Cancer Chemother Pharmacol (2017) 79:1–7
DOI 10.1007/s00280-016-3123-6

REVIEW ARTICLE

Rituximab to treat gemcitabine-induced hemolytic–uremic syndrome (HUS) in pancreatic adenocarcinoma: a case series and literature review

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Received: 5 July 2016 / Accepted: 29 July 2016 / Published online: 6 August 2016

Abstract
Purpose Hemolytic–uremic syndrome (HUS) is a rare side effect of gemcitabine, which is reported as having a high morbidity and mortality despite interventions with standard HUS therapies including plasmapheresis. The purpose of this report was to describe the successful treatment of gemcitabine-induced HUS (G-HUS) with rituximab. It also aims to summarize the literature regarding the morbidity and mortality of G-HUS in pancreatic adenocarcinoma depending on the treatment given, ultimately providing some guidance for beneficial therapies.
Methods This is a retrospective report of three patients with pancreatic adenocarcinoma who developed G-HUS and were treated with a combination of therapies including rituximab.
Results All three patients received a combination of therapies to treat their HUS. One patient appeared to have some benefit with plasmapheresis. Resolution occurred following one course of rituximab for all three patients. This resolution has been long lasting with a minimum of eighteen month's follow-up. Similarly, in our literature review a variety of therapies were utilized, but immune therapies appear to reverse HUS if other therapies are failing.
Conclusion Rituximab can be an effective therapy for reversal of hemolysis and stabilization of renal function in G-HUS when other therapies fail.

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Keywords Gemcitabine · Hemolytic–uremic syndrome · Rituximab · Pancreas adenocarcinoma

Introduction

Hemolytic–uremic syndrome (HUS) is a rare, but well-described side effect of gemcitabine. The reported incidence is between 0.015 and 1.4 % [1, 2]. The severity of gemcitabine-induced HUS (G-HUS) is difficult to predict with some patients improving with simple measures such as discontinuation of the drug, while other patients require intensive therapies including dialysis and plasmapheresis [3–5]. Despite intensive treatment, some patients require long-term dialysis or may even die from G-HUS [1, 5–7]. The reported mortality of G-HUS is hugely variable in the literature with a rate from 15 to 66 % [1, 2, 5, 6]. However, it seems that many of these patients die from progressive disease, rather than directly related to HUS, making its impact in an adjuvant setting potentially higher.

There is currently no consensus on the optimal treatment for G-HUS. Importantly, the use of plasmapheresis to treat this condition has recently been questioned [4, 9, 10]. However, due to the retrospective nature of the data it is unclear whether plasmapheresis is of benefit for those who receive it as they may have more severe disease than those who do not. The most important initial intervention is cessation of gemcitabine [4]. Recent studies have shown that treatments that target the immune system, including rituximab, an anti-CD20 monoclonal antibody, and eculizumab, an anti-complement C5 monoclonal antibody, do successfully treat refractory HUS [9–12].

The purpose of this report is to review the literature regarding current treatment options for G-HUS in pancreas adenocarcinoma and to describe a case series of

G-HUS-affected patients that were successfully treated with rituximab. Although G-HUS is reported in many different cancers including breast, ovarian, biliary, gastric and non-small cell lung cancer, we have limited this literature review to those patients who have had G-HUS in pancreas adenocarcinoma [1, 8, 13, 14]. This is because pancreas adenocarcinoma is among the most common neoplasms to be treated with gemcitabine [8] and we want to limit confounding factors through inclusion of multiple cancers.

Materials and methods

Patient selection

Three patients with G-HUS were consecutively identified and treated by the same two clinicians in the divisions of nephrology and oncology at Prince of Wales Hospital. After gaining approval of the internal ethics committee, the medical records for each patient were obtained and reviewed. The diagnosis of hemolytic–uremic syndrome was made via clinical measures with the development of hemolytic anemia, thrombocytopenia and new onset renal disease. All three cases were confirmed to have HUS with a renal biopsy performed.

Literature review

We performed a Medline and EMBASE search of the English literature between 1995 until June 28, 2015. Our search was based on combinations of the word "gemcitabine" with terms: "uremia," "renal insufficiency," "renal failure," "thrombocytopenia," 'hemolytic–uremic syndrome (HUS)," "thrombotic thrombocytopenic purpura (TTP)" and "thrombotic microangiopathy (TMA)." These articles were then limited to those that focussed on pancreas adenocarcinoma. Due to the rare nature of this condition, all levels of evidence were included in this review.

Results

Case series

Our three patients who were confirmed to have G-HUS all had similar presentations (see Table 1) with severe hypertension, peripheral edema, renal impairment and anemia. All three patients had synchronous treatment that initially involved a trial of supportive care, which included cessation of drug, antihypertensives and diuretics ± dialysis. However, despite a minimum 2-week trial of supportive care all three patients had worsening hemolysis and renal impairment that warranted further treatment. All three cases had a brief trial of steroids with no clear benefit. The first two cases had plasmapheresis, which appeared to have a small benefit in case one but not case two. Finally, all three patients had a course (four cycles) of rituximab with resolution of all biochemical (see Fig. 1a–c) and clinical evidence of disease. Importantly, this response has been long lasting with one case being in remission for over 2.5 years and the other over 20 months, while the third died of recurrent disease but with no recurrence in G-HUS over 4.5 years.

Literature review

Our search strategy resulted in a total of 496 papers to review. There were only 27 manuscripts that specifically addressed G-HUS in pancreas adenocarcinoma, and the data from these are presented in Tables 2 and 3. There were a total of 38 case reports of G-HUS in pancreas adenocarcinoma. Including our cases, the mortality rate directly related to G-HUS was 7 % (see Table 3), while the mortality rate due to progressive malignancy was 51 %. Interestingly, the rate of death from progressive malignancy was highest (70 %) in the patients who were solely managed with supportive measures, while the HUS-related death rate was only 5 % ($n = 1$). Plasmapheresis was the next most common modality used for treatment of this condition where again the mortality was mainly related to progressive disease (46 %), while the HUS-related mortality rate was 7 % ($n = 1$). Steroids alone also resulted in one HUS-related death (33 %) ($n = 1$). Immunological treatment modalities including rituximab and eculizumab had a smaller proportion of patients die from progressive disease (20 %) and had zero HUS-related deaths. The total number of patients who required ongoing hemodialysis was 22 % ($n = 9$), which is similar to previous reports [4], and this was evenly spread across all treatment modalities.

Discussion

Diagnosis and clinical presentation

Gemcitabine-induced HUS is a rare but now well-recognized complication. It is characterized by the development of hemolytic anemia, thrombocytopenia and renal impairment. Often the diagnosis may be delayed due to anemia and thrombocytopenia being attributed to myelosuppression secondary to chemotherapy. Clinical clues that point to a likelihood of HUS that have been consistently shown (as well as in this case series) include development of hypertension, increased peripheral edema and worsening renal function [2, 4].

Table 1 Summary of the patient characteristics, symptoms and signs, relevant results and management of our case series

	Case 1	Case 2	Case 3
Age (years)	52	68	65
Stage	T3N0M0	T2N0M0	T3N1M0
Past medical history	Hypothyroidism	Ischemic heart disease, peripheral vascular disease, hypercholesterolemia	Hypertension, hyperlipidemia, type II diabetes
Surgical management	Pancreaticoduodenectomy	Pancreaticoduodenectomy	Pancreaticoduodenectomy
Chemotherapy	6 cycles adjuvant gemcitabine	2 cycles neoadjuvant gemcitabine and protein-bound paclitaxel. 4 cycles adjuvant gemcitabine	2 cycles adjuvant gemcitabine
Cumulative dose	21,500 mg	22,100 mg	8000 mg
Symptoms/signs	Hypertension (BP 170/110 mm Hg) Peripheral edema	Hypertension Peripheral edema Dyspnoea (diagnosed with interstitial lung disease)	Hypertension (206/110 mm Hg) Peripheral edema
Blood results (see Fig. 1 for further blood results)	Blood film that showed moderate anisocytosis, slight round macrocytes, slight polychromasia and occasional schistocytes Haptoglobin <0.1 g/L Coagulation normal ADAMTS 13 activity normal Coomb's test was negative	Blood film occasional schistocytes Haptoglobin <0.1 g/L Coagulation studies normal ADAMTS 13 activity were normal Coomb's test was negative	Blood film occasional schistocytes Haptoglobin <0.1 g/L Coagulation studies normal ADAMTS 13 activity normal Coomb's test was negative
Urine	Proteinuria 770 mg in 24 h	Proteinuria urine spot protein/creatinine ratio: 127 mg/mmol	Proteinuria 2730 mg in 24 h
Renal biopsy	Capillary wall thickening Subendothelial thickening Fibrin thrombosis In keeping with thrombotic microangiopathy	Same as case 1	Same as case 1
Management (in order)	Supportive (blood and platelet transfusions, antihypertensives, diuretics) 5 cycles plasmapheresis (after 4-week trial of above). Some clinical benefit 1000 mg IV methylprednisolone 1 Course rituximab	Supportive (blood and platelet transfusions, antihypertensives, diuretics) 3-Week high-dose hydrocortisone 6 Cycles plasmapheresis (after 4-week trial of above). No clinical benefit 1 Course rituximab	Supportive (blood and platelet transfusions, antihypertensives, diuretics High-dose prednisone 1 course rituximab (after 3.5-week trial of above)
Length of remission from G-HUS to date	>4.5 years. He finally died from metastatic disease just over 5 years post-diagnosis.	>30 months	>20 months

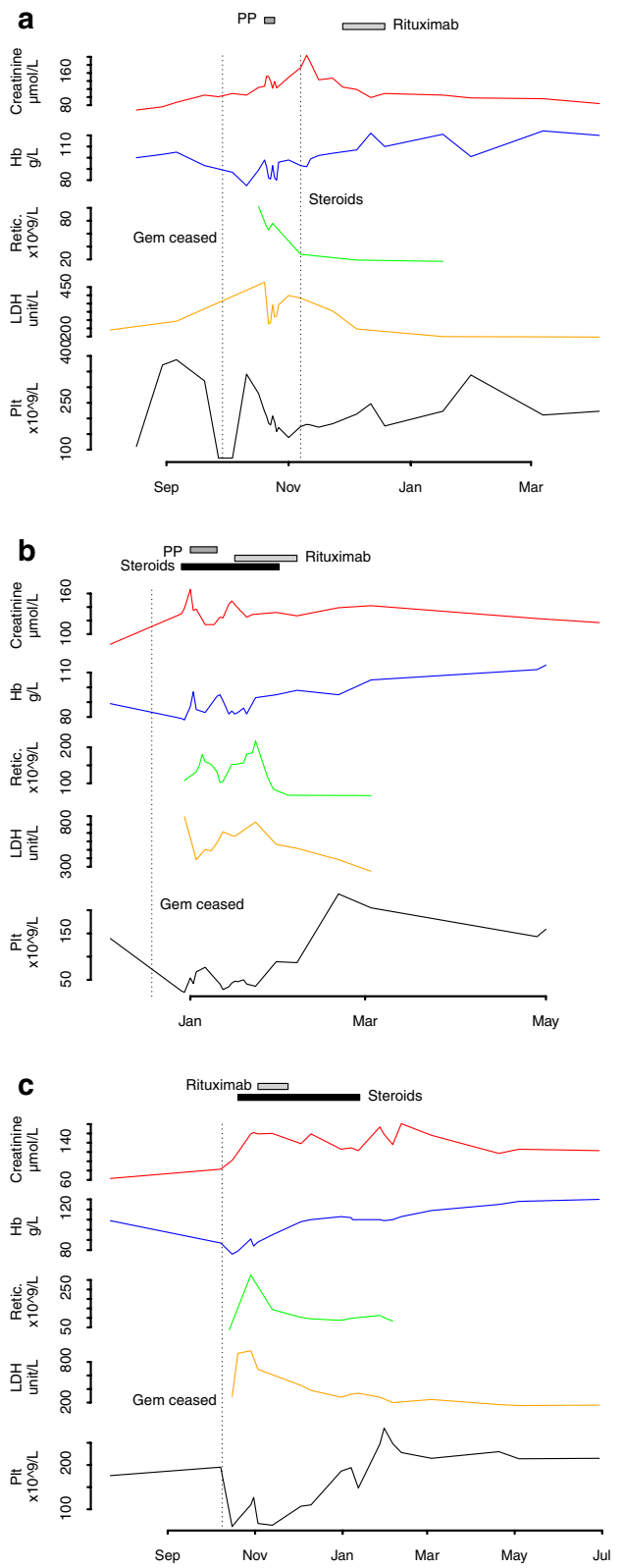

Fig. 1 **a** Case 1, **b** case 2, **c** case 3 time course of blood parameters compared to instituted treatment. *PP* plasmapheresis, *Gem* gemcitabine, *Retic* reticulocytes, *Hb* hemoglobin, *LDH* lactate dehydrogenase, *Plt* platelets

Pathogenesis

Typically, G-HUS is related to a cumulative dose of around 20 000 mg/m^2 [4]. However, authors also report wide ranges from 2 to 56 000 mg/m^2 [4, 25, 26]; similarly, we found a range of 8–22 000 mg/m^2. The mechanism of G-HUS is currently unknown. It has been proposed that there is likely an immunological basis. This is suggested to be caused by uncontrolled proximal alternative pathway complement activation leading to an increase in the terminal membrane attack complex that could lead to endothelial cell activation and subsequent platelet aggregation and activation [2, 10]. Pathological findings of complement and immunoglobulin deposition in the endothelium further support an immunological component [2]. In addition, Synder and co-workers [27] found that circulating immune complexes decrease in patients who respond to treatment of chemotherapy-associated HUS compared to those who do not respond to treatment.

Therapeutic modalities

The proposed mechanism through which rituximab breaks the HUS cycle involves multiple immunological pathways that could ultimately affect the amount of circulating immune complexes or immune activation within the endothelium. One hypothesis is that a decrease in the number of circulating B cells leads to a decrease in autoantibody secreting plasma cells and subsequent titers of autoantibody [28, 29]. Decreased numbers of circulating B cells would also decrease autoantigen-specific B cells ability to present antigens to autoreactive T cells, leading to less T cell activation, less cytokine release and less inflammation. An alternative theory is that of the immune decoy theory described by Taylor et al. [28]. They suggest that rituximab binding to B cells helps to generate a decoy cell with associated immune complexes that can act as an alternative target for activated monocytes and macrophages. This draws these effector cells from other places of immune complex deposition (such as in the kidneys in HUS) resulting in less inflammation and tissue destruction in the kidney endothelium.

Interestingly, eculizumab, a monoclonal antibody directed at C5, has also been shown to improve hemolytic–uremic syndrome in gemcitabine-induced HUS [10]. It is thought that this drug works by preventing the formation of the terminal complement attack complex C5b-9 [10]. However, we feel that in clinical practice eculizumab is less accessible due to cost with it being in the order of seven times more expensive than rituximab.

There is currently no consensus on the optimal treatment for gemcitabine-induced HUS. Recognition of this disease and immediate discontinuation of gemcitabine is the initial and most important step. Following this supportive treatment

Table 2 Summary of the previously published case reports of gemcitabine-induced hemolytic–uremic syndrome in pancreas cancer [1, 3–8, 10, 11, 13, 15–24]

References	Cases in article	Patient number (*n*)	Number of cases (*n*) in article based on treatment	HUS-related death	Death from malignancy	Hemodialysis continued
Bharthuar et al. [11]	1	1	Steroids, PP × 13, rituximab × 2	0	1	1
Boeck et al. [3]	1	2	PP × 5	0	0	0
Casper et al. [15]	1	3	Supportive	0	0	1
Choi et al. [16]	1	4	Supportive	0	1	1
De Smet et al. [6]	1	5	Supportive	1	0	0
Flombaum et al. [17]	3	6, 7, 8	6: Supportive 7: Steroids 8: steroids, PP ×1	0	0	0
Fung et al. [1]	4	9, 10, 11, 12	9: supportive 10, 11: PP 12: PP, immunoglobulin, Splenectomy	1 (*n*: 10)	2 (*n*: 9, 10)	1 (*n*: 11)
Glezerman et al. [4]	10	*n*: 13–23	13-23: Supportive	0	10	2
Humphreys et al. [13]	3	24, 25, 26	24: PP × 5 25, 26: Supportive	0	2 (*n*: 24, 25)	0
Leal et al. [8]	1	27	PP	0	1	0
Lee et al. [5]	1	28	PP × 19	0	1	0
Lhotta et al. [18]	1	29	Steroids	0	0	0
Maginnis et al. [19]	1	30	Supportive	0	0	0
Phelan et al. [20]	1	31	Supportive	0	0	0
Richmond et al. [21]	2	32, 33	32: Supportive 33: PP × 5	0	2	1 (*n*: 33)
Ruiz et al. [7]	1	34	Steroids	1	0	0
Saif et al. [22]	1	35	Steroids, PP × 5	0	1	1
Ustwani et al. [10]	1	36	Eculizumab × 6	0	0	0
Wato et al. [23]	1	37	PP	0	0	1
Zemtsov et al. [24]	1	38	PP × 3	0	0	0
Our data	3	39, 40, 41	39: Steroids, PP × 5, Rituximab × 4 40: Steroids, PP × 6, Rituximab × 4 41: Steroids, Rituximab × 4	0	0	0

Supportive therapy included antihypertensives, diuretics, blood and platelet transfusions and hemodialysis

Table 3 Summary table outlining the treatment each patient received and subsequent outcomes

Treatment	Total number of patients	HUS-related death	Death from malignancy	Hemodialysis continued
Supportive	20	1 (5 %)	14 (70 %)	4 (20 %)
Steroids only	3	1 (33 %)	0	0
PE ± steroids	13	1 (7 %)	6 (46 %)	4 (30 %)
Eculizumab × 6	1	0	0	0
Rituximab ± PE ± steroids	4	0	1 (25 %)	1 (25 %)
Total	41	3 (7 %)	21 (51 %)	9 (22 %)

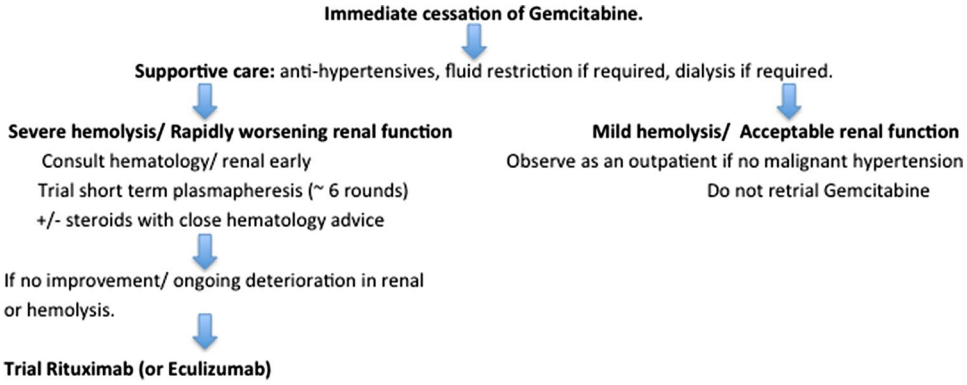

Fig. 2 Algorithm for various treatment modalities for gemcitabine-induced HUS

including antihypertensives, fluid restriction and dialysis can reverse the disease in some patients [4]. Unfortunately, this is of limited benefit and certainly did not help in our patient cohort despite 3–4 weeks of supportive management including trial of steroids, which is consistent with other case reports [10, 11]. The benefit of plasmapheresis is also controversial [4, 9]. While it may have provided some benefit in case one, similar to other case reports [1, 3, 8, 13, 21, 23, 24], our experience suggests that only a short trial of it is reasonable. Indefinite plasmapheresis could mean the opportunity for reversal of kidney damage and hemolysis could be missed [1, 11]. We feel that this could be the reason that the Bhather et al. 2009 patient required long-term dialysis despite the use of rituximab as the patient had 13 plasma exchange procedures with no improvement before rituximab was finally given (5 weeks later). In addition, this patient received a protocol with bevacizumab (under clinical trial) and already had developed grade 3 hypertension and nephrotic syndrome prior to the development G-HUS. In our view, if the HUS has not reversed quickly we would suggest a trial of rituximab. Although our patients did have sequential therapies, we believe that in each case rituximab made the key contribution to reverse the hemolysis and decline in renal function.

The use of gemcitabine as an adjuvant therapy in pancreas cancer is a standard of care [30]. Accordingly, the risk of sustained morbidity and higher mortality in the face of potential cure may be substantially higher than the current estimates principally derived from a metastatic setting. We have therefore developed a treatment algorithm to prevent excess morbidity and mortality (see Fig. 2).

Given our case series involves retrospective and uncontrolled data, this study is subject to the many limitations. However, due to the rarity of this condition it is unlikely that more definitive data will emerge.

Conclusion

We have described a rare side effect of gemcitabine. Given its increasing use, we highlight the importance of timely and aggressive treatment in order to minimize long-term health effects.

Acknowledgments Roche and Prince of Wales Hospital compassionately funded the rituximab doses for these patients.

Compliance with ethical standards

Conflict of interest David Goldstein has been an unremunerated advisor to Lilly, Celgene and Roche.

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