Accepted Manuscript online: 2022-07-21 Article published online: 2022-10-17

TC-325 hemostatic powder in the management of upper gastrointestinal malignant bleeding: a randomized controlled trial

OPEN ACCESS

Authors

Bruno Costa Martins[1], Andressa Abnader Machado[1], Rodrigo Corsato Scomparin[1], Gustavo Andrade Paulo[1], Adriana Safatle-Ribeiro[1], Sebastian Naschold Geiger[1], Luciano Lenz[1], Marcelo Simas Lima[1], Caterina Pennacchi[1], Ulysses Ribeiro[2], Alan N. Barkun[3,4], Fauze Maluf-Filho[1]

Institutions

1 Endoscopy Unit, Instituto do Cancer do Estado de Sao Paulo ICESP, Hospital das Clinicas HCFMUSP, Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil
2 Department of Gastroenterology, Instituto do Cancer do Estado de Sao Paulo ICESP, Hospital das Clinicas HCFMUSP, Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil
3 Division of Gastroenterology, McGill University Health Centre, McGill University, Montréal, Quebec, Canada
4 Department of Clinical Epidemiology, McGill University, Montréal, Quebec, Canada

submitted 30.1.2022
accepted after revision 20.7.2022
published online 21.7.2022

Bibliography
Endosc Int Open 2022; 10: E1350–E1357
DOI 10.1055/a-1906-4769
ISSN 2364-3722

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Corresponding author
Bruno Costa Martins, MD, PhD, Instituto do Cancer do Estado de São Paulo ICESP, Av. Dr. Arnaldo, 251, 2nd, Floor, 01246-000 – São Paulo, SP, Brazil
Phone: +55-11-3893-2296
bcm.bruno@gmail.com

ABSTRACT

Background and study aims Upper gastrointestinal bleeding (UGIB) from malignancy is associated with high re-bleeding and mortality rates. Recently, TC-325 powder has shown promising results in the treatment of UGIB, including malignant bleeding. The aim of this study was to compare the efficacy of TC-325 versus best clinical management.

Patients and methods From August 2016 to February 2020, all patients with evidence of UGIB from malignancy were randomized to receive TC-325 therapy or control group, in which endoscopic treatment was not mandatory. Exclusion criteria were hemoglobin drop without overt bleeding and UGIB from non-tumor origin. The primary outcome was 30-day mortality. Secondary outcomes were 30-day rebleeding, blood transfusion and length of hospital stay.

Results Sixty-two patients were randomized, three were excluded and 59 were included in the final analysis (TC-325 group = 28; control = 31). Groups were similar at baseline. Active bleeding was observed in 22 patients in the TC-325 group and 19 in the control group ($P = 0.15$). Successful initial hemostasis with TC-325 was achieved in all cases. Additional therapy (radiotherapy, surgery or arterial embolization) was equally performed in both groups (42.9 % vs 58.1 %; $P = 0.243$). There were no differences in 30-day mortality (28.6 % vs. 19.4 %, $P = 0.406$) or 30-day rebleeding rates (32.1 % vs. 19.4 %, $P = 0.26$). Logistic regression identified no significant predictors of rebleeding. Age, Eastern Cooperative Oncology Group (ECOG) score 3 to 4 and AIMS65 score > 1 predicted greater mortality.

Conclusions TC-325 was effective in achieving immediate hemostasis in malignant gastrointestinal bleeding but did not reduce 30-day mortality, 30-day rebleeding, blood transfusion or length of hospital stay. Age, ECOG 3–4, and AIMS65 > 1 were predictive factors of mortality.

Introduction

Upper gastrointestinal bleeding (UGIB) in patients with cancer is a challenging situation since these patients usually present a poor clinical condition and endoscopic hemostasis is difficult and only modestly effective. A 30-day mortality rate ranging from 10 % to 45 % has been reported [1–4]. In a retrospective study conducted at our institution, patients with malignant bleeding had a median survival of 20 days with a 30-day mortality rate of 44.9 % [1]. Moreover, rebleeding and mortality rates were not affected by endoscopic treatment.

Numerous endoscopic treatments have been described in small case series for hemostasis of malignant bleeding, with initial success rates ranging from 63 % to 100 % and rebleeding rates ranging from 30 % to 80 % [2, 3, 5–8]. Bleeding from malignant lesions is usually diffuse. In addition, the tumor surface is friable, reducing the efficacy of clipping, injection and elastic banding, even in the presence of focal bleeding.

In this sense, a thermal therapy like argon plasma coagulation (APC) is attractive, since it can be applied over large surfaces. However, in a retrospective comparative study conducted in our institution, we did not find any benefits in rebleeding and mortality rates comparing APC vs non-treated patients [5].

Recently, TC-325 powder (Hemospray; Cook Medical, Winston-Salem, North Carolina, United States), has emerged as a promising hemostatic therapy. Two recent meta-analysis reported immediate hemostasis rates of 93 % to 97 % and rebleeding rates of 14.4 % to 27 % [9, 10]. The role of TC-325 powder in GI malignancy was tested in a pilot randomized study (10 patients in each arm), achieving immediate hemostasis in 90 % of patients, 20 % rebleeding (180 days) and 30-day mortality of 50% [4].

The aim of this study was to compare the efficacy of TC-325 powder versus best clinical management in the treatment of malignant upper GI bleeding.

Patients and methods

This was a prospective randomized controlled trial conducted at the Cancer Institute of the University of São Paulo (Instituto do Cancer do Estado de São Paulo – ICESP) between August 2016 and February 2020 (when occurred a global recall of TC-325 hemostatic powder). This study was approved by the local research ethics committee of our institution (CAAE55377216.0.0000.0065) and was registered on ClinicalTrials.gov (NCT02820077). All patients registered in our institution must have a confirmed diagnosis of cancer.

Patient eligibility

All patients with malignancy referred to the endoscopy unit (inpatient or outpatients) with suspected UGIB were eligible to the study. Inclusion criteria were patients with a known diagnosis of malignancy from any site; history of hematemesis, hematochezia or melena in the last 48 hours and endoscopic confirmation of bleeding from neoplasia (primary or metastatic) located in the upper gastrointestinal tract. Exclusion criteria included bleeding from a non-malignant lesion; previous treatment by another endoscopic method in the last 48 hours; hemoglobin drop without overt bleeding, neoplastic hemobilia and patients under 18 years old. Written informed consent was obtained from patients or a legal responsible before performance of the index endoscopic procedure.

Randomization

If bleeding from a malignant lesion was confirmed at the index endoscopy, patients were randomized to either the TC-325 or control group. Randomization was performed by brown concealed envelopes arranged by blocks during index endoscopy. In the control group, endoscopic treatment was not mandatory. However, if the attending endoscopist judged that a specific treatment could benefit the patient, standard endoscopic therapies such as injection, clipping, argon plasm coagulation or others, could be applied. In the TC-325 group, the hemostatic powder was the only endoscopic therapy delivered. In the case of non-active tumor bleeding, but with tumor bleeding stigmata, endoscopic washing of the tumor surface with water jet was performed in order to remove the clot and reactivate bleeding or to induce brisk bleeding, so that TC-325 powder could adhere to the tumor surface and promote coagulation. If the tumor bleeding was not reactivated, the patient was excluded. Cross-over was not contemplated in this trial.

Clinical data as status of the primary tumor, symptoms of the bleeding episode, hemodynamic signs, comorbidities, Eastern Cooperative Oncology Group (ECOG) status, antiplatelet or anticoagulation drugs and laboratory exams, were collected. AIMS65 score was calculated based on albumin level, international normalized ratio (INR), alteration in mental status, systolic blood pressure and age.

All healthcare personal involved with the patient treatment were blinded to the allocation group (except the endoscopist) in order to minimize bias of clinical management and additional treatment. The information that the patient had been included in TC-325 protocol was included in the endoscopy report, without mention to the allocation group. The indication of hemostatic radiotherapy was let to the discretion of the attending physicians after the index endoscopy.

Definitions

Tumor bleeding was defined when active bleeding from a primary or metastatic malignant lesion was seen, or when there was coffee grounds stasis in the stomach, associated with bleeding stigmata in the tumor (visible vessel, clot attached to the lesion), without any other lesion that could justify the hemorrhagic condition (eg. ulcer, esophageal varices, angioectasia, etc).

Immediate hemostasis was defined when active bleeding was seen during endoscopy and TC-325 powder achieved sustained hemostasis during an observation period of 3 minutes after endoscopic intervention. Recurrent bleeding after the index endoscopy was defined if any of the following clinical criteria was noted: new episode of hematemesis, new episode of melena or hematochezia; exteriorization of red blood content from a nasogastric tube; hemodynamic instability (tachycardia or hypotension); or recurrent need of red blood cell package

transfusion. In the case of rebleeding after TC-325, an alternative hemostatic therapy could be applied.

Study outcomes

The primary outcome of this study was 30-day mortality rate and 30-day rebleeding rate. Secondary outcomes were blood transfusion and length of hospital stay.

Clinical evaluation and follow-up

Patients were monitored by dedicated research assistants through regular consultation of electronic medical charts and laboratory exams. In the case of early hospital discharge, telephone contact was made, inquiring about clinical signs and symptoms that may suggest rebleeding. All patients received omeprazole 40 mg daily for the entire follow-up period (30 days). Patients were withdrawn from the study if it was not possible to obtain their medical data or due to loss of follow-up.

Sample size calculation

The sample size was calculated based on our previous experience, in which a 30-day mortality rate of 44 % was expected. Alpha was set to 0.05 and a study power of 80 % was adopted. At the time of conception of this study, there were no studies with quality data on the use of TC-325 hemostatic powder in malignant bleeding. Thus, we assumed that a reduction of 30-day mortality from 44 % to 20 % would be considered clinically relevant. Considering a dropout rate of 5 %, a total of 47 patients would be necessary in each arm.

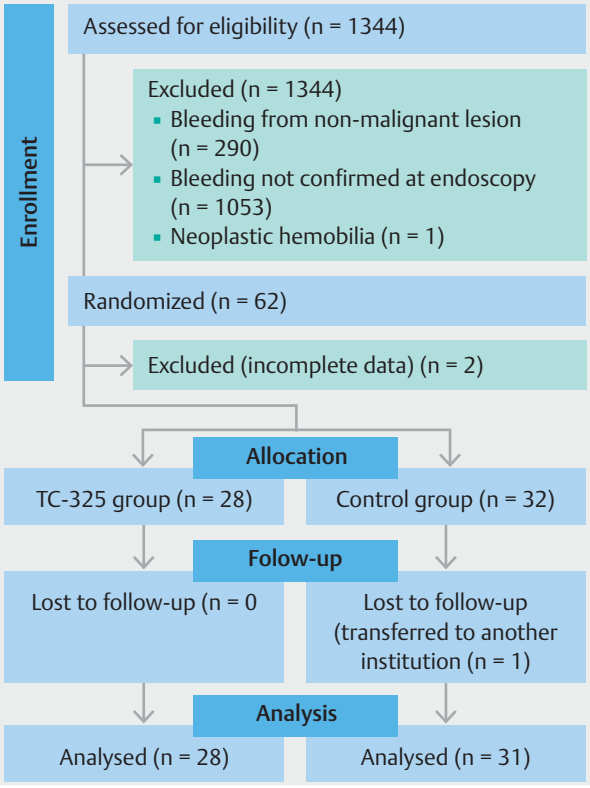
Statistical analysis

Descriptive analysis of quantitative data with normal distribution were expressed using means and standard deviations. Categorical variables were expressed with frequency and percentages. A normal distribution was verified using the Shapiro-Wilk test. Quantitative variables were compared using Student t-test, and categorical variables using chi-square or Fisher's exact test. Univariable analysis adopted logistic regression to explore significant correlations between predictive variables and outcomes. Variables with $P \leq 0.1$ were included in the multivariable analysis (Stepwise Backward Likelihood Ratio). $P \leq 0.05$ was considered statistically significant. Statistical modeling and tests were performed with the SPSS software, version 21.0 (SPSS Statistics for Windows, Version 21.0, IBM Corp., Armonk, New York, United States).

Results

Enrollment began in August 2016 and the last patient was included in January 2020. From 1406 eligible patients, 62 consecutive patients with confirmed upper malignant GI bleeding were randomized. Three patients were excluded because of incomplete data (2) and loss of follow-up (1). Finally, 59 patients were included in the final analysis, 28 in the TC-325 group and 31 in the control group (▶ **Fig. 1**).

Most patients were male (57.6 %) with a mean age of 58.7 years (range 32–86 years). The predominant primary tumor was gastric cancer (42.4 %), followed by esophageal cancer



▶ **Fig. 1** CONSORT flow diagram. From *Schulz KF, Altman DG, Moher D*, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Ann Int Med 2010; 1: 100–107

(10.2 %). The majority of patients had a "good" performance status (61 % ECOG 0, 1 or 2); antiplatelet or/and anticoagulant medications were used by eight patients (13.6 %). The mean hemoglobin at admission was 7.62 g/dL (range 2.9–14.3), with a mean INR of 1.28 (± 0.28). Complete patients' characteristics are shown in ▶ **Table 1**. Baseline clinical characteristics and laboratorial findings were similar between groups.

Endoscopic findings and therapy

The most frequent location of tumor bleeding was the stomach (57.6 %), with a predominance of bleeding from a primary neoplasm (67.8 %), followed by metastatic lesions (20.3 %) and direct invasion (11.9 %). Active bleeding was identified in 41 patients (69.5 %), 22 (78.6 %) in the TC-325 group and 19 (61.3 %) in the control group ($P = 0.15$). Immediate hemostasis was achieved in all patients treated with TC-325. Six patients (19.4%) in the control group received endoscopic therapy, including hemoclip application (n = 2) and injection of adrenaline (n = 4), while no patients in the TC-325 group required additional endoscopic therapy ($P = 0.049$; ▶ **Table 2**). There were no adverse events reported in either group.

Eighteen patients did not have spontaneous active bleeding in the beginning of endoscopic examination but presented tumor bleeding stigmata. Water jet irrigation was sufficient to in-

▶ **Table 1** Baseline clinical characteristics and laboratory findings.

Variables	Total	TC-325 group	Control group	*P*
	N = 59 (%)	N = 28 (%)	N = 31 (%)	
Gender				
▪ Male	34 (57.6)	17 (60.7)	17 (54.8)	0.648
▪ Female	25 (42.4)	11 (39.3)	14 (45.2)	
Mean age (years)	58.7 (14.1)	55 (15.3)	62.1 (12.1)	0.053
Origin				
▪ Inpatient	48 (81.4)	23 (82.1)	25 (80.6)	0.883
▪ Outpatient	11 (18.6)	5 (17.9)	6 (19.4)	
Primary tumor				0.647
▪ Esophageal	6 (10.2)	3 (10.7)	3 (9.7)	
▪ GE junction	3 (5.1)	2 (7.1)	1 (3.2)	
▪ Gastric	25 (42.4)	11 (39.3)	14 (45.2)	
▪ Duodenum	4 (6.8)	1 (3.6)	3 (9.7)	
▪ Colorectal	4 (6.8)	2 (7.1)	2 (6.5)	
▪ Hepatobiliary	3 (5.1)	1 (3.6)	2 (6.5)	
▪ Pancreas	3 (5.1)	2 (7.1)	1 (3.2)	
▪ Lung	1 (1.7)	1 (3.6)	0	
▪ Ovary	1 (1.7)	1 (3.6)	0	
▪ Breast	2 (3.4)	0	2 (6.5)	
▪ Lymphoma	3 (5.1)	2 (7.1)	1 (3.2)	
▪ Myeloma	2 (3.4)	0	2 (6.5)	
▪ Melanoma	1 (1.7)	1 (3.6)	0	
▪ Unknown	1 (1.7)	1 (3.6)	0	
ECOG score				
▪ 0–1-2	39 (66.1)	18 (64.3)	21 (67.7)	0.779
▪ 3–4	20 (33.9)	10 (35.7)	10 (32.3)	
Comorbidities				
▪ Hepatopathy	6 (10.2)	3 (10.7)	3 (9.7)	> 0.999
▪ Cardiac conditions	3 (5.1)	2 (7.1)	1 (3.2)	0.599
▪ Renal failure	5 (8.5)	3 (10.7)	2 (6.5)	0.661
▪ Others	24 (40.7)	8 (28.6)	16 (51.6)	0.072
▪ Current antithrombotic therapy	8 (13.6)	3 (10.7)	5 (16.1)	0.709
▪ First-time bleeding	48 (81.4)	23 (82.1)	25 (80.6)	0.883
Symptoms at admission				
▪ Hematemesis	31 (52.5)	17 (53.6)	14 (51.6)	0.880
▪ Melena	28 (47.5)	13 (46.4)	15 (48.4)	
▪ Mean hemoglobin (g/dL)	7.62	7.77 (± 2.43)	7.81 (± 2.04)	0.948
▪ Mean INR	1.28 (± 0.28)	1.29 (± 0.30)	1.25 (± 0.24)	0.523

▶ **Table 1** (Continuation)

Variables	Total	TC-325 group	Control group	*P*
	N = 59 (%)	N = 28 (%)	N = 31 (%)	
AIMS65				
▪ ≤1	28 (52.8)	14 (51.9)	14 (53.8)	0.884
▪ >1	25 (47.2)	13 (48.1)	12 (46.2)	

GE junction, gastroesophageal junction; ECOG, Eastern Cooperative Oncology Group; INR, international normalized ratio.

▶ **Table 2** Endoscopic findings and procedure-related characteristics.

Variables	Total	TC-325 group	Control group	*P*
	N = 59 (%)	N = 28 (%)	N = 31 (%)	
Time to endoscopy				
▪ <12	22 (37.3)	12 (42.9)	10 (32.3)	0.427
▪ 12–24	22 (37.3)	11 (39.3)	(35.5)	
▪ >24	15 (25.4)	5 (17.9)	10 (32.3)	
Location of tumor bleeding				
▪ Esophagus	8 (13.6)	5 (17.9)	3 (9.7)	0.607
▪ Stomach	34 (57.6)	16 (57.1)	18 (58.1)	
▪ Duodenum	17 (28.9)	7 (25.0)	10 (32.3)	
Type of cancer				
▪ Primary tumor	40 (67.8)	19 (67.9)	21 (67.7)	0.646
▪ Direct invasion	7 (11.9)	3 (10.7)	4 (12.9)	
▪ Distant metastasis	12 (20.3)	6 (21.4)	6 (19.4)	
Active bleeding (AB)				
▪ Spontaneous AB	41 (69.5)	22 (78.6)	19 (61.3)	0.150
▪ Induced AB	6 (10.2)	6 (21.4)	NA	
Signs of bleeding				
▪ Blood or clots in upper gastrointestinal tract	24 (40.7)	11 (39.3)	13 (41.9)	0.366
▪ Adherent clot	14 (23.7)	4 (14.3)	10 (32.3)	
▪ Non-bleeding vessel	2 (3.4)	1 (3.6)	1 (3.2)	
▪ Bleeding vessel	9 (15.3)	5 (17.9)	4 (12.9)	
▪ Surface diffuse bleeding	10 (16.9)	7 (25.0)	3 (9.7)	
Endoscopic therapy				
▪ TC-325	28 (47.5)	28 (100.0)	0	0.049
▪ Hemoclip	2 (3.4)	0	2 (6.5)	
▪ Adrenaline injection	4 (6.8)	0	4 (12.9)	

NA, not applicable.

▶ **Table 3** Patient outcomes after randomization and endoscopy.

Variables	Total	TC-325 group	Control group	*P*
	N = 59 (%)	N = 28 (%)	N = 31 (%)	
Rebleeding rate (30 days)	15 (25.4)	9 (32.1)	6 (19.4)	0.26
Mean time to recurrent bleeding (days)	6.7 (± 7.6)	8.2 (± 8.2)	4.5 (± 6.7)	0.376
New endoscopic therapy	2 (3.4)	1 (3.6)	1 (3.2)	> 0.999
Additional treatment				
▪ Surgery	3 (5.1)	1 (3.6)	2 (6.5)	0.615
▪ Arteriography embolization	2 (3.4)	0	2 (6.5)	0.493
▪ Radiotherapy	28 (47.5)	12 (42.9)	16 (51.6)	0.501
▪ Any	30 (50.9)	12 (42.9)	18 (58.1)	0.243
▪ Blood transfusion	45 (76.3)	20 (71.4)	25 (80.6)	0.41
▪ Length of hospital stay (days)	15.0 (± 15.9)	17.4 (± 17.7)	12.8 (± 14.1)	0.277
▪ Mortality rate (30 days)	14 (23.7)	8 (28.6)	6 (19.4)	0.406

duce brisk bleeding in all these patients, so they were all included in the study.

Outcomes

There were no differences in 30-day mortality rates (TC-325 28.6 % vs. control 19.4 %, $P = 0.406$). Recurrent bleeding at 30 days occurred in 9 (32.1 %) TC-325 patients and 6 (19.4 %) controls ($P = 0.26$). Of the nine patients in the TC-325 group who presented recurrent bleeding, endoscopy was repeated in 6, with associated endoscopic therapy in one patient (APC). Mean time to rebleeding was 8.2 (± 8.2) days in the TC-325 group and 4.5 (± 6.7) days in the control group ($P = 0.376$). ▶ **Table 3** shows patient's outcomes.

Twenty patients (71.4 %) required red blood cell transfusions in the TC-325 group compared to twenty-five (80.6 %) in the control group ($P = 0.41$; median 2 units/patient in each group). Additional non-endoscopic hemostatic treatment was used similarly in both groups: surgery (3.6 % vs 6.5 %; $P = 0.615$), arteriography embolization (0 vs 6.5 %; $P = 0.493$) and radiotherapy (42.9 % vs 51.6 %; $P = 0.501$). Length of hospital stay after bleeding was also comparable between groups (17.4 ± 17.7 days vs 12.8 ± 14.1 days; $P = 0.277$). ▶ **Table 3** shows patient's outcomes after randomization and endoscopy.

Risk factors for 30-day rebleeding and mortality

On univariate analysis, age ($P = 0.027$), ECOG 3 or 4 ($P = 0.009$) and AIMS65 > 1 ($P = 0.01$) were associated to higher mortality rates (▶ **Table 4**). All these factors were confirmed as risk factors for mortality on multivariate analysis: age (OR 1.07; [confidence interval] CI 1.01–1.13; $P = 0.032$); ECOG (OR 7.89; CI 1.39–44.6; $P = 0.019$); AIMS65 (OR 6.04; CI 1.06–34.28; $P = 0.042$). Logistic regression analysis did not identify any risk factor for rebleeding (▶ **Table 4**).

Discussion

This randomized controlled trial reports on the largest published experience with TC-325 in patients with malignant GI bleeding to date. Immediate hemostasis was achieved in all patients treated with TC-325, confirming results of prior studies. Chen et al. conducted a randomized pilot trial comparing TC-325 with a standard of care (SOC) group, achieving immediate hemostasis in 90 % of patients treated with TC-325 versus 40 % in the SOC group ($P = 0.057$) [4]. A cohort of 41 patients with gastrointestinal tumor bleeding treated with TC-325 achieved immediate hemostasis in 97.5 % and 28 days rebleeding in 22.5 % [11]. A retrospective study including 12 patients with gastric malignant bleeding treated with a similar hemostatic powder reported immediate hemostasis in all patients and rebleeding in 16 % [12]. A systematic review and meta-analysis including 11 prospective studies and four randomized trials found an immediate hemostasis rate of 93 % with TC-325 powder (95 % CI 90.3–95 %, $P < 0.001$) [10]. For the subgroup of tumor-related bleeding, immediate hemostasis was achieved in 95.3 % (95 % CI 89.6–97.3 %; $P < 0.001$) and rebleeding rate was 21.9 % (95 % CI 13.9–32.7 %, $P < 0.001$) [10].

Despite the encouraging immediate results, TC-325 did not reduce the incidence of 30-day recurrent bleeding (TC-325 32.1 % vs control 19.4 %; $P = 0.26$). This contrasts with the results reported by Chen et al. [4] which reported a recurrence rate of 20 % in TC-325 group and 60 % in SOC group. However, these results must be interpreted with caution, since 50 % of the patients allocated to the SOC group crossed over to receive TC-325 after failed hemostasis attempt. Thus, it is not known how many patients from the SOC group who presented recurrent bleeding were treated with TC-325. Moreover, this was a pilot trial with low number of patients and inferential analysis was not possible. Another non-randomized comparative study (10 patients in each group) reported lower 14-day rebleeding

▶ **Table 4** Logistic regression analysis for risk factors for 30-day rebleeding and mortality.

	30-day rebleeding			30-day mortality					
	Univariate analysis			Univariate analysis			Multivariate analysis		
	OR	CI (95 %)	*P*	OR	CI (95 %)	*P*	OR	CI (95 %)	*P*
Gender (male/female)	2.51	0.69 – 9.10	0.161	0.97	0.29 – 3.27	0.967			
Age	1.02	0.97 – 1.06	0.420	1.06	1.00 – 1.12	0.027	1.07	1.01 – 1.13	0.032
Origin (inpatient/outpatient)	4.12	0.48 – 35.27	0.197	3.71	0.43 – 31.95	0.232			
Primary tumor (gastric-GE junction/others)	0.67	0.2 – 2.19	0.504	0.53	0.15 – 1.83	0.318			
ECOG (3–4/0–1-2)	3.05	0.91 – 10.24	0.072	5.56	1.53 – 20.16	0.009	7.89	1.39 – 44.6	0.019
History (melena/hematemesis)	0.96	0.29 – 3.10	0.943	0.53	0.15 – 1.83	0.318			
AIMS65 score (> 1/ ≤ 1)	0.97	0.29 – 3.22	0.963	6.54	1.56 – 27.48	0.010	6.04	1.06 – 34.28	0.042
Time to endoscopy (< 12 h/ > 24 h)	3.03	0.53 – 17.25	0.211	2.43	0.42 – 14.16	0.321			
Time to endoscopy (12–24 h/ > 24 h)	2.44	0.42 – 14.16	0.321	2.43	0.42 – 14.16	0.321			
Location of tumor bleeding (esophagus/duodenum)	1.44	0.24 – 8.46	0.687	2.80	0.42 – 18.69	0.288			
Location of tumor bleeding (stomach/duodenum)	0.62	0.16 – 2.36	0.486	1.43	0.33 – 6.29	0.631			
Primary metastasis (primary tumor/metastasis)	2.27	0.65 – 7.92	0.200	1.71	0.47 – 6.22	0.410			
Active bleeding (yes/no)	0.84	0.24 – 2.94	0.783	3.31	0.65 – 16.67	0.147			
Hemoglobin level	0.95	0.73 – 1.24	0.716	0.91	0.69 – 1.21	0.543			
TC-325 therapy	1.97	0.6 – 6.51	0.264	1.66	0.49 – 5.59	0.408			

OR, odds ratio; CI, confidence interval; GE junction, gastroesophageal junction; ECOG, Eastern Cooperative Oncology Group.

rate in TC-325 group although not statistically significant (10 % vs 30 %; *P* = 0.60) [13]. In a retrospective study with 99 patients with active malignant gastrointestinal bleeding treated with TC-325, early recurrent bleeding occurred in 15 % and delayed bleeding occurred in 17 % [14].

Also, TC-325 did not reduce 30-day mortality, which was as high as 28.6 % (versus 19.4 % on control group). This study confirms malignant gastrointestinal bleeding as a pre-terminal or terminal event in the course of the patient's disease. In the study by Chen et al, 30-day mortality was 45 % and 180-day mortality was 80 % [4]. Pittayanon et al.[14] reported 6-month survival of 53.4 % in patients with active malignant GI bleeding treated with TC-325, and the hemostatic powder was not predictive of rebleeding or survival. Loftus et al. reported a median survival of 39 days after endoscopic therapy for UGIB from tumors [2]. In two other studies conducted at our institution, 30-day mortality varied from 20.8 % to 44.9 %, and predictably, endoscopic treatment did not impact mortality rates (43.9 % vs. 44.1 %, *P* = 0.677) [1, 5].

As expected, poor ECOG status and AIMS65 score were predictors of mortality. ECOG 3 to 4 presented 7.89 OR (CI 1.39–44.6; *P* = 0.019) compared to ECOG 0, 1 and 2 on multivariate analysis and AIMS65 > 1 presented 6.04 OR (CI 1.06–34.28; *P* = 0.042) compared to AIMS65 score 0 and 1. Age was also a predictor of mortality. Although the OR of 1.07 may suggest a weaker effect of age compared to ECOG and AIMS65, it is important to understand that this effect is cumulative with aging, impacting more significantly the older patients.

One may criticize that not all patients in this study presented active bleeding during index endoscopy and that this could diminish TC-325 efficacy since it needs active bleeding to absorb water, polymerize, activate and bind to the bleeding site. This was considered during the conception of this study. One factor that motivate us to try this therapy on these patients was the absence of effective endoscopy therapies to treat them. In a prior study conducted at our institution, APC showed discouraging results in reducing recurrent bleeding and mortality and, until now, we have no effective alternative to offer to these patients [5]. Therefore, we opted to attempt to reactivate bleeding by applying water spray jet in the tumor surface when evident malignant bleeding was diagnosed, so optimize TC-325 powder adherence to the tumor surface. In the present study, water spray jet proved to be an efficient maneuver to reactive

bleeding in all patients, allowing the application of TC-325 powder.

The presumption that TC-325 powder could reduce the incidence of recurrent bleeding is merely speculative, since the estimate dwelling time of TC-325 is around 12–24 h [15]. However, although TC-325 did not reduce 30-day rebleeding rates in this study, it presented excellent results of immediate hemostasis. This result may encourage its use in cases of active bleeding, allowing better clinical compensation and planning for additional therapy. In addition, treatment with TC-325 could be repeated in the case of rebleeding, due to its high immediate hemostasis rate, ease of use and safety profile. This hypothesis should be explored in future trials.

In this study, TC-325 did not reduce the need for additional treatment (surgery: $P = 0.615$; angiography: $P = 0.493$; radiotherapy: $P = 0.501$), the percentage of patients requiring a blood transfusion (71.4 % vs 80.6 %), or the length of hospital stay (17.4 vs 12.8 days). A strength of this study was that attending physicians caring for the patients after index endoscopy were blinded to group allocation, which helped to reduce the indication bias of additional treatment, blood transfusion and hospital stay.

This study had some limitations. First, this was a single-center study, conducted in a tertiary care academic center with very debilitated patients manifesting advanced disease. Selection bias may have influenced the results, which could limit the external validity of our findings. Second, due to prolonged time to recruit patients and the global recall of TC-325 in the beginning of 2020, the number of patients included in this study was smaller than initial planned. We achieved 62 % of the planned cohort, which impacted study power. The difficulty of recruiting patients had already being experienced by other authors [4]. Moreover, even if the planned cohort had been achieved, the sample size might have been too small to show an effect on rebleeding (a sample size of 124 patients would be required to test a reduction from 30 % to 10 % on rebleeding rates). Nonetheless it adds to a limited literature, especially in terms of controlled comparisons let alone randomized trials, attempting to identify effective endoscopic methods in this difficult patient population.

Conclusions

In conclusion, TC-325 was effective in achieving immediate hemostasis in patients with malignant GI bleeding, but did not reduce 30-day mortality, 30-day rebleeding, blood transfusion or length of hospital stay. Age, poor ECOG score, and AIMS65 score > 1 were significant predictors of mortality.

Competing interests

Dr. Barkun is a consultant for and the advisory boards of Cook Medical, Pharmascience, and Olympus; has received research support from Pharmascience and AtGen; and is on the advisory board for AtGen.

Clinical trial

ClinicalTrials.gov (http://www.clinicaltrials.gov/)
NCT02820077
TRIAL REGISTRATION: Randomized study NCT02820077 at ClinicalTrials.gov (http://www.clinicaltrials.gov/)

References

[1] Maluf-filho F, Martins BC, De Lima MS et al. Etiology, endoscopic management and mortality of upper gastrointestinal bleeding in patients with cancer. United Eur Gastroenterol J 2013; 1: 60–67

[2] Loftus EV, Alexander GL, Ahlquist DA et al. Endoscopic treatment of major bleeding from advanced gastroduodenal malignant lesions. Mayo Clin Proc 1994; 69: 736–740

[3] Savides TJ, Jensen DM, Cohen J et al. Severe upper gastrointestinal tumor bleeding: endoscopic findings, treatment, and outcome. Endoscopy 1996; 28: 244–248

[4] Chen YI, Wyse J, Lu Y et al. TC-325 hemostatic powder versus current standard of care in managing malignant GI bleeding: a pilot randomized clinical trial. Gastrointest Endosc 2020; 91: 321–328.e1

[5] Martins BC, Wodak S, Gusmon CC et al. Argon plasma coagulation for the endoscopic treatment of gastrointestinal tumor bleeding: A retrospective comparison with a non-treated historical cohort. United Eur Gastroenterol J 2016; 4: 49–54

[6] Mathus-Vliegen EMH, Tytgat GNJ. Analysis of Failures and complications of neodymium: YAG laser photocoagulation in gastrointestinal tract tumors. Endoscopy 1990; 22: 17–23

[7] Heller SJ, Tokar JL, Nguyen MT et al. Management of bleeding GI tumors. Gastrointest Endosc 2010; 72: 817–824

[8] Ahn D, Lee SH, Park YS et al. Hemostatic efficacy and clinical outcome of endoscopic treatment of Dieulafoy's lesions : comparison of endoscopic hemoclip placement and endoscopic band ligation. YMGE 2012; 75: 32–38

[9] Aziz M. Efficacy of Hemospray in non-variceal upper gastrointestinal bleeding: a systematic review with meta-analysis. Ann Gastroenterol 2020: doi:10.20524/aog.2020.0448

[10] Mutneja HR, Bhurwal A, Go A et al. Efficacy of hemospray in upper gastrointestinal bleeding: a systematic review and meta-analysis. J Gastrointest Liver Dis 2020; 29: 69–76

[11] Shin J, Cha B, Park J-S et al. Efficacy of a novel hemostatic adhesive powder in patients with upper gastrointestinal tumor bleeding. BMC Gastroenterol 2021; 21: 40

[12] Kim Y, Park J, Kim E et al. Hemostatic powder application for control of acute upper gastrointestinal bleeding in patients with gastric malignancy. Endosc Int Open 2018; 06: E700–E705

[13] Pittayanon R, Prueksapanich P, Rerknimitr R. The efficacy of Hemospray in patients with upper gastrointestinal bleeding from tumor. Endosc Int open 2016; 4: E933–E936

[14] Pittayanon R, Rerknimitr R, Barkun A. Prognostic factors affecting outcomes in patients with malignant GI bleeding treated with a novel endoscopically delivered hemostatic powder. Gastrointest Endosc 2018; 87: 994–1002

[15] Chen Y-I, Barkun AN. Hemostatic powders in gastrointestinal bleeding. Gastrointest Endosc Clin N Am 2015; 25: 535–552