



Gemcitabine-induced haemolytic uremic syndrome: high level of suspicion seems crucial

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Letter to the editor

Dear editor,

Gemcitabine is an antimetabolite agent used in the treatment of many tumours. The safety profile of gemcitabine is generally mild and it usually displays minimal toxicity in elderly too. Furthermore, its profile of side-effects does not seem to be related to patient's age.

There is no evidence of cumulative renal or hepatic toxicity and peripheral oedema has not been related to any cardiac, hepatic or renal dysfunction. Unfortunately, it has got its negative side as well. Although infrequent, haemolytic uremic syndrome (HUS) can be induced by this treatment. The incidence seems to be low, although underreporting could also be a possibility.

It has been published that around 0.078% patients in clinical trials, or 0.008% reported from daily clinic, developed HUS. This places the overall incidence at 0.015%^{1,2}. However, the mortality rate of these cases ranges from 10 to 40% in most series, but it could be as high as 70% in others^{3,4}.

This could be partly due to many cases included having disseminated disease, which make more difficult to know the cause of the HUS (underlying neoplasia or Gemcitabine)⁵.

Several authors have suggested that cancer associated HUS usually happens when the disease has already disseminated, whereas Gemcitabine-associated HUS is more frequent in patients under adjuvant treatment⁵.

In any case, this complication is underdiagnosed and this could be due to myelosuppression related to chemotherapy, poor oral intake or diarrhoea, especially in those patients who suffer from pancreatic insufficiency after Whipple's procedure and find difficult to find the correct personalised dose of pancreatic enzymes, or those having other comorbidities such as hypertension, vascular disease, diabetes, etc.

A high index of suspicion is necessary and should be applied when patients develop renal insufficiency in the presence of myelosuppression. This should

prompt a laboratory workup looking for hemolysis and microangiopathy signs. High levels of LDH, low levels of haptoglobin, increased reticulocyte count, a peripheral blood smear showing fragmented red blood cells, schistocytes, will help differentiate renal insufficiency associated to myelotoxicity or HUS. Moreover, a mild renal impairment will resolve quickly on rehydration or treatment of the underlying prerenal cause.

In addition, the Coombs' test should be negative if myelosuppression.

We have had two cases of Gemcitabine-induced HUS and both of them continue on hemodialysis. These two patients were receiving adjuvant Gemcitabine and both showed a significant drop in haemoglobin levels, from baseline, after commencing cycle 5 and at the same time, a significant drop in creatinine clearance. One of them did not finish cycle 6 but the other completed the 6 planned cycles.

We reviewed a total of 157 patients who had received adjuvant Gemcitabine for pancreatic carcinoma. We collected all data about haemoglobin, platelets, white cells count, creatinine clearance before each cycle of Gemcitabine. We calculated the maximum drop between baseline and minimum level of haemoglobin and creatinine clearance for all these patients. We found that all patients, except the two who developed HUS, had a maximum drop in haemoglobin of around 24% (22-27%) and around 17% in creatinine clearance (12-44%). Those two patients had a drop in haemoglobin of 37% and 34% and a drop in creatinine clearance of 41% and 31%.

Logistic regression analysis showed that a drop in haemoglobin >25% and in creatinine clearance >30% from baseline, increased significantly the chances of ending on hemodialysis (p 0.0001).

The patient who had a significant drop in renal function and recovered, showed at the same time a very mild drop in haemoglobin and other signs of myelotoxicity (low white cells count).

Conclusion

We would like to make professionals aware of this quite infrequent but serious complication and although we do not know the best way of getting an early

diagnosis or whether the early end of Gemcitabine cycles will improve final outcomes, we think that in cases of high suspicion levels, Gemcitabine should be at least delayed to undertake all those extra laboratory tests and confirm or dismiss this diagnosis before a final decision is made.

Acknowledgement(s)

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