Bleeding from gastrointestinal tract recurrence of non-seminomatous germ cell tumour testis, showing temporary response to gemcitabine and oxaliplatin chemotherapy

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Abstract
The first reported case of gemcitabine/oxaliplatin (GemOx) chemotherapy used for recurrent non-seminomatous germ cell tumour of the testis metastatic to the gastrointestinal tract causing uncontrolled bleeding which induced a temporary response.

Testicular cancers are the most common malignancy in men aged 15–35 years and have an incidence of 0.8% of all cancers in men worldwide, with a mortality rate of 0.1%. A higher incidence in Australian and New Zealand men (1.2%) is described. Non-seminomatous germ cell tumours (NSGCT) account for just under half of all testicular cancers reported.

With advancements in chemotherapy disease-free survival (DFS) and overall survival (OS) rates have been improving, but the 14% of patients with poor prognosis NSGCT have a 5-year OS rate of 48%. Patients who relapse after second-line or high-dose chemotherapy have a poor prognosis, with uncertain benefit from further chemotherapy.

Common sites of metastatic disease include; retroperitoneal lymph nodes, lungs and brain. A rare site of metastatic deposits is the gastrointestinal (GI) tract. When this occurs it can generate symptomatic haemorrhage leading to difficult treatment decisions.

Case report
A 24-year-old Caucasian male presented with a 4-month history of left testis swelling and a short history of 12 kg weight loss, lethargy, and fever. He had no past medical history.

Computed tomography (CT) scan showed extensive metastases in both lungs, and, left sided para-aortic lymphadenopathy. Orchidectomy demonstrated mixed non-seminomatous germ cell testicular cancer, 30% embryonal carcinoma, 70% immature teratoma. Serum tumour markers were all significantly elevated. Beta-HCG was 2800 IU/L (reference range [RR] 0–5 IU/L). Final staging was stage IIIC NSGCT of the testis.

He received bleomycin, etoposide and cisplatin chemotherapy. He relapsed at 7 months and received high dose chemotherapy. After both regimens his tumour markers normalised but had only modest reductions in the metastatic disease. Repeated cardiothoracic opinion stated that the thoracic disease was unresectable.
At further relapse after 15 months, gemcitabine and oxaliplatin (GemOx) palliative chemotherapy was accepted by the patient. Whilst being organised he presented acutely with collapse, melaena and a haemoglobin (Hb) of 37 g/L (RR for males 130–170 g/L).

CT showed increase in the size of his known disease with the development of extensive new liver and right kidney metastases. He required 2 units of blood per day to maintain his Hb.

Oesophagastroduodenoscopy (OGD) and colonoscopy demonstrated only mucosal erosion. CT angiogram showed a small pooling of contrast in a loop of small bowel (Figure 1). A trial of subcutaneous infusion of octreotide did not reduce the bleeding.

**Figure 1. CT angiogram demonstrating pooling of contrast into the small bowel and other areas of metastases**

![CT angiogram](image)

A – Pooling of contrast into the small bowel; B – Para-aortic metastases; C – Metastases in the right kidney; D – Liver metastases.

Due to the likelihood of multiple lesions a capsule endoscopy was organised but whilst awaiting the results his clinical condition deteriorated with a rise in beta-HCG from 60688 to 79423 IU/L over 3 days. The surgeons felt that intervention was unlikely to be beneficial. The remaining options were chemotherapy or terminal care. His case was discussed with our multidisciplinary team and the patient who agreed to have GemOx with an initial 25% dose reduction with the risk of causing catastrophic bleeding due to chemotherapy-induced thrombocytopenia.
Thalidomide 200 mg orally was started on day 8 from the start of the GemOx chemotherapy as advised by the gastroenterologist in attempt to reduce the bleeding. The capsule endoscopy showed multiple tumour deposits in the stomach and small bowel therefore, two lesions were clipped in the stomach via OGD. On day 10 his Hb dropped by 40 g/L and his platelets fell to $49 \times 10^9/L$ (RR $150–400 \times 10^9/L$), increase in the amount of melaena was reported.

On day 11 his platelets spontaneously rose to $80 \times 10^9/L$ then continued to rise and his Hb remained stable for 7 days without blood transfusion, his melaena ceased. His beta-HCG dropped in this time to 7136 IU/L indicating a response to the chemotherapy.

On day 20 small amounts of melaena reoccurred and his beta-HCG rose consistently to 20785 IU/L. He was offered further chemotherapy on a more intensive schedule with a greater risk of bleeding or palliative care; he chose palliative care and died 30 days after the start of chemotherapy.

**Discussion**

Cases of metastatic NSGCT to the GI tract have been reported either as an initial presenting feature or as relapsed disease. The most frequent histological type metastasising to the GI tract reported in the literature is choriocarcinoma. Other reported cases include teratoma and embryonal carcinoma.

Frequently patients with GI metastases have surgery to remove the GI lesion prior to chemotherapy. However, accurate mapping of lesions is difficult and lesions may be missed during surgery. The reported chemotherapy regimens administered whilst GI bleeding due to metastases was ongoing include; ifosfamide based, and actinomycin-D, etoposide and methotrexate. The first case presented with GI metastases and chemotherapy induced compete resolution of macroscopic tumour. The second case died due to metastases in the lung and brain. Another case treated with unspecified chemotherapy died 3 days later due to worsening haemorrhage.

On review of the literature this is the first case where GemOx and thalidomide have been used in a patient with bleeding NSGCT GI metastases.

**GemOx** was considered in this case, who had relapsed after two previous lines of chemotherapy, due to the results of 2 phase II trials using GemOx in relapsed NSGCT. These enrolled 28 and 35 patients respectively, with relapsed or cisplatin-refractory NSGCT. Response rates of 32 and 46% respectively were seen, 14 and 9% achieved a complete response. In the first trial 62% of patients experienced grade 3/4 neutropenia and 41% grade 3/4 thrombocytopenia. In the second trial 54% experienced grade 3 myelosuppression.

The usual indication of thalidomide in GI bleeding is for angiodysplasias or vascular malformations refractory to other treatments. There is only one reported case of thalidomide use with a non-haematological malignancy. This case was a gastric cancer causing severe bleeding resistant to tranexamic acid, etamsylate and sucralfate. Thalidomide was given at a dose of 300 mg orally a day and bleeding stopped within a week. The response appeared to be dose dependent with bleeding recurring at 100 mg per day.
This case demonstrates the difficult treatment decisions faced when managing palliative NSGCT patients with bleeding from GI metastases. The bleeding from the GI metastases reduced in concordance with the decrease in beta-HCG suggesting a response to the GemOx.

The GemOx did cause an increase in bleeding due to grade 3 thrombocytopenia for 1 day but induced a temporary tumour response which rendered the patient transfusion free for a week. It is unclear if there was any additional benefit from the use of thalidomide in our case.

Further research is required in the use of thalidomide in bleeding primary or metastatic GI cancers and optimum dosage. This is the first report of a patient receiving GemOx for this indication and gaining a temporary response.

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**Acknowledgements:** The authors thank the patient for his consent to publish this case report.

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