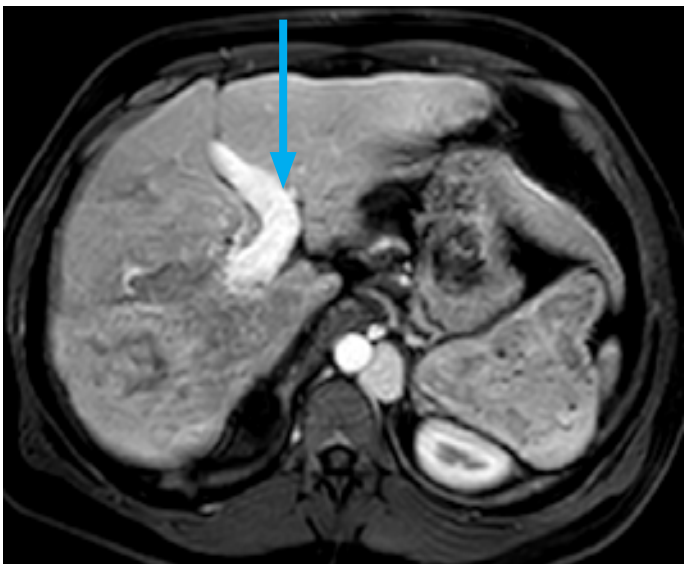


Figure 4. Common hepatic arteriogram showing anomalous branching pattern of the common hepatic artery and most tumour supply from the right hepatic artery with minimal contribution from a segment 4 artery.

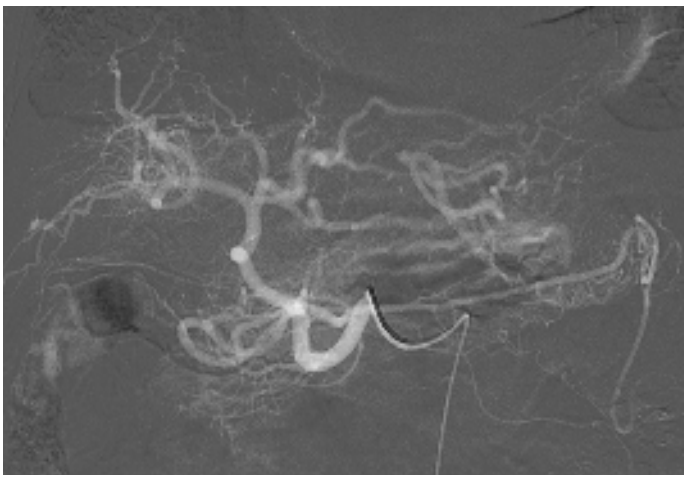


Figure 5a. Right hepatic arteriogram (early phase) showing coil in segment 4 artery (arrow) and the tumour vessels from right hepatic artery.

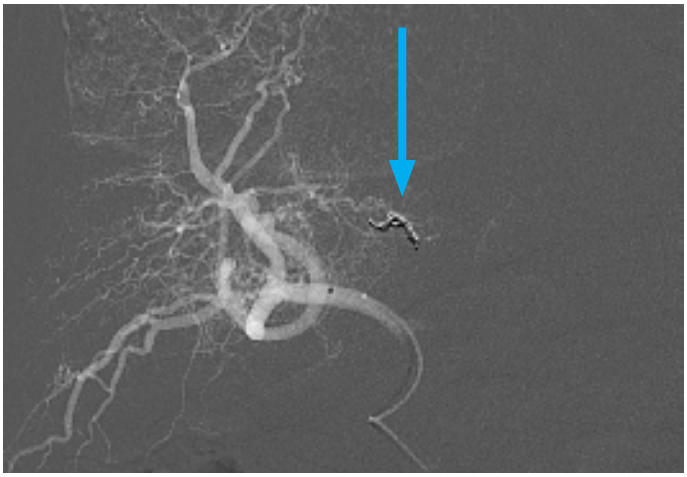


Figure 5b. Right hepatic arteriogram (late phase) showing tumour 'blush' in the right lobe and right portal vein tumour (circle).

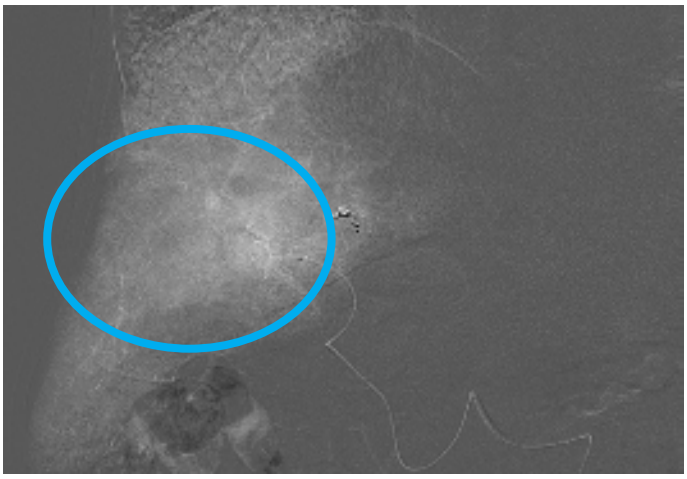
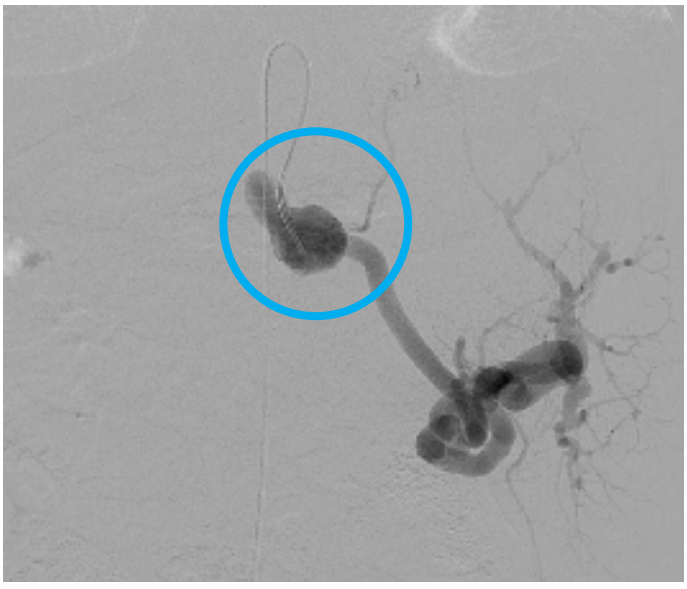


Figure 6: Splenic arteriogram showing the splenic artery aneurysm (circle)



performed. The lung shunt study from the isotope imaging revealed minimal shunting – percent shunt index of 3.2%. There was no evidence of extrahepatic (eg gastro-intestinal) isotope uptake.

The SIR-Spheres® radiation dose required was calculated by the Body Surface Area method based on the patient and tumour volume characteristics. The calculated activity for infusion was 1.80GBq. The patient underwent the TARE procedure in early March 2017. The interventional radiologist placed the infusion catheter in the right hepatic artery and the radiation dose was delivered by the radiation oncologist. The patient developed an access-site groin haematoma which was managed conservatively. The patient had no other procedure-related adverse effects.

A follow up MRI study was performed three months after the TARE which demonstrated a complete radiological response according to the EASL and mRECIST criteria. (figure 7).

Figure 7a. T1 late arterial phase MRI showing wedge shaped enhancement due to radiation induced parenchymal changes, tumour necrosis centrally (blue arrow) lobe and recanalised right portal vein (yellow arrow).

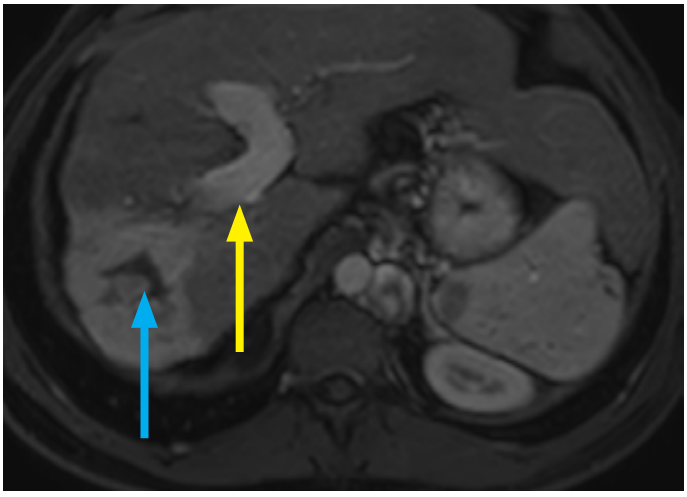
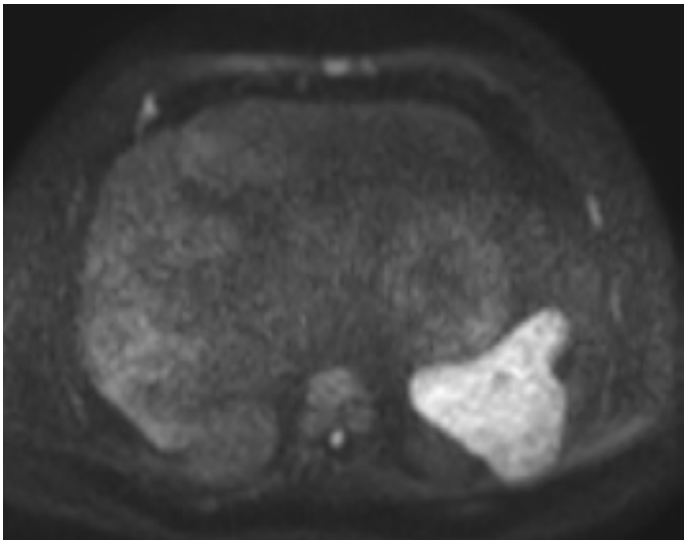


Figure 7b. DWI post TARE showing no restricted diffusion. Minimal signal, somewhat wedge shaped, is from T2 signal "shine through" of radiation induced changes



The patient was then was worked up for liver transplant. Transarterial coil embolisation of the splenic artery aneurysm was performed about two weeks before the liver transplant. In August 2017, a repeat AFP was 5.1kU/L. Mr. PC underwent liver transplant in September 2017 (about six months after the TARE) and histology revealed a complete pathological response and there was no evidence of HCC.

At time of writing the patient remained disease free with no evidence of liver or distal recurrence, almost 4 years following diagnosis.

Discussion

Transarterial radioembolization is a procedure whereby radioactive Yttrium-90 (^{90}Y) -labelled microspheres are injected directly into the feeding arteries of liver tumours.[5] This is possible due to a vascular anatomical advantage whereby liver tumours derive the majority (approximately 80%) of their blood supply from the hepatic arterial system whereas normal liver parenchyma receives most of their bloody supply by the portal system and about 20 – 30% from the arterial system.[6]

^{90}Y is a high-energy, β-emitting isotope with a half-life of 64.1 hours. It decays to stable Zirconium-90. Following administration about 95% of the dose is delivered in 11 days. The average energy of the particles is 0.9367MeV. The microspheres lodge preferentially in the microvasculature surrounding the tumour and induces tumour necrosis. The average tissue penetration is 2.5mm with a maximum range of 11mm.[7,8]

There are two commercially available microsphere devices, namely resin SIR-Spheres® (Sirtex Medical) and glass TheraSpheres™ (Boston Scientific). Resin SIR-Spheres® have an average size of 35-micron (range 20 – 60 micron) and in each 5ml vial there are 40-80 million spheres with a specific activity of 50Bq and these spheres are moderately embolic. Each vial contains 3GBq ^{90}Y at the time of calibration. Glass TheraSpheres™ are 20-30-micron particles with a specific activity of 2500Bq, there are 1.2 to 8 million microspheres per dose and they are minimally embolic.[7,8,9]

The study of ^{90}Y radioembolization for hepatic tumours started in the 1960s.[5] Over the decades TARE has been compared to various other locoregional and systemic therapies. It was found to demonstrate tumoricidal activity while being considered safe in well-selected patients for HCC across various disease stages, however, its use has also been controversial given the failure to demonstrate an overall survival benefit in several phase III studies comparing TARE to other therapies.[1,5,14,19,20] Despite this, and given the favourable safety profile, it is used in various instances across clinical stages for indications ranging from best local tumour control, to downstaging or bridging to surgery, to palliation.[5,27]

Efficacy and toxicity data

In 2008, a phase II study reported on by Kulik et al, 108 patients with unresectable HCC with and without PVT treated by TARE were evaluated.[10] The partial response (PR) was 42.2% using WHO criteria and 70% using EASL (European Association for the Study of Liver Cancer) criteria. Stable disease (SD) was present in 34.7% and 23.1% of patients had progressive disease (PD). There were no cases of radiation pneumonitis or radiation-induced gastritis.

In 2009, Salem et al analysed 291 HCC patients who underwent TARE and measured response rate, time to progression (TTP), survival and toxicity. Objective response rates (ORR) were 42% by WHO criteria and 57% by EASL criteria. TTP was 7.9 months for the entire study population (95% CI, 6-10.3). Survival was found to differ based on Child-Pugh status with Child-Pugh A having the longest survival compared to Child-Pugh B patients (17.2 vs 7.2 months; p=0.002). Patients with Child-Pugh B disease who also have PVT had the worst survival (5.6 months). Grade 1-2 toxicities included fatigue in 57%, abdominal pain in 23%, nausea and vomiting in 20% and anorexia in 15%. Grade 3-4 biochemical bilirubin toxicity occurred in 19%. The mortality rate at 1 month was 3% (n=9) and all the patients who died had PVT.

In 2013, Mazzaferro et al reported on a phase II study in HCC patients with intermediate and advanced disease.[12] In 52 patients the ORR was 40.4%. TPP was 11 months and OS was 15 months. The most common grade 3-4 toxicities included bilirubin toxicity of 16.9%, anorexia of 15.4% and nausea and vomiting at 9.6%. There was no pulmonary toxicity or gastroduodenal ulcers reported.

A 2016 meta-analysis of 17 studies reviewed 722 patients with HCC and PVT treated by TARE.[13] Complete response (CR) was 3.2%, PR was 16.5%, SD was 31.3%, PD was 28%. TTP was 5.6 months and OS was 9.7 months. The most common toxicities were fatigue (2.9-67%), abdominal pain (2.9-57%) and nausea and vomiting (5.7-28%) but in most cases these were mild.

In summary regarding safety, potential toxicities include a post-embolic syndrome which is usually mild, with fatigue, abdominal pain, nausea and fever. Biochemical toxicity with elevations of bilirubin and liver enzymes are mostly grade 1-2. Gastrointestinal ulceration, radiation-induced liver disease (RILD), cholecystitis and abscess formation are rare.

TARE compared to TACE

For BCLC B intermediate stage patients, TACE is currently the standard of care. Several studies comparing the two failed to demonstrate a survival benefit for TARE. In 2016, a meta-analysis by Lobo et al including over 550 patients from 5 studies comparing TARE to TACE[14] and found that although there was no survival benefit, when comparing the two modalities in terms of side effect profiles, TARE compared favourably with lower rates of post-embolisation pain.

A 2009 study by Lewandowski et al compared TARE to TACE in 86 patients for downstaging to transplant eligibility.[15] TARE resulted in significantly higher PR rates (61% vs 37%) as well as improved downstaging from United Network for Organ Sharing (UNOS) T3 to T2 (58% vs 31%). Furthermore, despite the absence of an OS benefit, in the phase II PREMIERE study, Salem et al in 2016 demonstrated a significantly longer median TTP of 26 months for TARE vs. 6.8 months for TACE (p=0.0012) in early-intermediate stage HCC and the authors concluded that TARE could hence potentially decrease transplant list dropout rates.[16]

Another advantage to TARE over TACE is in the setting of PVT. PVT has been considered a relative contra-indication to TACE due to an increased risk of liver toxicity whereas TARE has been shown to be well tolerated even in the setting of PVT. However, as noted before, the presence of PVT does influence prognosis and outcome in patients treated by TARE.[11,17,18]

TARE vs Sorafenib

Two phase III studies recently reported compared TARE to sorafenib. Both the SARAH study[19] (Vilgrain et al) and the SIRveNIB study[20] (Chow et al) failed to show an overall survival benefit for TARE, however, toxicity in the sorafenib arms in both studies were worse – most notably fatigue, abdominal pain, diarrhoea, skin reactions and haematologic effects – compared to TARE.

Evolving concepts and future directions

Current work in the field of radioembolization for HCC includes radiation segmentectomy in carefully selected patients as a method to safely allow for dose escalation to improve response rates and possibly outcomes. One study of 102 patients reported on by Vouche et al for solitary HCC lesions less than or equal to

5cm in size, radiation segmentectomy resulted in CR in 47%, PR in 39% and SD in 12% by mRECIST criteria, with a TTP of 33.1 months. In this study, a third of the patients proceeded to liver transplant and were found to have 90-100% necrosis, especially where the dose exceeded 190Gy.[23]

An interesting retrospective paper by Gordon et al in 2018 described the interesting concept of "Super Survivors" – patients who remain alive more than 3 years after treatment with TARE.[28] In this review, the authors identified 67 patients from their database of 1000 patients who underwent TARE between 2000-2017. Interestingly, the patients spanned BCLC stages A to D and Child-Pugh A to C. Multifocal disease was present in 40% of patients. Median overall survival was 67.5 months and the common variable the patients shared was an imaging response after TARE, suggesting that this might be a prognostic factor. Another notable finding was that patients who underwent segmental TARE were found to have longer OS compared to those undergoing lobar treatment – 80.2 vs 46.7 months (p=0.0024). These are interesting concepts which require further study.

Radioembolisation dosimetry is also an area of active interest given what is known about the tumoricidal effects of radiotherapy based on a dose-response curve noted in many tumour types. With technological advancements in recent years, there is an interest in measuring the radiation dose delivered to the tumour rather than the injected dose.[5] Technetium-99m Macroaggregated Albumin Single Positron Emission Computed Tomography (MAA SPECT/CT) is being used to calculate absorbed tumour dose, health injected liver dose and total injected liver dose. Some studies have shown differences in TTP and OS based on calculated tumour doses.[24,25] Radioembolisation dosimetry is an exciting area of investigation and may lead to further improvements in patient selection and precision medicine.

Conclusions

HCC has a poor prognosis for most patients diagnosed with this disease. Advanced stage disease (C) with PVT has a particularly dismal survival. Across the spectrum of disease stages, various surgical, loco-regional and systemic therapies may be appropriate. Careful patient selection within a multidisciplinary team is paramount to ensuring that the selected therapy results in increase in survival while maintaining the best possible quality of life for the patient. We present the case of a patient with advanced HCC and PVT who responded well to TARE and was able to undergo successful liver transplant. He was still alive at time of writing, almost 4 years following treatment.

References

1. *Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018 Mar 31;391(10127):1301-1314. doi: 10.1016/S0140-6736(18)30010-2. Epub 2018 Jan 5. PMID: 29307467.*
2. *Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424. doi: 10.3322/caac.21492. Epub 2018 Sep 12. Erratum in: CA Cancer J Clin. 2020 Jul;70(4):313. PMID: 30207593.*
3. *Kulik L, El-Serag HB. Epidemiology and Management of Hepatocellular Carcinoma. Gastroenterology. 2019 Jan;156(2):477-491.e1. doi: 10.1053/j.gastro.2018.08.065. Epub 2018 Oct 24. PMID: 30367835; PMCID: PMC6340716.*
4. *NCCN Guidelines Hepatobiliary Cancers Version 5.2020 – August 4, 2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed 2020.11.17*
5. *Saini A, Wallace A, Alzubaidi S, Knuttinen MG, Naidu S, Sheth R, Albadawi H, Oklu R. History and Evolution of Yttrium-90 Radioembolization for Hepatocellular Carcinoma. J Clin Med. 2019 Jan 7;8(1):55. doi: 10.3390/jcm8010055. PMID: 30621040; PMCID: PMC6352151.*
6. *Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol. 1954 Sep-Oct;30(5):969-77. PMID: 13197542; PMCID: PMC1942491.*
7. *Ibrahim SM, Lewandowski RJ, Sato KT, Gates VL, Kulik L, Mulcahy MF, Ryu RK, Omary RA, Salem R. Radioembolization for the treatment of unresectable hepatocellular carcinoma: a clinical review. World J Gastroenterol. 2008 Mar 21;14(11):1664-9. doi: 10.3748/wjg.14.1664. PMID: 18350597; PMCID: PMC2695906.*
8. *SIRTeX SIR-Spheres® Y-90 resin microspheres package insert. Available at: https://www.sirtex.com/media/169247/ssl-us-14-sir-spheres-microspheres-ifu-us.pdf. Accessed on 2020.11.17*
9. *TheraSphere™ Y-90 glass microspheres. Available at: https://www.bostonscientific.com/en-US/products/cancer-therapies/therasphere-y90-glass-microspheres/product-specifications.html. Accessed 2020.11.17*
10. *Kulik LM, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK, Sato KT, Benson A 3rd, Nemcek AA Jr, Gates VL, Abecassis M, Omary RA, Salem R. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology. 2008 Jan;47(1):71-81. doi: 10.1002/hep.21980. PMID: 18027884.*
11. *Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, Atassi B, Baker T, Gates V, Miller FH, Sato KT, Wang E, Gupta R, Benson AB, Newman SB, Omary RA, Abecassis M, Kulik L. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology. 2010 Jan;138(1):52-64. doi: 10.1053/j.gastro.2009.09.006. Epub 2009 Sep 18. PMID: 19766639.*
12. *Mazzaferro V, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, Maccauro M, Marchianò A, Bongini M, Lanocita R, Civelli E, Bombardieri E, Camerini T, Spreafico C. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. Hepatology. 2013 May;57(5):1826-37. doi: 10.1002/hep.26014. Epub 2013 Mar 22. PMID: 22911442.*
13. *Jia Z, Jiang G, Tian F, Zhu C, Qin X. A systematic review on the safety and effectiveness of yttrium-90 radioembolization for hepatocellular carcinoma with portal vein tumor thrombosis. Saudi J Gastroenterol. 2016 Sep-Oct;22(5):353-359. doi: 10.4103/1319-3767.191139. PMID: 27748320; PMCID: PMC5051218.*
14. *Lobo L, Yakoub D, Picado O, Ripat C, Pendola F, Sharma R, ElTawil R, Kwon D, Venkat S, Portelance L, Yechieli R. Unresectable Hepatocellular Carcinoma: Radioembolization Versus Chemoembolization: A Systematic Review and Meta-analysis. Cardiovasc Intervent Radiol. 2016 Nov;39(11):1580-1588. doi: 10.1007/s00270-016-1426-y. Epub 2016 Sep 1. Erratum in: Cardiovasc Intervent Radiol. 2017 May 25;: PMID: 27586657.*
15. *Lewandowski RJ, Kulik LM, Riaz A, Senthilnathan S, Mulcahy MF, Ryu RK, Ibrahim SM, Sato KT, Baker T, Miller FH, Omary R, Abecassis M, Salem R. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant. 2009 Aug;9(8):1920-8. doi: 10.1111/j.1600-6143.2009.02695.x. Epub 2009 Jun 22. PMID: 19552767.*
16. *Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, Mulcahy MF, Baker T, Abecassis M, Miller FH, Yaghmai V, Sato K, Desai K, Thornburg B, Benson AB, Rademaker A, Ganger D, Kulik L, Lewandowski RJ. Y90 Radioembolization Significantly Prolongs Time to Progression Compared*

With Chemoembolization in Patients With Hepatocellular Carcinoma. Gastroenterology. 2016 Dec;151(6):1155-1163.e2. doi: 10.1053/j.gastro.2016.08.029. Epub 2016 Aug 27. PMID: 27575820; PMCID: PMC5124387..

17. *Han K, Kim JH, Ko GY, Gwon DI, Sung KB. Treatment of hepatocellular carcinoma with portal venous tumor thrombosis: A comprehensive review. World J Gastroenterol. 2016 Jan 7;22(1):407-16. doi: 10.3748/wjg.v22.i1.407. PMID: 26755886; PMCID: PMC4698503.*
18. *Silva JP, Berger NG, Tsai S, Christians KK, Clarke CN, Mogal H, White S, Rilling W, Gamblin TC. Transarterial chemoembolization in hepatocellular carcinoma with portal vein tumor thrombosis: a systematic review and meta-analysis. HPB (Oxford). 2017 Aug;19(8):659-666. doi: 10.1016/j.hpb.2017.04.016. Epub 2017 May 25. PMID: 28552299.*
19. *Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, Sibert A, Bouattour M, Lebtahi R, Allaham W, Barraud H, Laurent V, Mathias E, Bronowicki JP, Tasu JP, Perdrisot R, Silvain C, Gerolami R, Mundler O, Seitz JF, Vidal V, Aubé C, Oberti F, Couturier O, Brenot-Rossi I, Raoul JL, Sarran A, Costentin C, Itti E, Luciani A, Adam R, Lewin M, Samuel D, Ronot M, Dinut A, Castera L, Chatellier G; SARAH Trial Group. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2017 Dec;18(12):1624-1636. doi: 10.1016/S1470-2045(17)30683-6. Epub 2017 Oct 26. PMID: 29107679.*
20. *Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, Choo SP, Cheow PC, Chotipanich C, Lim K, Lesmana LA, Manuaba TW, Yoong BK, Raj A, Law CS, Cua IHY, Lobo RR, Teh CSC, Kim YH, Jong YW, Han HS, Bae SH, Yoon HK, Lee RC, Hung CF, Peng CY, Liang PC, Bartlett A, Kok KYY, Thng CH, Low AS, Goh ASW, Tay KH, Lo RHG, Goh BKP, Ng DCE, Lekurwale G, Liew WM, Gebski V, Mak KSW, Soo KC; Asia-Pacific Hepatocellular Carcinoma Trials Group. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. J Clin Oncol. 2018 Jul 1;36(19):1913-1921. doi: 10.1200/JCO.2017.76.0892. Epub 2018 Mar 2. PMID: 29498924.*
21. *Bang A, Dawson LA. Radiotherapy for HCC: Ready for prime time? JHEP Rep. 2019 May 21;1(2):131-137. doi: 10.1016/j.jhepr.2019.05.004. PMID: 32039361; PMCID: PMC7001576.*
22. *Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745. PMID: 32402160.*
23. *Vouche M, Habib A, Ward TJ, Kim E, Kulik L, Ganger D, Mulcahy M, Baker T, Abecassis M, Sato KT, Caicedo JC, Fryer J, Hickey R, Hohlastos E, Lewandowski RJ, Salem R. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: multicenter radiology-pathology correlation and survival of radiation segmentectomy. Hepatology. 2014 Jul;60(1):192-201. doi: 10.1002/hep.27057. Epub 2014 May 27. PMID: 24691943.*
24. *Garin E, Lenoir L, Edeline J, Laffont S, Mesbah H, Porée P, Sulpice L, Boudjema K, Mesbah M, Guillygomarc'h A, Quehen E, Pracht M, Raoul JL, Clement B, Rolland Y, Boucher E. Boosted selective internal radiation therapy with 90Y-loaded glass microspheres (B-SIRT) for hepatocellular carcinoma patients: a new personalized promising concept. Eur J Nucl Med Mol Imaging. 2013 Jul;40(7):1057-68. doi: 10.1007/s00259-013-2395-x. Epub 2013 Apr 24. PMID: 23613103; PMCID: PMC3679421.*
25. *Hermann AL, Dieudonné A, Ronot M, Sanchez M, Pereira H, Chatellier G, Garin E, Castera L, Lebtahi R, Vilgrain V; SARAH Trial Group. Relationship of Tumor Radiation-absorbed Dose to Survival and Response in Hepatocellular Carcinoma Treated with Transarterial Radioembolization with 90Y in the SARAH Study. Radiology. 2020 Sep;296(3):673-684. doi: 10.1148/radiol.2020191606. Epub 2020 Jun 30. PMID: 32602828.*
26. *Viveiros P, Riaz A, Lewandowski RJ, Mahalingam D. Current State of Liver-Directed Therapies and Combinatory Approaches with Systemic Therapy in Hepatocellular Carcinoma (HCC). Cancers (Basel). 2019 Jul 31;11(8):1085. doi: 10.3390/cancers11081085. PMID: 31370248; PMCID: PMC6721343.*
27. *Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: A systematic review and pooled analysis. Liver Transpl. 2015 Sep;21(9):1142-52. doi: 10.1002/lt.24169. Erratum in: Liver Transpl. 2016 Jan;22(1):138. PMID: 25981135.*
28. *Gordon AC, Gabr A, Riaz A, Uddin OM, Abouchaleh N, Ali R, Kallini J, Salem R, Lewandowski RJ. Radioembolization Super Survivors: Extended Survival in Non-operative Hepatocellular Carcinoma. Cardiovasc Intervent Radiol. 2018 Oct;41(10):1557-1565. doi: 10.1007/s00270-018-2008-y. Epub 2018 Jun 12. PMID: 29948005; PMCID: PMC6128743.*

THE ONLY GENERIC OMEPRAZOLE 40 mg

available in South Africa [2]

40 mg

- Omeprazole 40 mg increases acid control and symptom relief *[3]
- In some duodenal ulcer patients refractory to other treatment regimens, 40 mg once daily may be effective [4]

OMEPRAZOLE BRAND WORLDWIDE[1] #1

* vs. 20 mg omeprazole

References: **1.** IQVIA, MIDAS Database, MAT September 2019 [IQVIA Copyright 2019. All rights reserved]. **2.** MIMS Volume 59 Number 10, November 2019. **3.** Thomson ABR. Are the Orally Administered Proton Pump Inhibitors Equivalent? A Comparison of Lanosprazole, Omeprazole, Pantoprazole, and Rabeprazole. *Curr Gastroenterol Reports* 2000;**2**:482-493. **4.** OMEZ Package Insert; Dr Reddy's Laboratories (Pty) Ltd. 2007. Ⓢ4 Omez 40. Each capsule contains omeprazole 40 mg. Reg. No. 34/11.4.3/0301. Dr. Reddy's Laboratories (Pty) Ltd. Reg. No. 2002/014163/07. Block B, 204 Rivonia Road, Morningside, Sandton 2057. Tel: +27 11 324 2100, www.drreddys.co.za. For full prescribing information refer to package insert approved by the medicines regulatory authority. ZA/02/2020-2022/OMEZ/005. 38086 03/20

Dr.Reddy's

Your partner in heartburn management

A case of Achalasia and Thymoma-associated Myasthenia Gravis

ME Seabi, D Mokgoko
Division of Gastroenterology, Department of Internal Medicine, University of the Witwatersrand and Charlotte Maxeke Johannesburg Academic Hospital. Johannesburg, South Africa.

Case report

We are presenting a clinical case of a 35 year old man that was referred to our outpatient department by his neurology team. He was known to them with myasthenia gravis diagnosed in 2017. The myasthenia gravis was paraneoplastic, associated with a thymoma (Figure 1) for which he had required a thymectomy in late 2017. He was on maintenance with an anticholinesterase inhibitor, and immunosuppression with prednisone and azathioprine.

He was referred to the gastroenterology clinic for investigation of progressive, persistent dysphagia, odynophagia and regurgitation associated with loss of weight. These symptoms persisted despite control of his neurological symptoms and treatment of oral (and presumed oropharyngeal) candidiasis. On clinical examination he was found to be underweight, with no other clinical signs of significance. His blood investigations were unremarkable. Initial investigation with upper gastrointestinal endoscopy revealed: a mildly dilated oesophagus with a tight oesophago-gastric junction, through which the endoscope was easily passed. No other structural abnormalities were found during endoscopy.

A contrast barium swallow demonstrated a dilated oesophagus with delayed emptying of contrast through the OGJ into the stomach (Figure 2).

A high resolution manometry (HRM) was planned in view of the dysphagia and significant loss of weight. The HRM revealed an elevated integrated relaxation pressure (IRP) of 21 mmHg and 100% failed swallows with 90% of swallows displaying panoesophageal pressurization (Figure 3).

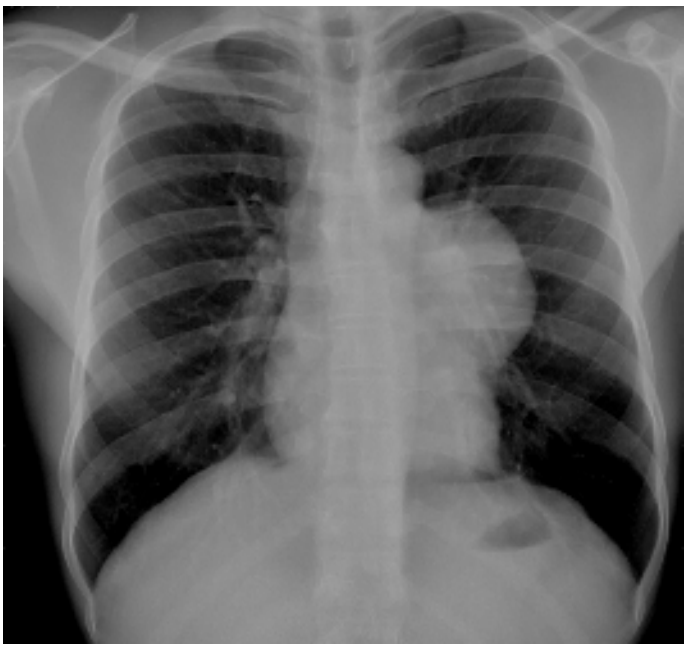
These findings, as per the Chicago classification, were in keeping with achalasia subtype II. The patient was counselled regarding his therapeutic options and opted for surgical management. A laparascopic Heller's myotomy was performed successfully, with good outcome and symptomatic relief. At subsequent follow up visits, the patient felt better and was tolerating a solid diet and managed to gain some weight. His Eckhardt score had improved from 12 at diagnosis to 6.

He was planned for a subsequent timed barium swallow and repeat manometry to assess him for intermittent dysphagia, unfortunately the patient demised recently due to COVID related complications.

Discussion

Achalasia is a clinical condition that is characterized by the inadequate relaxation of the lower oesophageal sphincter and aperistalsis of the distal oesophageal body. Typical symptoms include dysphagia, odynophagia, chest pain, regurgitation and weight loss. Although the pathology in primary achalasia being the destruction of inhibitory neurons of the myenteric plexus is well documented and accepted, the aetiology that results in this destruction remains unclear. A t-cell predominant inflammatory process in the lower oesophageal sphincter has been associated with this destruction of myenteric neurons.[1] This has resulted in the hypotheses that a combination of genetic predisposition, molecular mimicry triggered by viral infections and autoimmune inflammation are potential contributing factors to the aetiology of achalasia. In addition, serum autoantibodies directed against these myenteric neurons have been detected in patients with achalasia, however, the clinical significance of these antibodies is limited as they can be found in healthy controls.[1]

Figure 1. Chest radiograph showing a mediastinal mass



Achalasia and autoimmune disease

The potential autoimmune aetiology of achalasia is further supported by its association with other autoimmune disorders. A retrospective review conducted by Booy F.D et al of 193 patients with idiopathic achalasia showed that they were overall 3.6 times

Correspondence
D Mokgoko
email: d.mokgoko@gmail.com

Figure 2. Barium contrasted swallow: showing a dilated proximal oesophagus and typical bird's beaking of contrast at the OGJ

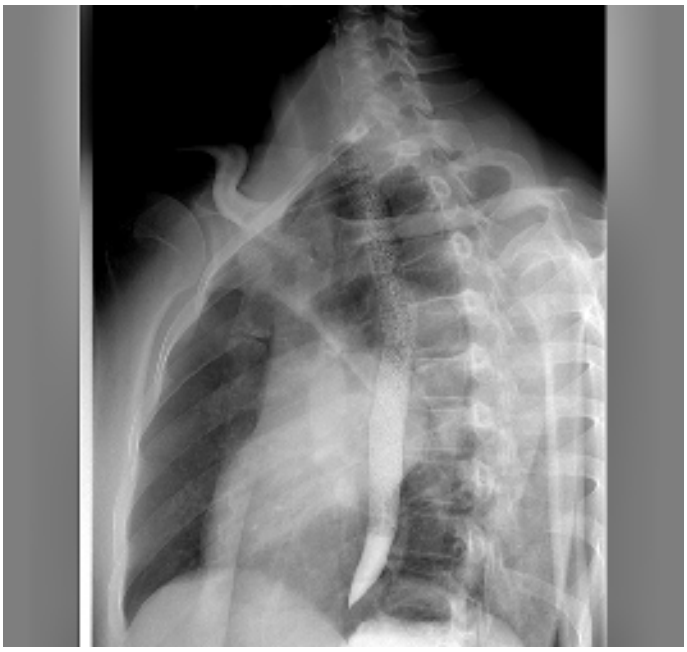
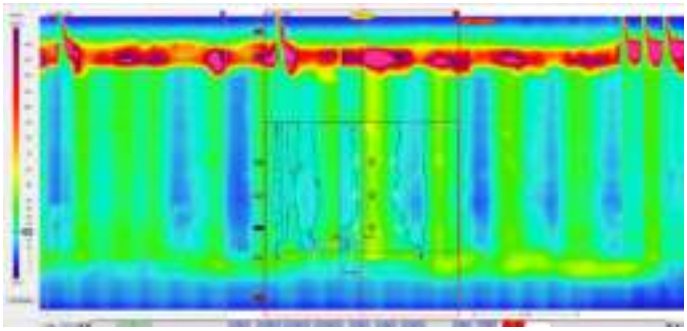


Figure 3. HRM demonstrating failure of LES relaxation (open arrow) and panoesophageal pressurization (solid arrows)



more likely than the general population, to be diagnosed with a co-existing autoimmune disease. The autoimmune disorders that were most associated with achalasia included systemic lupus erythematosus (SLE), uveitis, Sjogrën's syndrome, type 1 diabetes mellitus and autoimmune thyroiditis.[1]

Achalasia and myasthenia gravis

Myasthenia gravis (MG) is an autoimmune neuromuscular disorder characterized by autoantibodies against acetylcholine receptors on the post synaptic neuromuscular junction. At least 10-15% of patients with myasthenia gravis will have a thymoma.[2] This tumour compromises the normal positive and negative selection of t-lymphocytes, and predisposes these patients to autoimmune disorders. Thymoma-associated myasthenia gravis has therefore been shown to overlap with other t-cell mediated autoimmune disorders such as thyroid disease, autoimmune hepatitis, and certain skin conditions.[3] These paraneoplastic immune disorders tend to respond to immunosuppression and resection of the thymic tumour, although this clinical improvement may be delayed by months to years.[3]

Achalasia and thymoma-associated myasthenia gravis

The symptom of dysphagia in a patient with a thymoma and myasthenia gravis may be considered to be due to extrinsic compression of the oesophagus from mass effect of the mediastinal tumour or from bulbar symptoms related to the myasthenia gravis. However, in the absence of bulbar symptoms and considering the location of the thymoma in the anterior mediastinum in relation to that of the oesophagus in the posterior mediastinum, the persistent of dysphagia prompts further investigation.

There are a few case reports in the literature describing the presence of achalasia in patients with thymomas. Demos et al[4] reported on a case of thymoma and megaoesophagus in a 46 year old patient presenting with dysphagia and chest pain. Endoscopy confirmed a massively dilated oesophagus with retained food residue and a tight lower oesophageal sphincter that couldn't be passed. This patient responded well to treatment with a thymectomy and an open myotomy.

Approximately 30 years later, Kaminski H reported on case of new onset dysphagia in a 75 year old female patient with myasthenia gravis, and recurrence of a previously resected thymoma.[5] Oesophageal manometry confirmed failure of relaxation at the lower oesophageal sphincter associated with spasm of the oesophageal body. A successful Heller's myotomy was performed in this patient following failure of medical and endoscopic therapies.

In addition to achalasia, colonic pseudo-obstruction has been reported in seropositive thymoma-associated myasthenic patients, where anti-acetylcholine receptor antibodies may affect the autonomic ganglia of the colonic wall.[1,2] Paraneoplastic demyelinating neuropathies resulting in gastrointestinal dysmotility have also been reported in patients with thymomas.[5] The above indicate that there may be a link between thymomas and gastrointestinal motility disorders but due to the few cases, this may be difficult to prove.

Conclusion

In summary, the association between achalasia and thymoma associated myasthenia gravis is rare and limited to a few case reports in the medical literature. To the authors' knowledge, this is the first case of this clinical entity reported in the South African setting. Our patient had pre-existing paraneoplastic myasthenia gravis associated with a thymoma which had required a thymectomy. He developed persistent dysphagia associated with significant weight loss approximately two years following his thymectomy and in the absence of significant neurologic deterioration which prompted further investigation. The diagnosis of achalasia was made based on high resolution manometry and he was successfully treated with a Heller myotomy. This case highlights the possible autoimmune pathogenesis of achalasia and its occurrence in patients with thymoma which may represent a paraneoplastic immune disorder rather than the coincidence of two disease processes in one patient. It is therefore reasonable for clinicians to consider and investigate patients with thymomas, in whom dysphagia is a major symptom, for achalasia.

References

1. *Booy JD, Takata J, Tomlinson G, Urbach DR. The prevalence of autoimmune disease in patients with esophageal achalasia. Dis Esophagus. 2012;25(3):209–13.*
2. *Tormoehlen LM, Pascuzzi RM. Thymoma, Myasthenia Gravis, and Other Paraneoplastic Syndromes. Hematol Oncol Clin North Am. 2008;22(3):509–26.*
3. *Hung C'T, Tsai TF, Chen JS, Hsieh MS. Thymoma-associated multiorgan autoimmunity. BMJ Case Rep. 2019;12(8):2–5.*
4. *Demos NJ, Yadusky RJ, Timmes JJ, Poulos PP. Thymoma associated with megaesophagus. A case report. J Thorac Cardiovasc Surg [Internet]. 1966;51(5):708–13. Available from: http://dx.doi.org/10.1016/S0022-5223(19)43299-6*
5. *Kaminski HJ. Achalasia and myasthenia gravis in a patient with thymoma. Vol. 52, Neurology. 1999. p. 425–6.*

HATS OFF to PICOLAX®

The patient-friendly ORANGE CHOICE

An effective, well-tolerated and Easy-to-Take Bowel Cleanser[1-4]

PICOLAX®

sodium picosulphate + magnesium oxide + citric acid

References: 1. Hookey LC, Vanner SJ. Pico-salax plus two-day bisacodyl is superior to pico-salax alone or oral sodium phosphate for colon cleansing before colonoscopy. *Am J Gastroenterol* 2009;104:703-709. **2.** Worthington J, Thyssen M, Chapman G, *et al.* A randomised controlled trial of a new 2 litre polyethylene glycol solution versus sodium picosulphate + magnesium citrate solution for bowel cleansing prior to colonoscopy. *Curr Med Res Opin* 2008; 24:(2)481-488. **3.** Regev A, Fraser G, Delpre G, *et al.* Comparison of two bowel preparations for colonoscopy: sodium picosulphate with magnesium citrate versus sulphate-free polyethylene glycol lavage solution. *Am J Gastroenterol* 1998;93:(9)1478-1482. **4.** Parente F, Marino B, Crosta C. Bowel preparation before colonoscopy in the era of mass screening for colo-rectal cancer: A practical approach. *Dig Liver Dis* 2009;41:87-95.

FERRING PHARMACEUTICALS

S3 **PICOLAX® Powder for oral solution.** Each sachet contains the following active ingredients: Sodium picosulphate 10,0 mg, Magnesium oxide, light 3,5 g and Citric acid, anhydrous 12,0 g. Reg. No A39/11.5/0058.

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
Ferring (Pty.) Ltd. Route 21 Corporate Park, 6 Regency Drive, Irene Ext 30, Pretoria, South Africa. Tel: +27 12 345 6358. Fax: +27 12 345 1156. www.ferring.co.za.
 2020/063 Date of preparation: September 2020.

Oesophageal stricture in a patient with Epidermolysis Bullosa Acquisita (EBA) requiring multiple dilatations

CL Gounden, VG Naidoo
Department of Gastroenterology, Inkosi Albert Luthuli Central Hospital, UKZN, Durban KwaZulu-Natal, South Africa

ABSTRACT
Background: Epidermolysis bullosa acquisita (EBA) is a rare type of autoimmune bullous skin disease causing inflammation of the skin and mucous membranes. Dysphagia in these patients is usually due to repetitive food bolus trauma of the fragile oesophagus leading to a stricture.
Case presentation: Herein we describe a case of a benign oesophageal stricture in a man with EBA requiring multiple oesophageal dilatations to treat his dysphagia.
Conclusion: To the best of our knowledge, EBA with an oesophageal stricture has not been previously reported in South Africa. This case highlights effective management of this complex condition.

Keywords: Epidermolysis bullosa acquisita, dysphagia, oesophageal stricture, dilatation

Introduction

Epidermolysis bullosa acquisita (EBA) is an autoimmune bullous disease characterised by chronic inflammation, blistering and scarring of the skin and mucous membranes. It is associated with autoantibodies to collagen type VII. Mucous membranes with squamous epithelium in the mouth, pharynx, oesophagus, epiglottis, conjunctiva, genitalia, anus, and respiratory tract may be involved. It is a rare disease with an incidence of <0.5 per million.[1]

EBA was found to be overrepresented in patients of African descent and linked with HLA-DRB1*15:03 (54% Black vs 3% White patients). High EBA frequencies have also been reported in African American patients significantly associated with HLA-DR2. This evidence has resulted in a recommendation that EBA should be suspected for every autoimmune bullous disease in black patients.[2]

We report a case of EBA resulting in a long-standing oesophageal stricture leading to severe malnutrition and the management thereof. Consent was obtained from the patient to publish the case.

Case report

A 37-year-old African male was diagnosed with EBA of cicatrizing type. Clinical features and skin biopsy supported the diagnosis.

Onset of blistering skin lesions over hands, feet, chest and face began in 2015. He had accompanying lesion on both eyes and loss of vision. These lesions began over areas of friction and minor trauma. An ulcer over the tongue developed shortly after this. Dysphagia to both solids and liquids was reported simultaneous to skin lesions. He modified his diet to soft food consumption. Due to ongoing weight loss and worsening dysphagia he was referred to gastroenterology in 2019.

He did not have other medical illnesses, previous surgery nor family history of dermatological disease. He did not smoke cigarettes and consumed alcohol occasionally.

The patient was emaciated with a body mass index of 16kg/m^2 There was no pallor, jaundice, lymphadenopathy nor oedema.

Skin lesions consistent with EBA were erosions, scarring, erythematous plaques and papules on soles and palms (Fig 1A, B), and multiple atrophic, cicatrizing lesions on his neck (fig 2 a) and chest (fig 2 b). He had an oral ulcer (fig 3). His hand had a small bullous lesion and milia cysts over the metacarpophalangeal joints. (Fig 4).

Eye examination showed bilateral upper lids adherent to cornea, and right eye symblepheron on lower lid with opaque cornea and partial loss vision. The left eye had an inferior corneal ulcer and complete loss vision (Fig 5).

Endoscopic findings included marked ulceration of mucosa to mid oesophagus and a stricture at 30cm (Fig 6). The endoscope was not able to traverse the stricture. Biopsy of the mucosal ulcerations revealed acute on chronic inflammation and granulation tissue with no pathogens or neoplastic tissue.

Barium swallow (Fig. 7) showed a short segment stricture at T5 level with pre-stenotic dilatation. Contrast traversed the stricture with no significant hold up.

Correspondence
CL Gounden
email: goundenc@ukzn.ac.za

The stricture was managed with sequential gentle bougie (Savary-Gilliard) dilatation every 2 weeks, for 6 months starting in February 2019. Bouginage over a guidewire with conscious sedation and under fluoroscopic control was used for each session. Maximum dilatation with a 42F dilator was achieved. No perforations, mucosal tears, peri-procedure bleeding, nor infection occurred. Successful dilatation defined by improvement in dysphagia score from 4 (complete dysphagia to solids and liquids) to 1 (some difficulty with solids) was achieved (Table I). Ulceration of oesophageal mucosa persisted (Fig 8). At follow up the patient still required repeated sessions after 6 months

Table 1. Table I: Dysphagia score[6]

Grade 0	ability to eat a normal diet
Grade 1	ability to swallow some solid food was retained
Grade 2	soft diet was possible
Grade 3	able to swallow only liquids
Grade 4	complete dysphagia

Figure 1a

Figure 1b

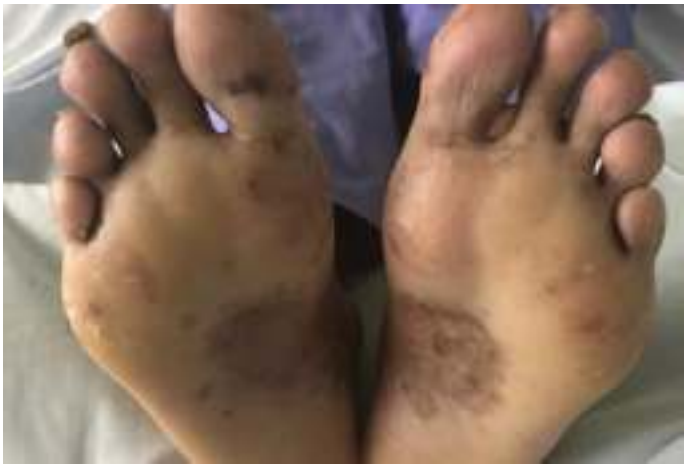


Figure 2a

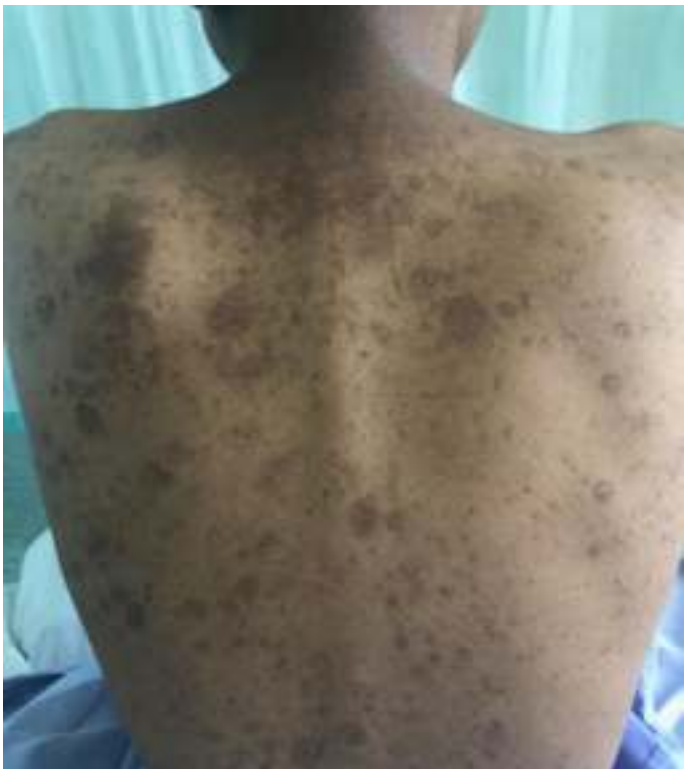


Figure 2b

Figure 3

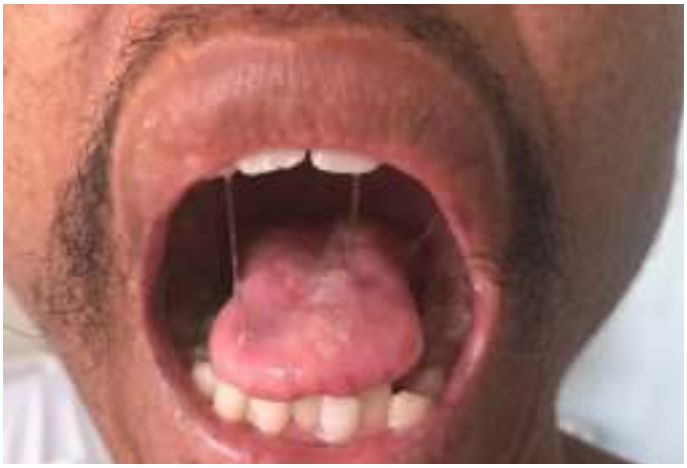


Figure 4

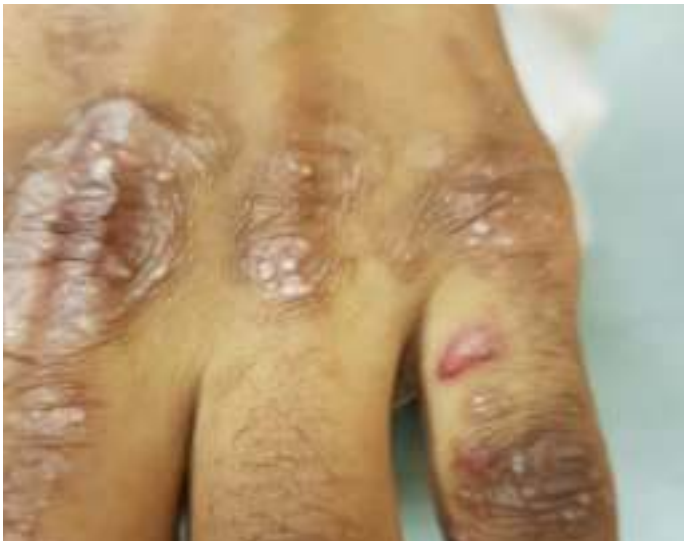


Figure 5

Figure 6

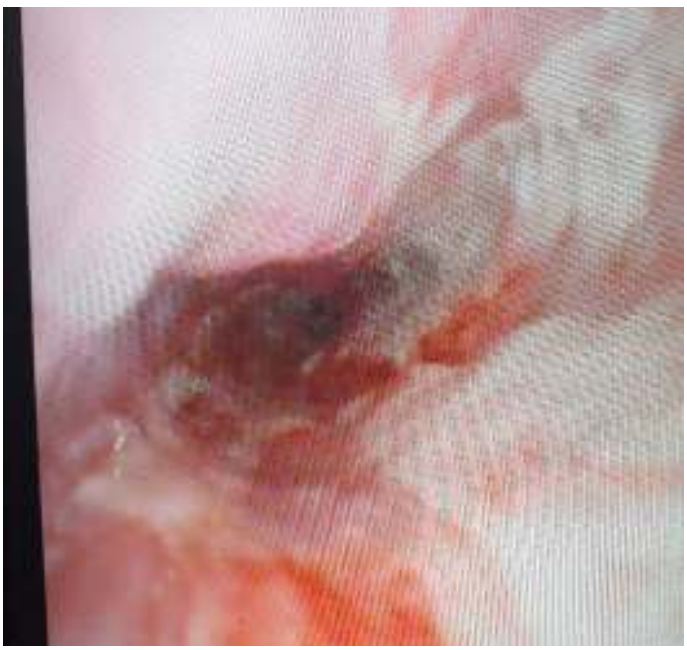


Figure 7

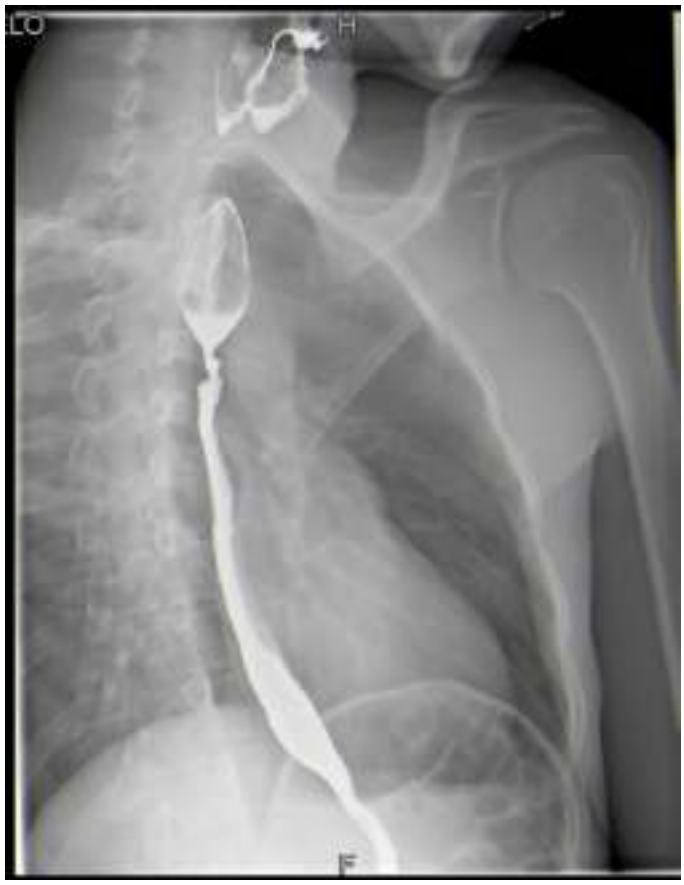
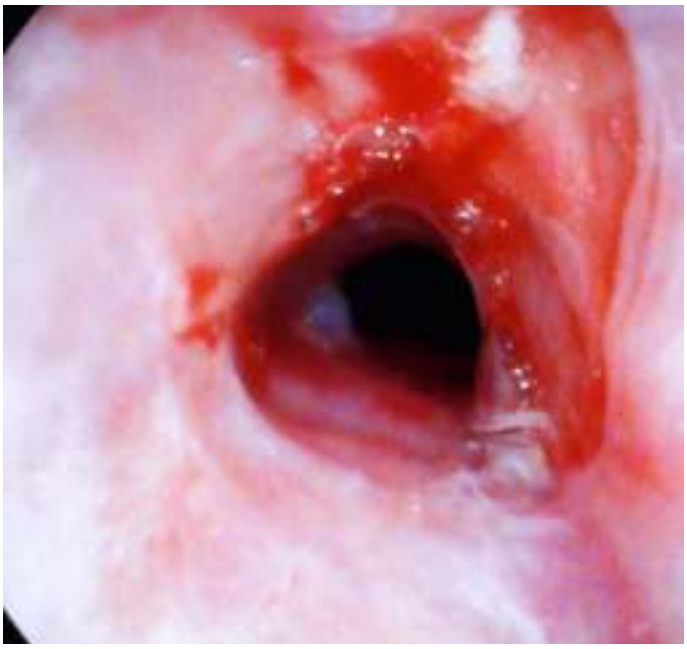


Figure 8



but less frequently. There was a dramatic improvement in his nutritional status. Of interest, he had asymptomatic COVID-19 infection in September 2020 which was discovered on routine testing prior to oesophageal dilatation. The procedure was postponed and the patient only required self-isolation.

Discussion

The pathophysiologic mechanism of oesophageal involvement

in EBA is based on mechanical trauma to the fragile mucosa by food and/or hot drinks resulting in bulla formation, ulceration, and oedema. Consequently, healing results in formation of a fibrotic web causing typical EBA oesophageal strictures.[3]

A French series of 39 patients reported a low frequency of oesophageal involvement in EBA at 6%. The involvement is higher for nasal mucosa (11%) and the conjunctiva (25%).[4] Conjunctival involvement in this patient has led to loss of vision. Most oesophageal lesions present as linear erosions or stenosis located mainly in the upper oesophagus as these areas are narrower and more susceptible to trauma.[5] In contrast to previous reports, the patient described had a mid-oesophageal stricture and no stricture in the upper oesophagus. Given the natural history of the disease, we anticipate that he may develop additional upper oesophageal strictures.

Treatment of EBA is challenging as there are no randomized control trials due to its rarity. Existing therapies for skin lesions include systemic corticosteroids, immunosuppressants, immunoglobulins, rituximab, plasmapheresis and extracorporeal photochemotherapy.[1]

Management of EB oesophageal strictures includes conservative medical therapy (most commonly with proton pump inhibitors). However, this treatment alone has poor results especially in tight web like strictures.[6] Additional therapy includes surgical repair, endoscopic pneumatic balloon dilation and fluoroscopically guided balloon dilation.[5] Even though balloon dilators are recommended there are no randomised controlled trials illustrating its superiority or safety over bougienage. Surgical colonic interposition in this condition was previously shown to have high mortality and morbidity rates.[7] In most severe cases, with severe malnutrition placement of a gastrostomy tube has been used.[9]

Indications for dilatation of the stricture in the patient described in this report included the presence of a short, tight stricture, grade 4 dysphagia, poor nutritional status of the patient (underweight) and poor response to PPI. The stricture was in the mid oesophagus and this was previously shown be an area of lower risk of perforation during dilatation.[5]

Owing to availability of equipment, mid-oesophageal location of the stricture and familiarity with its use we felt that it was safe to dilate the stricture with bougienage. This was done cautiously and deliberate avoidance of larger gauges due to the friability of the mucosa. Successful dilatation and clinical improvement in dysphagia from score from Grade 4 to 1 was achieved without complications.

Similar success with dilatation of such strictures was described in a case series of 19 patients with EB.[6] Here oesophageal strictures were mostly located in the upper oesophagus and managed with fluoroscopically guided balloon dilatation instead. Balloon dilatation has been shown to reduce risk of oesophageal perforation in upper oesophageal strictures.[8] There was a high rate of clinical improvement in mean pre -procedural dysphagia score from 2 to post procedural score 1 in 96.7% of the patients. Re-intervention rate due to clinical recurrence was high at 94.7%. A dilatation free interval longer than 3 years was low at 10.5% (2 of 19 patients).[6] Therefore, ongoing monitoring for dysphagia, weight loss and recurrence of significant stenosis is recommended. Repeat endoscopy and dilatation as soon as dysphagia scores increases above 1 is advised.

Despite advances in medicine, a targeted therapy for EBA has not been established yet. As described in other case reports his skin lesions are being treated with Dapsone 50mg daily.[10] The exact mechanism of action of dapsone in autoimmune bullous diseases is not fully understood. It may be related to inhibition of neutrophils' adherence to autoantibodies as well as interleukin 8 release.[10] The most common cause of death in patients with EB is oesophageal squamous cell carcinoma and ongoing surveillance is warranted.[6] To the best of our knowledge, this is one of the few cases reported of an oesophageal stricture caused by EBA requiring repeated dilatation.

References

1. *Koga H, Prost-Squarcioni C, Iwata H, Jonkman MF, Ludwig RJ and Bieber K (2019) Epidermolysis Bullosa Acquisita: The 2019 Update. Front. Med. 5:362.*
2. *Zumelzu C, Le-Roux-Villet C, Loiseau P, et al. Black patients of African Descent and HLA-DRB1*15:03 frequency overrepresented in Epidermolysis Bullosa Acquisita. 2011 Journal of Investigational Dermatology; 131:2386-2393.*
3. *Kern IB, Eisenberg M, Willis S. Management of oesophageal stenosis in epidermolysis bullosa dystrophica. 1989 Arch Dis Child; 64:551–556.*
4. *Le Roux-Villet C, Prost-Squarcioni C. Epidermolysis bullosa acquisita: clinical, histological and immunologicalanalysis of 39 cases. Ann Dermatol Venereol. 2002; 129(Suppl. 1): S71–2.*
5. *Marsden RA, Gowar FJ, MacDonald AF, Main RA. Epidermolysis bullosa of the oesophagus with oesophageal web formation. 1974 Thorax; 29:287–295.*
6. *Spiliopoulos S, Sabharwal T, Krokidis M, Gkoutzios P, Mellerio J, Dourado R Adam A. Fluoroscopically Guided Dilation of Esophageal Strictures in Patients with Dystrophic Epidermolysis Bullosa: Long-Term Results. 2012 AJR; 199:208–212.*
7. *Inal M, Soyupak S, Akgül E, Aksungur EH, Akinoglu A. Fluoroscopically guided endoluminal balloon dilatation of esophageal stricture due to epidermolysis bullosa dystrophica. 2002 Dysphagia; 17:242–245.*
8. *Gottschalk A, Venherm S, Vowinkel T, Tübergen D, Frosch M, Hahnenkamp K. Anesthesia for balloon dilatation of esophageal strictures in children with epidermolysis bullosa dystrophica: from intubation to sedation. 2010 Curr Opin Anaesthesiol; 23:518–522.*
9. *Michalak A, Cichoż-Lach, Prozorow-Król B, Buk L, Monika Dzida et al. A rare case of skin blistering and esophageal stenosis in the course of epidermolysis bullosa - case report and literature review. 2018 BMC Gastroenterology 18:47.*
10. *Russo I, Ferrazzi A, Zanetti I, et al. BMJ Case Rep Published online: [please include Day Month Year] doi:10.1136/bcr-2015210210*

Makes colon cleansing plain sailing...

Sodium Picosulphate Oral Powder for Solution.

For bowel cleansing in conjunction with:

- Intravenous Pyelograms (IVP)
- Bowel Evacuation
- Abdominal X-Ray Examinations
- Surgery
- Colonoscopy

S3 Each sachet contains: Sodium Picosulphate 10mg, Magnesium Oxide Ph Eur 3.5g, Citric Acid Ph Eur 12.0g, Aspartame 36mg. Reg.No A38/11.5/0389.

Gastrocutaneous Fistula; An atypical Presentation

AHZ Lee[1], MH Wellmann[2], F Kimmie[3]
[1] MBChB, Department General Surgery, Robert Mangaliso Sobukwe Hospital, Kimberley, South Africa
[2] MBChB, Department General Surgery, Robert Mangaliso Sobukwe Hospital, Kimberley, South Africa
[3] Specialist Consultant Surgery, MBChB,FCS Department General Surgery, Robert Mangaliso Sobukwe Hospital, Kimberley, South Africa

ABSTRACT
Gastrocutaneous fistula (GCF) are rare but serious post-operative complication, usually as a result of previous surgery to the alimentary tract.[1,2] The most well described conditions etiologically related to GCFs include breakdown of gastroenteric anastomosis, disruption of gastric suture lines following bariatric surgery, chronic inflammatory disease, failure of gastrostomy tract healing, and others. We report a 47-year-old female who developed a Gastrocutaneous fistula secondary to gastric inflammation and ulceration.

Introduction

A Gastrocutaneous fistula (GCF) represents a fistula connecting the stomach with the skin.

Gastrocutaneous fistula have been well described as post-operative complications following surgery to the alimentary tract as well as a host of inflammatory conditions.[1,3,4] (See table 1 for a list of etiological conditions.)

Table 1. Aetiological conditions resulting in GCF

Surgical (traumatic)	Non-Surgical (Inflammatory)
Iatrogenic gastric injury following splenectomy and other procedures	Carcinoma
Breakdown of Gastroenteric anastomosis	Chronic inflammatory disease
Disruption of Gastric suture line following bariatric or conventional Surgery	Pancreatitis or Pancreatic Abscess
Failure of Gastrostomy tract healing	Radiation

Isolated primary spontaneous Gastrocutaneous fistulae are a seemingly rare occurrence, and literature in this respect is lacking. In patients with chronic inflammatory disease a GCF can be precipitated by inflammatory erosion of the gastric wall, creation of an abscess and finally fistula formation.[1,3,4]

Presenting complaints and complications vary according to underlying aetiology. Post-surgical complication such as abdominal pain, painful bowel obstruction and fever have been described.

Diagnosis is clinical, but largely dependent on gastroenterography.[1,3,4]

Gastric fistula cases may be treated conservatively, including the administration of drugs such as somatostatin, antibiotics and supportive care with total parental nutrition. Certain cases may be treated using the injection of fibrin sealant. However, only 6% of all cases close spontaneously, and surgery should be performed in cases that have persisted for 120 days following diagnosis.[1,2,5,6,7,8]

Generally, patient outcome is good in patients with gastric fistula due to the administration of timely therapy. However, among patients with normal body weight who underwent recent gastric surgery the mortality rate is about 35%.[7]

Correspondence
AHZ Lee
email: adelaidelee@ymail.com

Case

49-year-old female with no known co-morbidities presented to the surgical casualty at Robert Mangaliso Sobukwe Hospital in Kimberley, South Africa with a 2-day history of food contents draining from an open wound 2cm superior to the umbilicus. This was preceded by a 1-week history of a painless, pustular lesion that spontaneously ruptured. No associated abdominal pain, reflux or change in bowel habits was noted. Background history revealed a 3-month loss of appetite, with +- 8kg weight loss. A 22-pack year smoking history was noted, however; alcohol, chronic medication, non-steroidal anti-inflammatory and alternative medication use was denied. The patient reports 5 previous uncomplicated normal vaginal deliveries with an open post-partum tubal ligation in 2008.

On examination, the patient appeared chronically ill with generalized wasting, with no other peripheral features suggestive of underlying malignancy. Her abdomen was soft, non-tender and not distended, with an open wound in the midline epigastric region 2cm superior to the umbilicus. The wound had exposed, hyperemic mucosa and was actively discharging what appeared to be partially digested food particles and gastric fluid. Also noted was the pfannenstiel incision from her previous bilateral tubal ligation.

Blood chemistry analysis demonstrated renal functions and electrolytes to be within normal parameters. The estimated Glomerular filtration rate greater than 60, Albumin of 18g/L and haemoglobin of 8.7g/dL respectively. Chest X-ray was unremarkable.

An oral and Intravenous Contrast Enhanced Computed Tomography scan was done to confirm diagnosis and to aid surgical planning. Contrast was seen extending from the stomach into the anterior abdominal wall. Subcutaneous extension of contrast was also seen. No contrast was seen extending intraperitoneally. Thus, confirming a Gastrocutaneous fistula with subcutaneous extension. (See figure 1 and 2)

A failed conservative approach with total parenteral nutrition together with patient preference necessitated a surgical approach.

Elective laparotomy after pre-operative nutritional status

Figure 1. Saggital view Contrasted CT showing contrast extravasation. Images not to scale

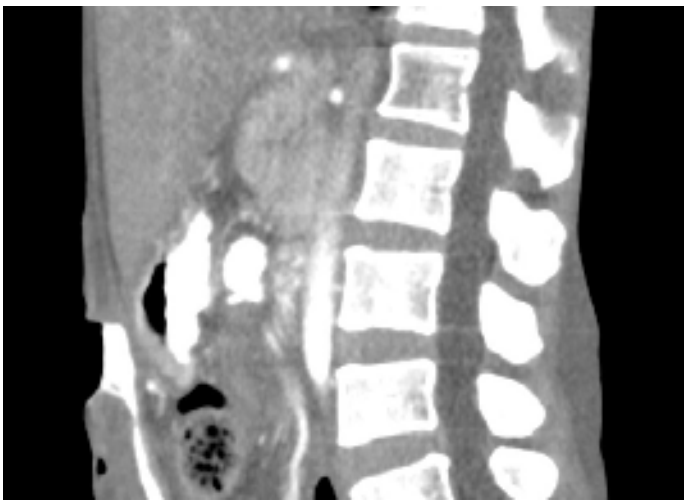
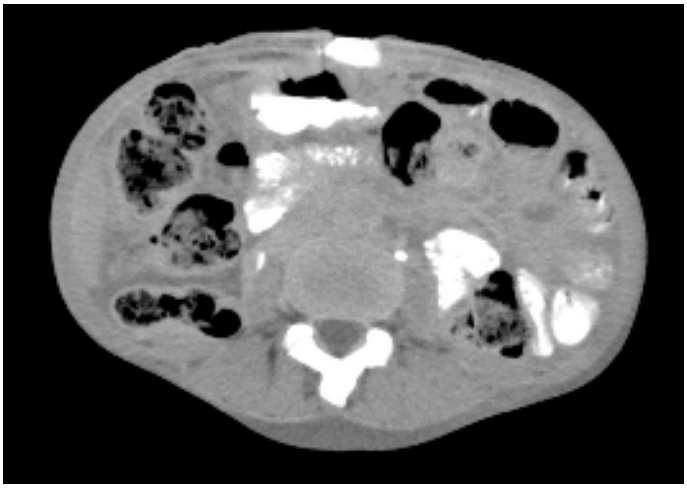


Figure 2. Axial view Contrasted CT. Images not to scale



optimization was undertaken, Intraoperatively the fistula was noted to extend from the greater curvature of the stomach, proximal to the antrum to the skin. The fistula and the tract were excised. The defect in the stomach was primarily closed with an absorbable monofilament suture. Extensive adhesions between the stomach, liver and anterior abdominal wall, as well as pelvic adhesions of the small bowel to the uterus were noted.

Histopathology reported both skin and gastric tissue in the spcimens, and concluded gastric inflammation and ulceration to be the underlying cause of this fistulous tract. No organisms, dysplasia, malignancy or H. pylori were not demonstrated. (See figure 3 for Microscopy.)

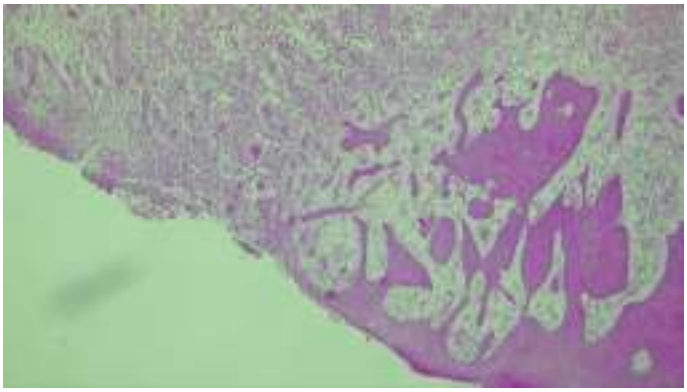
Post-operative management was unremarkable with the patient tolerating a full diet upon discharge wit Oral Proton pump inhibitors. At 1 month follow up, no issues were raised by the patient, with her wound having healed completely. Further endoscopic follow up was prescribed.

Written informed consent was obtained from the patient for publication of this case study.

Discussion

GCF have mostly been described as post-surgical complications and infrequently as a result of a Gastric inflammatory condition. Chronic untreated gastric inflammation can have the ultimately sinister complication of gastric ulceration and fistula formation.

Figure 3. Microscopy slide demonstrating subacute dermatitis and ulceration secondary to gastric acid irritation



Presenting complaints and symptoms are not well described, and in this case conflicting. Furthermore, incidence and prevalence rates have yet to be defined.

Conversely to the described case, one other study reported a patient with a GCF secondary to gastric ulceration. A 1-year history of abdominal pain was noted, conversely to described case in which the patient was relatively asymptomatic, manifesting only weight loss and decreased appetite.[9]

Insidious presentations can be mistaken for non-benign etiology, risking an investigation dilemma.

Clinical diagnosis of GCF should be complemented by gastroenterography, which also serves to aid surgical planning. Treatment based on determining the underlying aetiology is often dependent on histopathological investigation.

Conclusion

We present a case of GCF secondary to gastric inflammation and ulceration.

Disclosure Statement

No potential conflict of interest was reported by the author(s)

References

1. *Theodossis S. Papavramidis, Konstantinos Mantzoukis, Nick Michalopoulos. Confronting gastrocutaneous fistulas Ann Gastroenterol. 2011; 24(1): 16–19.*
2. *Foster CE, III, Lefor AT. General management of gastrointestinal fistulas. Recognition, stabilization and correction of fluid and electrolyte imbalances. Surg Clin North Am. 1996;76:1019–1033. doi: 10.1016/S0039-6109(05)70496-5.*
3. *Graves HA, Nelson A, Byrd B. Gastrocutaneous fistula as a postoperative complication. Ann Surg. 1970;171:656–660.*
4. *Pearlstein C, Jones CE, Polk HC. Gastrocutaneous fistula: Etiology and treatment. Ann Surg. 1978;187:223–226.*
5. *Dudrick SJ, Maharaj AR, McKelvey AA. Artificial nutritional support in patients with gastrointestinal fistulas. World J Surg. 1999;23:570–576.*
6. *Kowalski C, Kastuar S, Mehta V, Brolin RE. Endoscopic injection of fibrin sealant in repair of gastrojejunostomy leak after laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2007;3:438–442. doi: 10.1016/j.soard.2007.02.012.*
7. *Meguid MM, Campos ACL. Preface: surgical management of gastrointestinal fistulas. Surg Clin North Am. 1996;76:1035–1080.*
8. *Rose D, Yarborough MF, Canizaro PC, Lowry SF. One hundred and fourteen fistulas of the gastrointestinal tract treated with total parenteral nutrition. Surg Gynecol Obstet. 1986;163:345– 350.*
9. *Kaushik S, Madhu BS, Kumar SH. Spontaneous gastrocutaneous fistula. Arch Int Surg 2014;4:60-2.*

SANDOZ A Novartis Division

THE RIGHT TO CHOOSE

S4 **NEXMEZOL™**
Esomeprazole 20/40 mg

S4 **Sandoz Omeprazole 20**
Omeprazole

S4 **TOPRAFLUX TABS**
Pantoprazole

S4 **RABEMED™**
Rabeprazole

S4 **NEXMEZOL™** 20 tablets; **NEXMEZOL™** 40 tablets; Reg. No. 44/11.4.3/0335; 44/11.4.3/0336. **COMPOSITION:** Nexmezol™ 20 / Nexmezol™ 40 contains: 20 mg / 40 mg esomeprazole respectively. **PHARMACOLOGICAL CLASSIFICATION:** A 11.4.3 Medicines acting on gastro-intestinal tract. Other.
S4 **SANDOZ OMEPRAZOLE 20** (capsules). Reg. No. 36/11.4.3/0430. **COMPOSITION:** Each Sandoz Omeprazole 20 capsule contains 20 mg omeprazole in a gastro-resistant formulation. **PHARMACOLOGICAL CLASSIFICATION:** A 11.4.3 Medicines acting on the gastrointestinal tract – Other.
S4 TOPRAFLUX™ 20; TOPRAFLUX ™ 40 enteric coated tablets. Reg. No.: 43/11.4.3/0483; 43/11.4.3/0484. **COMPOSITION:** Contains pantoprazole sodium sesquihydrate equivalent to 20 mg / 40 mg pantoprazole, respectively. **PHARMACOLOGICAL CLASSIFICATION:** A11.4.3 Medicines acting on the gastrointestinal tract. S4 **RABEMED™** 10 (tablets); RABEMED™ 20 (tablets). Reg. No: 44/11.4.3/0597; 44/11.4.3/0598. **COMPOSITION:** Each gastro-resistant tablet contains rabeprazole sodium 10 mg; 20 mg respectively. **PHARMACOLOGICAL CLASSIFICATION:** A.11.4.3 Medicines acting on gastro-intestinal tract. **For full prescribing information refer to the package inserts approved by the medicines regulatory authority.**

Sandoz SA (Pty) Ltd. Reg. No. 1990/001979/07. 72 Steel Road, Spartan, Kempton Park, 1619. Tel: +27 (0)11 929 9000, Fax: +27 (0)11 394 7895. Customer Care Line: +27 (0)861 726 225/ +27 (0)861 SANCAL. www.sandoz.com SAN.GIT.2019.01.02

Best of G-ECHO 2020

The first G-ECHO session was held on Thursday 3 September 2020 with an invited lecture from Peter Malfertheiner. Since then we have had weekly interactive webinars, starting with a lecture on a key topic, followed by case discussions. Our online audience has grown each week and the sub - specialties rotate each week and include GI Endoscopy, IBD, Patient Blood Management (PBM) with Pathology the most recent addition. In 2021 a multi-disciplinary program on the screening and treatment of Liver cancer in sub Saharan Africa is planned.

Thursday
3 September 2020:
''Key notes on H.pylori''

Prof Peter Malfertheiner

Thursday
10 September 2020:
''Colonoscopy and CRC in sub Saharan Africa''

Prof Sandie Thomson

Thursday
17 September 2020:
''Conventional therapy in the management of IBD''

Prof Gill Watermeyer

Thursday
8 October 2020:
Patient Blood Management (replacing blood with iron)
'' Iron physiology & the diagnosis of iron deficiency anaemia''
Prof Vernon Louw

''Investigating iron deficiency anaemia – a gastroenterologist's approach''

Prof Mashiko Setshedi

Thursday
15 October 2020:
''Endoscopic interventions for refractory benign esophageal strictures: what's new''

Dr Kulwinder Dua, Medical College of Wisconsin, Milwaukee, USA

Thursday
22 October 2020:
IBD: ''Best use of anti-TNF's in 2020'' Prof Gill Watermeyer

Thursday
5 November 2020:
''Practical Endotherapy for non variceal bleeding''
Dr Galya Chinnery

Thursday
12 November 2020:
Hepatology:
''Clinico-pathological case presentations''

Prof Martin Hale

Thursday
19 November 2020:

''The medical management of severe acute Ulcerative Colitis''
Dr R Atreya, Friedrich-Alexander-University of Erlangen-Nürnberg, Germany
''The surgical management of severe acute colitis''
Dr W Bemelman, Academic Medical Centre, The Netherlands

Thursday
3 December 2020:
''Patient Blood Management, replacing blood with iron: cases'' Prof Vernon Louw

Thursday
10 December 2020 :
Endoscopy

All of these webinars are recorded and are available on www.gastrofoundation.co.za under Events

Abbott

See what **Creon®** can bring to the table

- **Smart digestion** in PEI[1,2,3]
- The only PERT with **>5 million patient treatment years** of experience[4]
- **Effective substitution** of pancreatic enzymes if they are deficient[2]

Creon® is indicated as a supplement for pancreatic exocrine insufficiency which may be caused by chronic pancreatitis, cystic fibrosis and partial pancreatectomy.[2]
PEI - pancreatic exocrine insufficiency; PERT - pancreatic enzyme replacement therapy

References: 1. Domínguez-Muñoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. *J Gastroenterol Hepatol* 2011;26 Suppl 2:12–16. 2. Creon® 25000. Approved package insert February 2016. 3. Creon® 10000. Approved package insert September 2005. 4. Solvay Pharmaceuticals. NDA 20-725 for Creon® (Pancrelipase Delayed-release Capsules) Briefing Document for December 2, 2008 Antiviral Drugs Advisory Committee.

S1 Creon® 10000. Each capsule contains enteric coated granules of Pancreatin 150 mg. S1 Creon® 25000. Each capsule contains enteric coated granules of Pancreatin 300 mg.

Registration Numbers:	Mauritius	Namibia	South Africa
Creon® 10000	R7435/02/16	04/11.1/1015	33/11.1/0340
Creon® 25000	-	04/11.1/1016	28/11.1/0645

For full prescribing information refer to the package insert approved by the Medicines Regulatory Authority.

Abbott Laboratories S.A. (Pty) Ltd. 1940/014043/07. Abbott Place, 219 Golf Club Terrace, Constantia Kloof, 1709. Tel: (011) 858 2000. Publication Date: April 2018.
Promotional review number: ZAECRE170148a
12797

Creon®
Pancreatic Enzyme Replacement Therapy

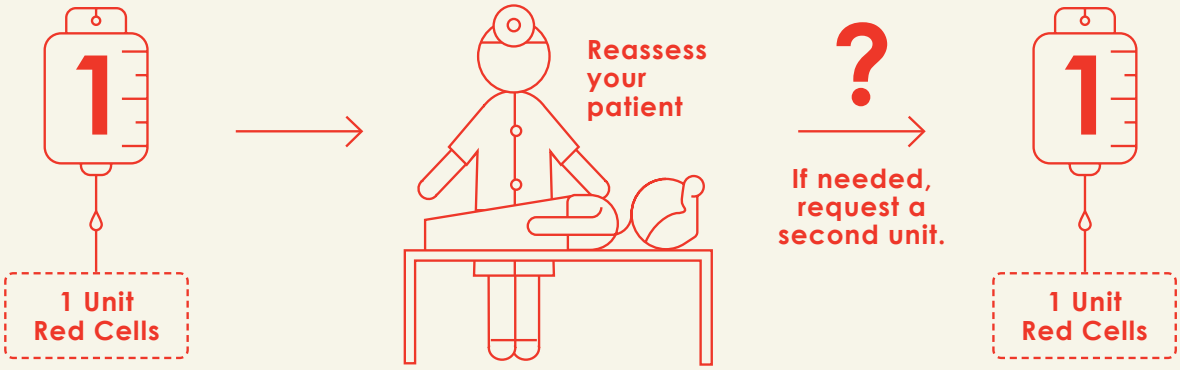
1 unit at a time

Single unit transfusions reduce risks to patients.

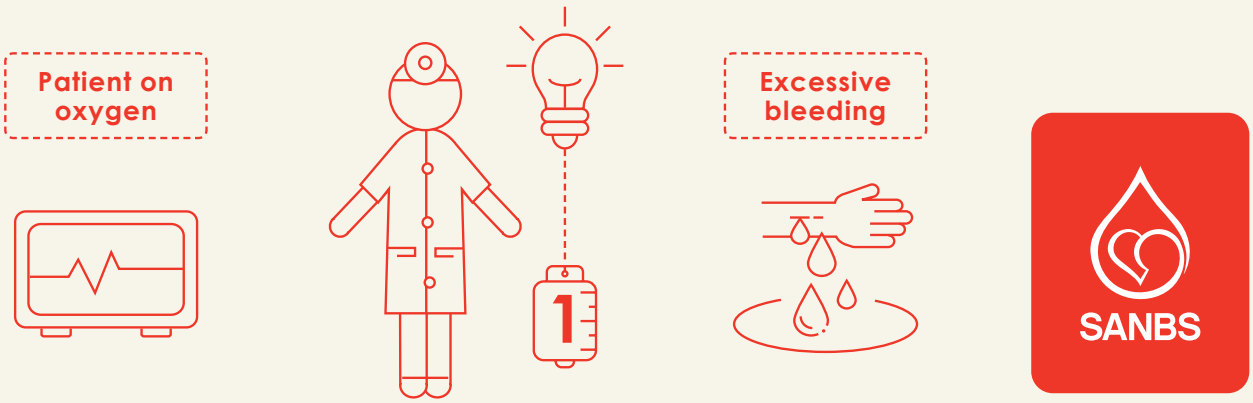
Why?

- Transfusion risks are per unit transfused – not per transfusion episode.
- Literature shows a dose-dependent increase in negative patient outcomes with clinically inappropriate transfusions.
- Restrictive transfusion thresholds have been proven as safe/safer than liberal transfusion thresholds.

Clinically symptomatic patient with no active/clinically significant bleeding:



Order additional unit if:



INF-MLD-088
1063843 Rev 1 (17/07/2020) · Reg No. 2000/026390/08

ASSA • SAGES
CONFERENCE 2021

SAVE THE DATE

CALL FOR ABSTRACTS:
Opens 1 February
and closes 14 May 2021

ASSA SAGES 2021

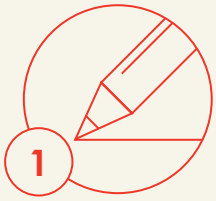
19 - 22 August
Drakensberg
Convention Centre
KwaZulu-Natal
www.assasages.co.za

Conference Management:
Eastern Sun Events
+27 41 374 5654
assasages@easternsun.co.za

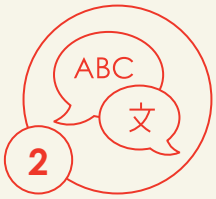
Informed Consent

The Process of Informed Consent (IC):

- Informed consent is not merely a signature on a piece of paper. It entails a process that consists of various steps and contains several components:



A patient gives informed consent for a specified health service.

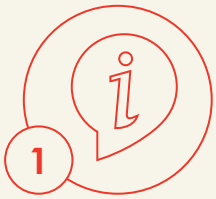


Information about a specific service should be provided in a language, format and at a literacy level that the patient would understand. A translator / cultural leader should be used if necessary.

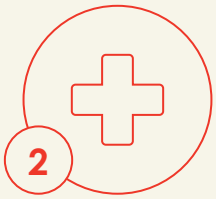
Sufficient information should be given, as to enable the patient to make an informed decision.

NB: *The patient must be deemed capable and competent by the HCW to give informed consent. The competent, capable patient must show an understanding of what he/she is consenting to.*

Informed consent should:



Provide Information regarding the nature of treatment to be provided, risks, benefits, complications, implications, costs, recuperation time and social implications should be given to the patient.

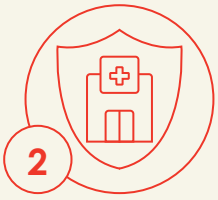


Be administered by the treating HCW.

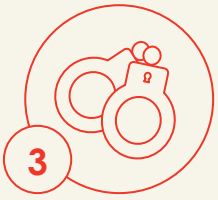
Be given voluntarily. No manipulation, coercion or persuasion must be involved.

Importance of Informed consent (IC):

The IC will protect the treating doctor from litigations that may arise as a result of blood transfusion.



The IC will also protect the hospital from civil claim by the patient.



Any form of treatment administered without the patient's consent is considered as assault.

PS: *A doctor who fails to administer an IC for transfusion may be found to be negligent even if the indication for transfusion is justified.*

INF-MLD-089
1063846 Rev 0 (13/07/2020) · Reg No. 2000/026390/08

See template below:

Nature of product/ Service and why it is needed (benefits):	Risks and complications
e.g. Red blood cells (RBC) increase oxygen delivery to cell in cases of blood loss, bone marrow failure or chronic illness. **Platelets(Plt)** as treatment of bleeding disorders due to congenital or bone marrow failure **Fresh frozen plasma (FFP)** give clotting factors to stop bleeding **Whole blood:** For exchange transfusion	**1. Transfusion transmissible infections (TTI`s)** **Causes:** *Bacteria/virus/prions/protozoa* **2. Adverse events** **a) Acute intravascular haemolysis** ***Causes:*** *Blood group incompatibility* **b) Delayed extravascular haemolysis** ***Causes:*** *antigens: RBC, Plt, white blood cells* **c) Transfusion associated circulatory overload(TACO)** ***Causes:*** *too much, two fast* **d) Metabolic and other:** *e.g. citrate toxicity, Ca/K imbalance, acidosis, hypothermia, embolism, febrile non haemolytic transfusion reaction or Allergic /anaphylactic reaction.* **e) Transfusion related lung injury (TRALI)** ***Causes:*** *activation of recipient neutrophils by donor-derived antibodies.* **f) Transfusion associated graft vs. host disease (TaGvH)** *Causes: The introduction of immuno-competent lymphocytes into a susceptible host.* **NB:** Notify and send a completed adverse reaction form to blood bank immediately. **Regulation 179, 10.4 states:** The blood transfusion service must inform the Director-General or a person specifically designated by him or her, verbally immediately of any report received in terms of any serious or life threatening reaction or death and confirm such report in writing as soon as possible. **3. Negative clinical outcomes** ***Causes:*** *Allo-immunization and immune-modulation* **4. Delays** ***Causes:*** *poor logistics/ irregular antibodies* **5. Costs-** blood safety and waste

Discussed with the patient. *(Tick applicable box)* **Yes** ☐ **No** ☐

Information regarding:

Costs of products	Recuperation time	Social implications	Implications
Variable every year.	Studies show length of stay increases with increase in number of units transfused. **Advice:** heed Patient Blood Management (PBM) principles.	**e.g.** Jehovah's witnesses believe that breach the following rules will damage their relationship with God: • Receive Whole blood or major components transfusion. • Pre and intra-operative storage of blood for later autologous (self) transfusion.	**e.g.** Jehovah`s witness child court order obtained to transfuse blood. PS: Social worker involvement necessary.

Discussed with the patient. *(Tick applicable box)* **Yes** ☐ **No** ☐

- Sign only if informed consent given to patient as above:
- Sign only if understood above discussion:

Signature of treating doctor: _____ **Date:** _____

Signature of patient: _____ **Date:** _____

Signature of Witness: _____ **Date:** _____

Signature of legal guardian: _____ **Date:** _____

The Solly Marks Scholarship

PURPOSE

The purpose of the award is to honour the memory of Professor Solly Marks by recognizing clinicians or researchers of distinction in the field of gastroenterology/hepatology on an annual basis. This is an educational grant that is to be used for the upskilling of an individual and that will benefit the general good of gastroenterology in South Africa, as Prof Marks would have wanted. It is not to be used as a top up fund, but rather for a specific endeavour.

IF AWARDED, GRANT FUNDING MAY BE USED FOR:

1. A finite research project.
2. Buying out of time from teaching or clinical responsibilities to enable the nominee to make substantial headway in a large research project or to complete a Masters or PhD.
3. Paying for research assistance.
4. Supporting a period of travel for research purposes (in or outside South Africa).
5. Conference attendance.
6. Attending a gastroenterology/hepatology course, which will advance the nominee's skills.

BUDGET

The funding level is up to a maximum of R 100 000 per award, which must be fully accounted for by the end of the grant period.

ELIGIBILITY

1. Nominations will only be accepted from members of SAGES in good standing for at least a year.
2. Nominations from trainees/ fellows in formal GIT fellowship posts will be considered. However, the project should be completed before the end of the gastroenterology/hepatology fellowship.
3. Researchers/ basic scientists in the field of gastroenterology or hepatology will be eligible.

SUBMISSION PROCESS

There is no application template for this funding opportunity. All applications must be typed. Applicants' written motivation should include:

1. A CV.
2. A letter of motivation indicating the applicant's specific intended use of the award.
3. If applying for an educational activity, proof of that activity must be submitted (e.g. letters of invitation, advertising brochures etc). If the educational activity is attendance of a conference, this will only be funded if the individual is presenting an abstract and *will not be funded retrospectively*.
4. If applying for a research project, a proposal must accompany the application, including a budget.
5. Applications for research projects that have ethics approval will have an advantage.

DEADLINES AND MEETING DATES

Applications will be considered once a year.
Deadlines for submission of applications must be sent to Karin Fenton at karin.fenton@uct.ac.za no later than January 15th 2021.
The academic sub-committee which meets before the SAGES meeting will decide on the recipient based on the merits of the proposal. Outcome dates: Scholarships to be announced in February 2021

CONDITIONS

1. The grant will only be paid once proof of ethics approval has been received. Should the study not be commenced within one year of the grant being awarded, the grant is to be returned.
2. The successful applicant will be required to submit a report to the committee before the SAGES meeting in the following year after the award.
3. Any publications emanating from such funding must acknowledge the Solly Marks Scholarship.

SAGES
South African Gastroenterology Society

Abbott
A Promise for Life

Abbott Laboratories S.A. (Pty) Ltd SAGES award: R50 000

for research in one of the following categories:

a) Pancreatic Disease
b) Irritable Bowel Syndrome
c) General Gastroenterology Disorders

Applications are invited for this combined Abbott/SAGES award which encourages both basic and clinical research into the diseases of the pancreas, irritable bowel syndrome or any other relevant gastroenterology condition.

Conditions/ Requirements:

- The applicant must be a South African citizen or have permanent residence.
- The applicant must be a SAGES member.
- Trainees in medical or surgical gastroenterology, or gastroenterologists, are eligible.
- The award will be made for a clinical or laboratory-based research project involving the study of the pancreas and its pathology.
- The project must be carried out under the auspices of a medical faculty or gastroenterology department.
- A 6-monthly progress report is required.
- The work must be presented at the SAGES annual congress.
- Sponsorship of the work is to be acknowledged in all publications.
- The funds will be administered through the nominated university or the sponsor.
- The grant will only be paid once proof of ethics approval has been received. Should the study not be commenced within one year of the grant being awarded, the grant is to be returned.

Application forms are available on request from the SAGES secretariat, karin.fenton@uct.ac.za
The closing date is 15 January 2021. Awards to be announced in February 2021.

Abbott Laboratories S.A.(Pty) Ltd, Abbott Place, 219 Golf Club Terrace, Constantia Kloof, 1709. Tel: (011) 858 2000. Fax: (011) 858 2137. Promotional Material Review No: CREON-0312-0001-S-0102. April 2012.

Gastro Foundation 12th Weekend for Fellows

Friday 5th – Sunday 7th February 2021

Spier Hotel & Conference Centre, Stellenbosch

Postgraduate Training in Gastroenterology

SSA
GASTROENTEROLOGY FOUNDATION OF SUB-SAHARAN AFRICA
ESTABLISHED 2006

Supporting Gastroenterology for the future

All gastroenterology and hepatology (medical and surgical) and paediatric gastroenterology fellows in training are welcome and encouraged to attend.
Registration fee: R3 500
Please RSVP to karin.fenton@uct.ac.za

Enquiries: karin.fenton@uct.ac.za
www.gastrofoundation.co.za

1692 Spier

O&G FORUM

Published by:
inhouse PUBLICATIONS

Visit our website:
www.ihpublishing.co.za

S4 PENTOZ®

pantoprazole 20 mg, 40 mg

In the pursuit of perfection...

pantoprazole is packed with potential [1]

- **Efficacy** is independent of the patient's age [1]
- **Symptomatic improvement** (e.g. heartburn, acid regurgitation, pain on swallowing) [2]
- **Long-term management and prevention** of relapse in gastro-oesophageal reflux disease (GORD) [2]
- **Reduced risk of drug-drug interactions** due to a lower affinity for cytochrome P450 system [1]
- **No dosage adjustments required** in elderly or with renal impairment [1,2]
- **Does not increase platelet aggregation** in patients receiving dual antiplatelet therapy [3]

References: 1. Calabrese C, Fabbri A, Di Febo G. Long-term management of GERD in the elderly with pantoprazole. *Clin Interventions Aging* 2007;**2**(1):85-92. **2.** PENTOZ® approved package insert. Dr. Reddy's Laboratories (Pty) Limited. 19 March 2010. **3.** Choi YJ, Kim N, Jang IJ, Cho JY, *et al.* Pantoprazole Does Not Reduce the Antiplatelet Effect of Clopidogrel: A Randomized Controlled Trial in Korea. *Gut and Liver* 2017;**11**(4):1-8. S4 Pentoz 20. Reg. No.: 41/11.4.3/0641. Each film-coated tablet contains pantoprazole sodium sesquihydrate equivalent to pantoprazole 20 mg. S4 Pentoz 40. Reg. No.: 41/11.4.3/0642. Each film-coated tablet contains pantoprazole sodium sesquihydrate equivalent to pantoprazole 40 mg. Dr. Reddy's Laboratories (Pty) Ltd. Reg. No. 2002/014163/07. Block B, 204 Rivonia Road, Morningside, Sandton 2057. Tel: +27 11 324 2100, www.drreddys.co.za. For full prescribing information refer to package insert approved by the medicines regulatory authority. ZA/02/2020-2022/PENTOZ/001.

38087 03/20

Dr. Reddy's