

Original Article

## Long-Term Effectiveness, Safety and Mortality Associated with the Use of TC-325 for Malignancy-Related Upper Gastrointestinal Bleeds: A Multicentre Retrospective Study

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### Abstract

**Background and Study Aims:** Malignant-related upper gastrointestinal bleeding (MRUGIB) is difficult to treat by conventional endoscopic methods. We sought to determine the efficacy, safety and mortality associated with the use of TC-325 for the treatment of MRUGIB.

**Patients and Methods:** This is a multicentre, retrospective study at the University of Calgary and University of Ottawa performed between January 1, 2010, and July 30, 2016. TC-325 use was identified via staff polling, product order forms and endoscopic records review. Once identified, patient charts and online records were examined to identify MRUGIB cases and to assess our primary and secondary endpoints.

**Outcomes:** The primary outcome was hemostasis at seven days. Secondary outcomes include immediate hemostasis, early hemostasis, hemostasis at 14 days, 30-day mortality, adverse events related to TC-325 therapy and the need for repeat endoscopic intervention, surgery or transarterial embolization.

**Results:** Twenty-five patients were identified. The median age was 62 years (interquartile range [IQR] 52.5–76), and most were male (64%). TC-325 was the primary treatment modality in 20 patients (80%). Hemostasis was 88%, 89%, 58% and 50% at 24 hours, 72 hours, 7 days and 14 days, respectively. Five patients underwent repeat endoscopy, two patients required surgical intervention, and transarterial embolization was not required. Twelve patients died by 30 days (48%). There were no complications directly attributed to the use of TC-325.

**Conclusions:** TC-325 is effective for achieving and maintaining hemostasis in patients with malignancy-related upper gastrointestinal bleeding, and most patients do not require additional interventions. The 30-day mortality risk in this group of patients is high.

**Keywords:** TC-325; Malignancy-related upper gastrointestinal bleeds

### Abbreviations:

MRUGIB,	Malignancy-related upper gastrointestinal bleeds;
THA,	Topical hemostatic agent;
EGD,	Esophagogastroduodenoscopy;
IQR,	Interquartile range

Malignancy-related upper gastrointestinal bleeds (MRUGIB) are difficult to control by conventional endoscopic methods such as epinephrine injection, clips and argon plasma coagulation (1, 2). Overall, the effectiveness of these interventions varies widely, with immediate hemostasis being achieved in 31% to 40% of patients and the short-term rebleeding rate as high as

80% (3, 4). Salvage therapies such as surgery and embolization can be effective but are more invasive and resource intensive. The 30-day mortality rate for patients with MRUGIB requiring endoscopy has been shown to range from 21% to 43% (1, 5), with 90-day mortality as high as 95% (6).

TC-325 is a mineral-based topical hemostatic agent (THA) that has been approved for use in Canada and the United States for upper gastrointestinal bleeding. TC-325 is one of the five commercial THAs available and the first to have been approved by the United States Food and Drug Administration for the management of gastrointestinal bleeding (7). Although the exact mechanism of action of TC-325 remains unknown, it may achieve hemostasis in gastrointestinal bleeds via three mechanisms: 1) mechanical barrier formation over the bleeding site, 2) serum separation, thus increasing clotting factor concentration, and 3) activation of the intrinsic clotting cascade (8, 9).

Some single-centre studies have demonstrated that TC-325 is over 90% effective at achieving immediate hemostasis in patients with MRUGIB (10, 11). On the other hand, the ability of TC-325 to sustain hemostasis is unclear. For instance, Pittayanon et al. observed that one of 10 patients (10%) with MRUGIB treated with TC-325 rebled after 14 days (12). The largest investigation examining TC-325 use in the context of MRUGIB observed that 25% of patients rebled at eight days, and 38% may rebled by 30 days post-treatment (13). Information regarding the use of additional interventions to achieve hemostasis, long-term outcomes and survival associated with TC-325 treated MRUGIBs in Canada has not previously been reported.

It has been suggested that TC-325 is best used as an upfront bridging therapy to more definitive interventions such as further endoscopic treatment, vascular embolization and surgery. The 30-day poor prognosis in this patient population suggests that a palliative end-of-life framework is required when planning the medical care for these patients. This includes the avoidance of unnecessary invasive intervention that may lead to patient discomfort, adverse events, premature iatrogenic death, high health care costs and perceived loss of dignity (14, 15) (Figure 1).

We sought to examine the long-term efficacy and safety of TC-325 as the sole modality to achieve hemostasis and the need for additional interventions to manage these patients.

## PATIENTS AND METHODS

The institutional ethics review board at the University of Calgary, Calgary, Alberta, Canada, and The Ottawa Hospital, Ottawa, Ontario, Canada, have both independently approved this study. Patient consent was waived for this project.

### Patients

This is a multicentre, retrospective study at the University of Calgary and the University of Ottawa. Patients with upper

gastrointestinal bleeds between January 1, 2010, and July 30, 2016, requiring TC-325 use were identified by staff polling, product order records and endoscopic records review (Endopro®, Calgary and vOACIS, Ottawa, Canada). Once TC-325 use was identified, patient charts and online records (Sunrise Clinical Manager, Calgary; vOACIS, Ottawa, Canada) were reviewed to identify those with malignant upper gastrointestinal bleeds. We used the following inclusion criteria: 1) adult patients more than 17 years of age; 2) endoscopic evidence of active bleed from a malignant tumour; 3) pathological confirmation that the lesion was malignant; and 4) the use of TC-325 to achieve hemostasis.

### Instruments and Procedure

TC-325 (Hemospray®, Cook Medical, Winston-Salem, North Carolina, USA) was used as either the primary treatment modality or as an adjunctive therapy for patients with MUGIB. Following medical resuscitation (16), patients underwent a therapeutic esophagogastroduodenoscopy (EGD) by an experienced endoscopist who was trained in using TC-325. The agent was applied to the site of bleeding via either a 7Fr or 10Fr catheter.

### Data Extraction and Study Outcome Measures

Data extraction was performed by KM in Calgary and MZW in Ottawa. The collected data included patient demographics, clinical presentation (including patient hemodynamics and need for blood transfusions), laboratory markers, endoscopic findings (including location of the malignancy and Forrest Classification of the bleeding source), endoscopic treatments, malignancy pathology, and use of follow-up endoscopic, surgical and radiological interventions.

The primary outcome was hemostasis at seven days post-treatment. Secondary outcomes included immediate hemostasis, hemostasis at 24 hours, hemostasis at 14 days, 30-day adverse events risk, need for additional interventions to achieve hemostasis (such as repeat endoscopy, surgery or vascular embolization) and 30-day mortality. The adverse events considered included aspiration, perforation, infection and thromboembolism. Hemostasis was defined as the absence of rebleeding, as described in international consensus guidelines set out by Laine et al (17). This includes clinical evidence of gastrointestinal bleeding, hemodynamic instability and decrease in hemoglobin by 20 g/L after two consecutive stable hemoglobin values, defined as a decrease less than or equal to 5 g/L, three or more hours apart.

### Statistical Analyses

The Blatchford Score was calculated for all cases. Continuous variables were expressed as median and interquartile range (IQR), and categorical variables are expressed as percentages.

Statistics were performed using Microsoft Excel®, 2016 (Redmond, Washington, USA).

## RESULTS

### Patient Characteristics

We identified 25 patients who experienced a MRUGIB and were treated with TC-325 in Calgary (11) and Ottawa (14) (Figure 2). Of these, 16 were male, and the median age was 62 years (Table 1). The majority (76%) of the malignancies were located in the stomach, and the bleeding lesions were mostly classified as Forrest class 1B. The median Blatchford score was 11.

### TC-325 Efficacy

Hemostasis at 24 hours was achieved in 22 out of 25 patients (88%). At 72 hours, 17 out of 19 patients (89%) maintained adequate hemostasis (Table 2).

Nineteen patients could be followed to day seven post-treatment (Figure 2). Eleven of them maintained hemostasis (58%). At 14 days post-treatment, nine of 18 (50%) patients maintained hemostasis.

### TC-325 Safety

There were no adverse effects linked directly to TC-325 as the definitive cause.

One patient was hypoxemic during the procedure, with desaturations down to 72% that improved after termination of the procedure and application of a non-rebreather face mask. The event was not reported to be attributable to TC-325 application.

### Need for Additional Interventions

Five patients underwent a repeat endoscopy within 30 days. Indications were esophageal stent migration (n=1) and clinical evidence of rebleeding (n=4). The four patients with rebleeding were retreated with TC-325. One patient continued to bleed after repeat treatment, while two did not exhibit any further bleeding seven days after retreatment. One patient required the repeat endoscopy five months after initial therapy with TC-325.

Two patients received surgery after the use of TC-325. One underwent a repeat gastroscopy within two days and was retreated with TC-325 followed by a gastrectomy on day nine post-initial TC-325 treatment for ongoing bleeding. The second patient had a gastrectomy on day seven post-TC-325 treatment for the purposes of complete tumour resection and not bleeding recurrence.

TC-325 was used as an adjunct to other endoscopy therapy in eight patients: three were treated with epinephrine injection and endoscopic clipping, three were treated with epinephrine alone, one was treated with endoscopic clipping alone, and one was treated with cauterization alone.

### Mortality

Twelve patients died within 30 days of TC-325 treatment, with none of the deaths attributed to their MRUGIB or the use of TC-325. Causes of deaths include respiratory failure (2) and biliary sepsis (2). One patient died from perforated duodenal ulcer 11 days after the use of TC-325, and the perforation was not attributed to the use of TC-325. One patient with continued MRUGIB despite repeat therapy with TC-325 committed suicide, and this was not reported as being related to their bleeding or the use of TC-325. Half of the deaths (six patients) were related to malignancy progression.

## DISCUSSION

This is the largest North American multicentre study examining the long-term safety, efficacy and mortality associated with the treatment of MRUGIB with TC-325. Hemostasis was maintained in 50% of patients over 14 days. Only six (33%) patients required further intervention over this time, including the need for further endoscopy. Out of the five patients that required repeat endoscopies, four were attributed to rebleeding. Overall, mortality risk unrelated to the MRUGIB was high at 48%, with progression of cancer being the most common cause of death. None of the patient deaths were attributed to MRUGIB or the use of TC-325.

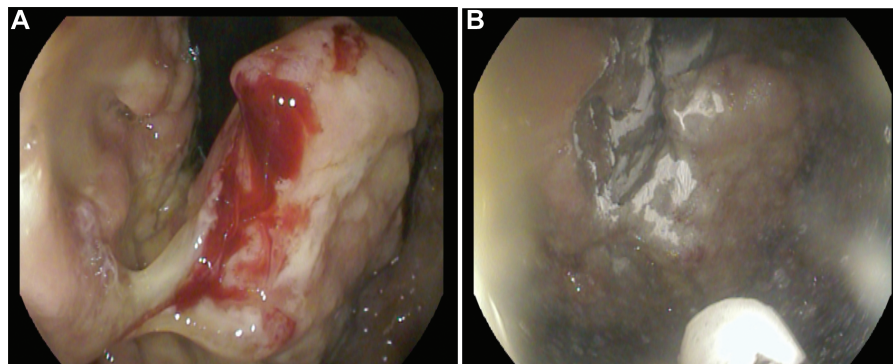


Figure 1. A, Gastric cardia bleeding lesion from diffuse large B cell lymphoma pre-treatment with TC-325. B, post-treatment with TC-325.

**Table 1.** Patient demographics and clinical characteristics

	Calgary n (%) <sup>*</sup>	Ottawa n (%)	Total n (%)
Median Age (IQR)	70 (59–78)	60.5 (48–71.5)	62 (52.5–76)
Male	7 (64)	9 (64)	16 (64)
On antiplatelet agents <sup>**</sup>	4 (36)	5 (36)	9 (36)
On anticoagulation <sup>***</sup>	2 (18)	3 (21)	5 (20)
Malignancy Location			
Esophagus	3 (27)	2 (14)	5 (36)
Stomach	6 (55)	7 (50)	13 (52)
Small Bowel	2 (18)	5 (36)	7 (28)
Malignancy Type			
Adenocarcinoma	8 (73)	7 (50)	15 (60)
Lymphoma	1 (9)	2 (14)	3 (12)
Squamous Cell Carcinoma	1 (9)	0 (0)	1 (4)
Pancreatic Cancer	1 (9)	4 (29)	5 (20)
Metastasis	0 (0)	1 (7)	1 (4)
Forrest Classification			
1A	1 (9)	1 (7)	2 (8)
1B	10 (91)	9 (64)	19 (76)
Hemoglobin on admission (median, IQR)	74 (86–111)	75 (61–101)	81 (70–106)
INR at admission (median, IQR)	1.1 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Blatchford Score (median, IQR)	11 (5–13)	11 (8.25–12.75)	11 (8–13)

<sup>\*</sup>unless otherwise specified

<sup>\*\*</sup>Antiplatelet agents include: aspirin, P2Y12 receptor inhibitors

<sup>\*\*\*</sup>Anticoagulation includes: vitamin K antagonists, LMWH, Heparin, Direct oral anticoagulants

**Table 2.** Outcomes and use of additional therapies

	Calgary n (%)	Ottawa n (%)	Total n (%)
Hemostasis Achieved			
24 hr	9/11 (82)	13/14 (93)	22/25 (88)
72 hr	5/6 (83)	12/13 (92)	17/19 (89)
7 day	1/6 (17)	10/13 (77)	11/19 (58)
14 day	1/6 (17)	8/13 (62)	9/18 (50)
Repeat Endoscopy	4 (36)	1 (7)	5 (20)
Surgery	2 (18)	0 (0)	2 (8)
Embolization	0 (0)	0 (0)	0 (0)
30-day mortality	7 (64)	5 (36)	12 (48)
Cause of Mortality			
Malignancy Related	3	3	6
Respiratory Failure	2	0	2
GI Bleed	0	0	0
Others	2	2	4
TC-325 associated adverse events	0	0	0

The mechanism of serum separation and activation of the intrinsic clotting cascade is unique to THAs as compared with traditional endoscopic therapies, which fail to cause diffuse

tamponade or initiate the clotting cascade across a wide tumour surface area. Traditional endoscopic therapies were designed to treat single-vessel sources of bleeding and may be limited by a



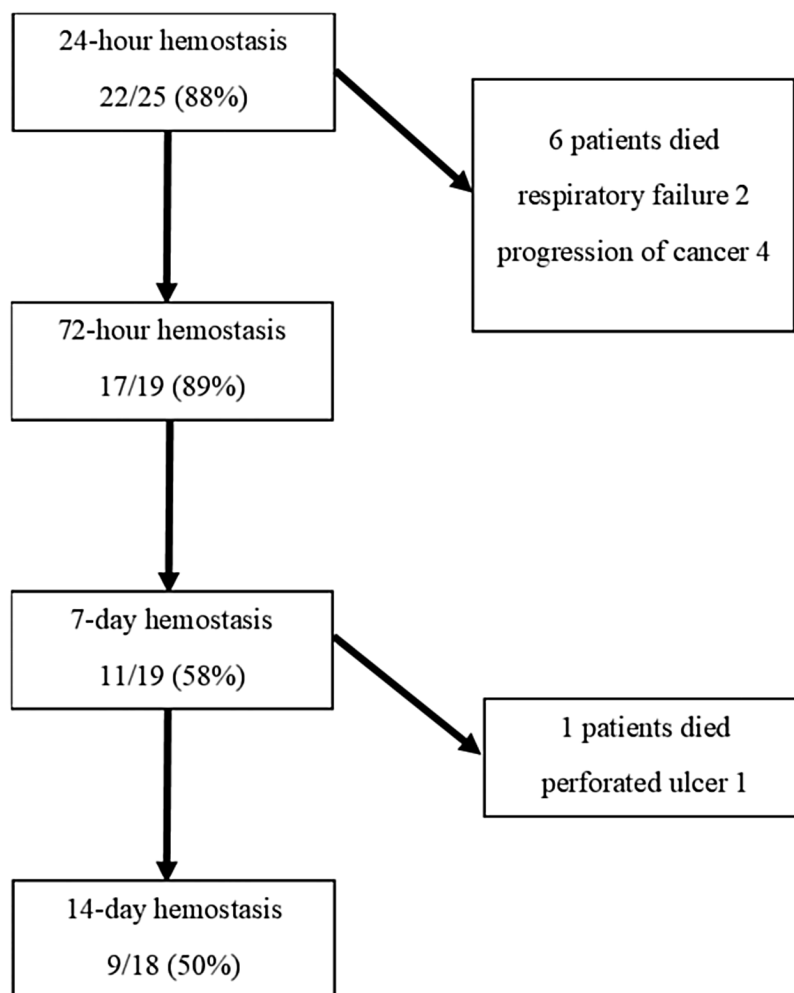


Figure 2. Flow chart of cumulative hemostasis rate at different time intervals.

lack of adequate access to the site of hemorrhage. Since tumour bleeding tends to be diffuse in nature, they are uniquely suited to the broad topical application offered by THAs. Furthermore, THAs allow for easy, nontraumatic application, in contrast to the mechanical methods which rely on the manipulation of fragile and hemorrhagic tissue (13, 18).

Chen et al. were the first to describe the use of TC-325 in a case series of five patients with MRUGIB; none of these patients had rebleeding within the five days of follow-up (10). In 2015, the same author expanded their cohort size to 19 patients and noted that immediate hemostasis (defined as less than 24 hours post-treatment), early hemostasis (less than 72 hours), and delayed hemostasis (72 hours to 30 days post-treatment) were 100%, 95%, and 68%, respectively. These numbers are comparable to the 88% and 89% rate of immediate and early hemostasis seen in our study. They demonstrated a greater rate of maintained hemostasis using TC-325; however, the use of adjunct interventions was not well described.

Our findings are generally consistent with the observations of others; however, some discrepancies are worth noting. In 2016,

Pittayanon et al. described 10 patients with MRUGIB that were treated with TC-325 (12). The hemostasis rate at 14 days was 90%, which is higher than what we observed (50%). One possible explanation was that they excluded those who received chemoembolization or radiation therapy within 72 hours after treatment with TC-325. These patients may have been at an increased risk of rebleeding potential. Immediate and early hemostasis rates were not examined. Haddara et al. found that out of the 61 patients with MRUGIB, 75% of patients achieved hemostasis at eight days (13), which is similar to the 58% seen in our study at seven days. Longer-term outcomes, use of additional interventions and mortality rates were not described.

Pittayanon et al. recently examined 79 patients with MRUGIB treated with TC-325 (19). Interval hemostasis at seven and 14 days were 93% and 92%, respectively. Cumulative hemostasis rates were not presented. They note that 27% of patients rebled within 30 days. Fifty-nine of the patients in their study received follow-up treatment for bleeding within one month. Whether these interventions were in response to clinical evidence of ongoing bleeding or a pre-emptive approach

to definitive treatment was not explained in their report. Their 30-day mortality was reported at 28%; the differences observed in mortality risk between their study and ours may be attributable to the types of malignancies treated. Forty-two percent of MRUGIB cases were due to the presence of a primary tumour in their study, whereas 75% of the MRUGIB cases we identified were related to a primary tumour. Also of note, 48% of their study population were treated in Asia, which may limit the generalizability of their findings.

TC-325 has been described as a useful therapy that can act as a bridge to more definitive endoscopic, surgical or other interventions (1, 4, 13). Given the high mortality rate of patients in our study, the interventions for these patients should be in line with the principles of end-of-life care. More invasive treatment options such as surgery and vascular embolization may pose an excess risk and burden to patients, especially when considering the principles of end-of-life care. The use of THAs avoids the need for additional interventions in the majority of cases and, therefore, can be the most appropriate first-line modality for the management of MRUGIB.

Strengths of this study include the multicentre and the multiple relevant outcomes in both safety and efficacy. The main limitation of this study is its retrospective nature. This can potentially lead to bias. As with previous studies examining TC-325 in MRUGIB, we were limited to a relatively small cohort of patients. Our study is one of the largest of its kind, however, and it is reassuring, that our results are generally comparable to the experience of other centres. We observed a higher mortality risk among patients with MRUGIB than previously reported. These deaths were not related to bleeding or the use of TC-325. As the 30-day mortality risk among published studies ranges between 20% and 50% (5, 12, 19), there is a consistent implication that the principles of end-of-life care should be considered when deciding the optimal and least invasive management strategy for patients with MRUGIB.

The concurrent use of other agents along with TC-325 in a small group of patients within this study diminishes the evaluation of TC-325 as a sole agent; however, the avoidance of requiring further embolization and surgery in these patients speaks to the usefulness of this hemostatic agent, even if it is with the combination of other endoscopic interventions. We examined hemostasis outcomes defined for the evaluation of non-variceal gastrointestinal bleeding and not MRUGIB specifically. Although clinical evidence of gastrointestinal bleeding, hemodynamic instability and decrease in hemoglobin are meaningful outcomes in these patients, variables that consider the unique nature of MRUGIB and principles of end-of-life care may be needed. Prospective, multicentre studies using meaningful outcomes are necessary to truly illicit the exact effectiveness of THAs and other interventions on MRUGIB.

In conclusion, TC-325 is a safe and effective first-line therapy for achieving intermediate and long-term hemostasis in patients with MRUGIB. The high mortality associated with MRUGIB and the safety and efficacy of TC-325 suggest that this may be the least invasive intervention in keeping with the principles of end-of-life care.

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**Conflicts of Interest:** Zhao Wu Meng, Kaleb Marr, Rachid Mohamed, and Paul James have no conflicts of interest or financial ties to disclose.

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