Eculizumab in Gemcitabine-Induced Thrombotic Microangiopathy: Experience of the French Thrombotic Microangiopathies Reference Centre

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Abstract

Background

Gemcitabine is a broadly prescribed chemotherapy, the use of which can be limited by renal adverse events, including thrombotic microangiopathy (TMA).

Methods

This study evaluated the efficacy of eculizumab, a monoclonal antibody targeting the terminal complement pathway, in patients with gemcitabine-induced TMA (G-TMA). We conducted an observational, retrospective, multicenter study in 5 French centres, between 2011 and 2016.

Results

Twelve patients with a G-TMA treated by eculizumab were included. The main characteristics were acute renal failure (100%), including stage 3 acute kidney injury (AKI, 58%) and renal replacement therapy (17%), hypertension (92%) and diffuse oedema (83%). Eculizumab was started after a median of 15 days (range 4–44) following TMA diagnosis. A median of 4 injections of eculizumab was performed (range 2–22). Complete hematological remission was achieved in 10 patients (83%) and blood transfusion significantly decreased after only one injection of eculizumab (median of 3 packed red blood cells (range 0–10) before treatment vs 0 (range 0–1) after one injection, $P < 0.001$). Two patients recovered completely renal function (17%), and 8 achieved a partial remission (67%). Compared to a control group of G-TMA without use of eculizumab, renal outcome was more favourable. At the end of the follow up, median eGFR was 45 vs 33 ml/min/1.73m^2 respectively in the eculizumab group and in the control group.

Conclusions

These results suggest that eculizumab is efficient on haemolysis and reduces transfusion requirement in G-TMA. Moreover, eculizumab may improve renal function recovery.

Key Points

- In G-TMA, eculizumab is efficient in controlling the hematological disorders and may improve renal function recovery
- C5b9 deposits in kidney biopsies suggest the role of complement activation in gemcitabine-induced TMA

Background

Thrombotic microangiopathy (TMA) syndromes are characterized by a microangiopathic hemolytic anemia, peripheral thrombocytopenia, and organ injury of variable severity[1]. The principal subtypes of TMA are thrombotic thrombocytopenic purpura (TTP) mainly due to anti-ADAMTS13 autoantibodies and the hemolytic uremic syndrome (HUS) associated with shigatoxin-related endothelial toxicity or with complement alternative pathway dysregulation. TMA may also result from drug exposure, the most usual agents being calcineurin inhibitors, quinine, antiplatelet agents as well as antineoplastic agents[2]. Gemcitabine is a pyrimidine antimetabolite used for the treatment of a wide range of malignancies. The reported incidence of gemcitabine-induced TMA (G-TMA) in the literature was initially low (0.015%)[3] but an important number of cases have been documented in the literature since, with the increasing use of gemcitabine[4–7].

Beyond permanent discontinuation of gemcitabine and supportive care, the management of G-TMA is not well codified[5,8]. As opposed to TTP, G-TMA generally responds poorly to therapeutic plasma exchange (TPE) and prognosis is dismal[9]. Although there is no complement alternative pathway-related abnormalities described, the usual severe renal involvement and the normal activity of the von Willebrand factor-cleaving protease ADAMTS13 relate G-TMA to atypical HUS, in which complement blockade is remarkably efficient[10]. Single reports suggested the efficacy of eculizumab in G-TMA[11], a monoclonal antibody directed against the complement protein C5 that has been approved for treatment of atypical HUS. In this context, the present study evaluated the efficacy of eculizumab in a retrospective series of patients with G-TMA.

Methods

Study design

We conducted an observational, retrospective, multicenter study including all patients with G-TMA treated by eculizumab in 5 French centres, between 2011 and 2016.

Patients

Patients who were included in the study met the following criteria: evidence of microangiopathic hemolytic anemia, including schistocytes on peripheral blood smear, thrombocytopenia, increased lactate dehydrogenase levels, low serum haptoglobin and/or renal TMA proven by kidney biopsy. Patients with a TMA attributed to an uncontrolled cancer, as defined by erythromyelemia, metastatic bone marrow infiltration, impaired general condition, and low-cumulative dose

gemcitabine were excluded[11–13]. Patients treated with another chemotherapy concomitantly than gemcitabine were excluded. Patient with a positive shiga-toxin or ADAMTS13 activity <10% were also excluded.

Patients were treated with eculizumab according to the regimen previously reported[14]. It consisted generally in 4 weekly infusions 900 mg IV. In responders, a maintenance treatment was started every two weeks at week 5, 1200 mg. The number of infusions was left at the discretion of the practitioner.

Hematological and renal responses were evaluated, based on data that were systematically extracted from the clinical record. Hematological response was defined by normalization of hematologic values (a normal platelet count and lactate dehydrogenase level) as previously described[14]. The transfusion needs were calculated over a period going from the admission of the patient to the end of the treatment with eculizumab. Renal response was considered as complete if serum creatinine level returned to baseline and as partial if serum creatinine level decreased by 15% or more.

Acute renal injury (AKI) was assessed according to KDIGO classification 2012. To make possible the comparison between the two groups, we chose to use the CKD-EPI formula for the estimation of the eGFR (glomerular filtration rate), despite we are aware of the limits in the context of AKI. The eGFR of dialysed patients was estimated at 0ml/min.

We compared patients with G-TMA treated with eculizumab with a control cohort of patients who didn't receive eculizumab treatment. Using the French national network, 14 patients were selected using criteria of G-TMA described above without eculizumab therapy. Patients were matched by age and baseline renal function.

This study was approved by the institutional review board of Rouen University Hospital in accordance with the Declaration of Helsinki, and the French Data Protection Authority ("Commission Nationale Informatique et Libertés," CNIL, authorization n°911539, and "Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé," CCTIRS, authorization n°11.537, Paris, France).

Statistical methods

Median with range and percentage (%) were respectively determined for continuous and categorical variables. Differences between groups were assessed by the chi-square test or Fisher's exact test for categorical variables and by the Mann–Whitney U test for continuous variables[15].

Results

Twelve patients with a G-TMA treated by eculizumab were included (10 women, 2 men). None had a past history of chronic renal failure. Gemcitabine was prescribed for ovarian (n = 5, 41.7%), pancreatic (n = 4, 33.3%), pulmonary (n = 2, 16.7%) or uterine (n = 1, 8.3%) cancer. TMA occurred after a median of 6 months (range 1.7–16) after initiation of gemcitabine and a median cumulative dose of 31.2g (range, 9.0–48.0) (**Table I**). The main characteristics were microangiopathic hemolytic anemia (100%), thrombocytopenia (92%), negative shiga-toxin and ADAMTS13 activity > 10% (100% both), acute renal failure (100%), including stage 3 acute kidney injury (AKI, 58%), and renal replacement therapy (17%), hypertension (92%) and diffuse oedema (83%). The median maximum serum creatinine level was 21mg/l (range, 10–76). Quantitative analysis of the complement alternative pathway (CFH, CFI, C3, C1 inhibitor, CD46/MCP and anti-factor H antibodies) was available in 9 patients (75%), and revealed no factor deficiency. Screening for genetic mutation was performed for one patient and was negative. Bone marrow aspiration was realized in 4 patients with no evidence of metastatic infiltration.

Table I. Clinical features of patients in the eculizumab group.

Patient	Age (years old)	Type of cancer	Cumulative dose of gemcitabine (mg)	Time to eculizumab initiation (days) after TMA / Number of injection	Staging of AKI	Hemoglobin level (g/dl)	Platelets rate (G/l)	LDH level (x normal)	Serum Creatinine level at diagnosis (mg/l)	Hematological response	Renal response
1	36	Ovarian	23760	7 d / 4	2	9.3	76	1.8	18.0	Yes	Partial
2	64	Ovarian	16300	7 d / 3	3, RRT	6.9	23	2.5	28.0	No	No
3	54	Pancreatic	31000	44 d / 22	2	8.5	27	2.2	14.3	Yes	Partial
4	69	Pancreatic	9040	27 d / 3	3, RRT	7.3	11	2.4	18.0	No	No
5	64	Ovarian	48000	13 d / 7	2	9.7	130	2.2	22.5	Yes	Partial
6	68	Pancreatic	30000	34 d / 14	3	7.9	13	4.6	17.1	Yes	Complete
7	59	Pulmonary	31200	6 d / 5	3	11.0	137	1.5	31	Yes	Partial
8	57	Pulmonary	42500	26 d / 4	3	7.6	150	1.5	76	Yes	Partial
9	52	Uterine	47000	4 d / 2	3	8.7	48	2.2	70	Yes	Partial
10	50	Pancreatic	15000	19 d / 2	1	8.0	139	2.2	10.2	Yes	Complete
11	56	Ovarian	38000	18 d / 3	3	7.3	144	3.7	24	Yes	Partial
12	55	Ovarian	32000	7 d / 4	3	8.1	122	1.8	64	Yes	Partial

TMA = Thrombotic microangiopathy; AKI = Acute kidney injury (AKI was assessed according to KDIGO classification 2012), LDH = Lactate dehydrogenase; RR therapy.

Table II. Characteristics of patients in the control group.

Patient	Age (years old)	Type of cancer	Staging of AKI	Hemoglobin level (g/dl)	Platelets rate (G/l)	LDH level (x normal)	Serum Creatinine level at diagnosis (mg/l)	Hematological response	Renal response	Outcome / Time to death or time of last follow-up for still alive patients (months)
1	56	Pancreatic	3	12.3	79	1.9	44	Yes	Partial	Deceased / 72m
2	33	Ovarian	2	6.2	58	1.4	18	Yes	Partial	Deceased / 10m
3	80	Pancreatic	2	7.3	81	1.7	10	Yes	Complete	Deceased / 14m
4	65	Pancreatic	3	9.7	70	1.2	35	Yes	Partial	Deceased / 18m
5	74	Pancreatic	3, RRT	9.7	34	2.9	35	No	No	Alive / 3m
6	66	Pulmonary	3, RRT	4	146	3.9	94	Yes	No	Deceased / 1m
7	59	Pancreatic	3	6.9	85	1.5	41	Yes	Partial	Alive / 3m
8	55	Pancreatic	3	8.7	100	3.0	41	Yes	No	Deceased / 2m
9	78	Pancreatic	3	7.2	450	1.0	29	Yes	Complete	Alive / 24m
10	56	Breast	2	7.5	61	1.0	17	Yes	Complete	Alive / 2m
11	58	Hepatic	3, RRT	10.4	42	6.5	32.4	Yes	No	Deceased / 8m
12	60	Pancreatic	3	8.7	202	2.5	23	Yes	No	Deceased / 7m
13	52	Hepatic	3	9.1	96	5.8	50	Yes	Partial	Deceased / 10m
14	73	Pancreatic	3	9.9	430	3.1	29	Yes	Partial	Deceased / 14m

TMA = Thrombotic microangiopathy; AKI = Acute kidney injury (AKI was assessed according to KDIGO classification 2012), LDH = Lactate dehydrogenase; RRT = Renal replacement therapy.

Renal TMA was proven by kidney biopsy in 3 cases. We compared our patients with 4 patients who had a kidney biopsy for glomerular diseases (minimal change disease). By immunofluorescence, we found deposits of the membrane attack complex C5b9 along the glomerular and tubular membrane and also in the capillary wall in our patients as compared to control patients, suggesting the activation of complement cascade in this form of TMA (Fig. 1).

All patients had their gemcitabine treatment stopped. First-line therapeutic plasma exchange (TPE) was performed in 5 patients (42%), with a median of 7 sessions (range 4–9) without significant benefit on hemolysis or renal function recovery. Eculizumab was started after a median delay of 15 days (range 4–44) following TMA diagnosis. A median of 4 injections (900 mg/injection, total 3600mg) of eculizumab was administered (range 2–22). Of note, only three patients had received more than four injections of eculizumab. Hematological response was obtained in 10 patients (83%) and blood transfusion significantly decreased after the first infusion of eculizumab (median of 3 packed red blood cells (range 0–10) before treatment vs 0 (range 0–1) after one injection, $p < 0.001$) (Fig. 2). Two patients recovered renal function completely (17%), and 8 achieved a partial renal response (67%), with a median reduction of 8.5mg/l of maximum creatinine level (range 2.5–47) (**Table I**). After a median follow-up of 13 months, seven patients (58%) had persistent chronic renal failure with an estimated glomerular filtration rate (eGFR) below 60ml/min/1.73m^2. No treatment-associated adverse event was reported. Especially, no meningococcal infection was recorded during follow-up. No exacerbation or relapse of TMA were recorded after eculizumab discontinuation. Six patients (50%) died during follow-up, as an indirect complication of TMA with hemorrhagic shock (1 case) despite eculizumab treatment, or to cancer progression after a median of 9 months (range 2–13) following eculizumab initiation (5 cases). Six patients (50%) were in complete hematological response and at least partial renal response of TMA after eculizumab discontinuation allowing a switch to another antineoplastic agent (**Table I**).

We compared patients with G-TMA treated with eculizumab with a control cohort of 14 patients who didn't receive eculizumab treatment (**Table II**). TPE were performed in 8 of them. Median baseline eGFR was comparable in the 2 groups, 95 (47–147) ml/min/1.73m^2 in the control group and 106 (59–132) ml/min/1.73m^2 in the eculizumab group. Compared to the control cohort, patients with G-TMA treated by eculizumab had a better renal outcome (Fig. 3). 83% of patients in eculizumab group had improvement of their renal function versus 64% in control group, and median eGFR was 45 (0-119) vs 33 (0–66) ml/min/1.73m^2 respectively at the end of the follow up (**Table III**). Of note, 2 patients (16%) still had end stage renal failure in the eculizumab group versus 3 patients (21%) in the control group.

Table III. Outcome of patients.

	Eculizumab group N = 12 (%)	Control group N = 14 (%)
Renal response	10 (83)	9 (64)
Partial	8 (66)	6 (43)
complete	2 (17)	3 (21)
eGFR at onset (ml/min/1.73m$^{2)}$	19 (0–76)	12 (0–31)
eGFR at the end of follow up	45 (0-119)	33 (0–66)

eGFR = estimated glomerular filtration rate. Quantitative values are expressed as median with range.

Discussion

We report here the largest case series of G-TMA treated by eculizumab. In our patients, we found that the transient use of eculizumab was efficient in controlling the hematologic disorders, by reducing significantly transfusion needs and by correcting thrombocytopenia. Remarkably, hematologic improvement was usually observed just after the two first injections of eculizumab, which strongly suggests a therapeutic action of eculizumab. As in atypical HUS[14,16], the use of eculizumab in G-TMA may improve renal function recovery. Indeed, 83% of patients in our study had a complete or partial renal remission within 2 to 4 weeks after complement blockade, suggesting again that eculizumab was efficient in controlling TMA. This two-step response with first a rapid improvement in cytopenias after the initiation of eculizumab followed by a more progressive renal improvement is reminiscent of the schedule of response observed in atypical HUS[14].

The pathophysiology of G-TMA is not well established. However, our data show C5b9 deposits in kidney biopsies supporting the hypothesis that the pathophysiology of G-TMA is at least partially related to complement activation, which may result from a direct endothelial toxicity of the drug. This transient complement activation seems to have no genetic background. A recent work has not revealed any pathogenic variant involved in the regulation of the alternate pathway of complement[17].

Reports of patients with G-TMA treated by eculizumab are rare[18-27]. To our knowledge, only 13 cases have been reported in literature, and a similar good outcome was observed. However, these results must be interpreted with caution due to publication bias. As opposed to the hematological response, renal remission is generally observed later and may occur after several weeks because of the process of endothelial healing. One could hypothesize that, similar to atypical HUS, an earlier initiation of eculizumab could allow a greater improvement in renal function recovery[14]. Moreover, there has been no exacerbation or relapse of TMA following eculizumab discontinuation, suggesting that a limited number of infusions may be sufficient to control the TMA process, in association with definitive gemcitabine withdrawal.

Although eculizumab raises cost concerns, these considerations should be weighted against a decreased burden of care, including lower transfusion needs, reduced needs for TPE, and possibly less renal replacement therapy with reduced length of hospitalisation in the intensive care unit during the early stages of AKI. As a result, this strategy could allow a significant improvement in patients' quality of life, particularly when the underlying malignancy has a favourable prognosis.

Our results have the usual limitations of those of a retrospective study; moreover, the number of patients is relatively limited. Therefore, further larger controlled studies are needed to definitely confirm our results. These studies should also address whether gemcitabine should be considered contraindicated after resolution of G-TMA.

List Of Abbreviations

AKI
Acute Kidney Injury
eGFR
Estimated Glomerular Filtration Rate
G-TMA
Gemcitabine-induced Thrombotic Microangiopathy
HUS
Hemolytic Uremic Syndrome
LDH
Lactate Dehydrogenase
RRT
Renal Replacement Therapy

TMA
Thrombotic Microangiopathy
TPE
Therapeutic Plasma Exchange
TTP
Thrombocytopenic Thrombotic Purpura

Declarations

Ethics approval and consent for participate : All patients and/or parents/guardians provided written informed consent for entry into the current study. This study was approved by our institutional review board (Rouen University Hospital) in accordance with the Declaration of Helsinki, and the French Data Protection Authority ("Commission Nationale Informatique et Libertés," CNIL, authorization n°911539, and "Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé," CCTIRS, authorization n°11.537, Paris, France).

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AUTHORSHIP CONTRIBUTION

MG and SG performed and design the research, and analysed the data.

MG, SG and PC wrote the paper.

All authors provided cases and have read and approved the final version of the manuscript.

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Figures

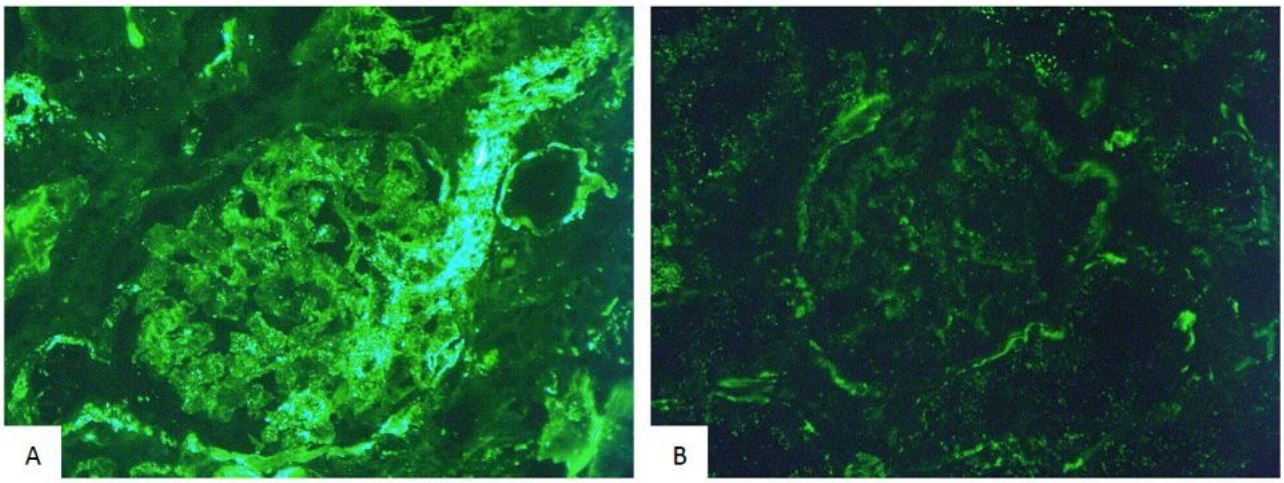

Figure 1

Kidney biopsy in gemcitabine-induced TMA. By immunofluorescence, kidney biopsy of G-TMA patients (A) showed deposits of membrane attack complex C5b9 in the glomerular and tubular membrane and also in the capillary walls, as compared to control patients with glomerular disease (minimal change disease) (B).

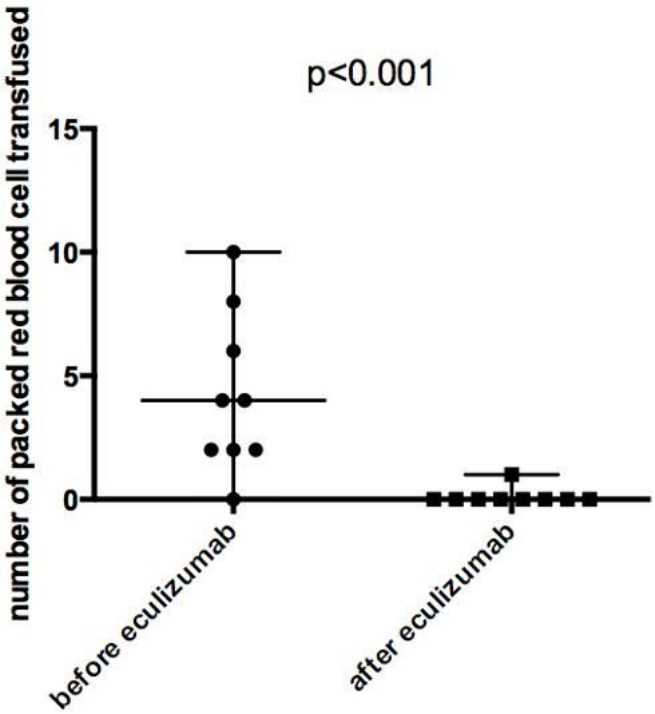

Figure 2

Comparison of packed red blood cell transfusion before and after eculizumab therapy. Quantitative values are expressed as median with range.

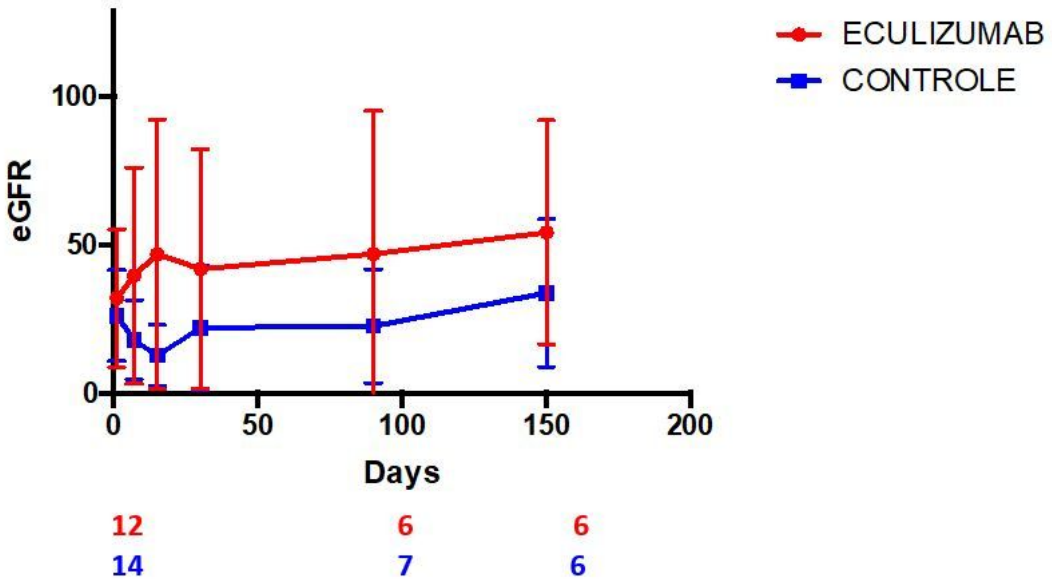

Figure 3

Evolution of renal function as a function of time in the eculizumab group and in the control group. Values expressed as mean and standard deviations

Supplementary Files

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- SupplementalData.docx