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Mitomycin C-Induced Renal Toxicity, a Dose-Dependent Side Effect?

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Abstract—*Mitomycin C (MMC) has been known to be nephrotoxic since* 1971. *Whether this side effect was dose-dependent is unknown, while data on incidence are scanty. The presently-reported prospective study was initiated with the objective to obtain more data on these subjects. Forty-four patients treated with MMC entered the study,* 37 *were evaluable. All patients were subjected to extensive serial laboratory tests to study renal function and to detect hemolysis or coagulation disorders. The results were evaluated per cumulative dose level. One patient developed a lethal hemolytic uremic syndrome after* 40 *mg/m*^{2} *MMC. None of the laboratory tests predicted this side effect. None of the other patients developed renal toxicity, while all laboratory tests remained within normal ranges. All available literature on this subject was also reviewed. Based on the results of the present study, as well as on the literature review, it is concluded that MMC-related renal toxicity is a dose-dependent side effect, occurring at cumulative dose levels of* 30 *mg/m*^{2} *or more. The incidence is likely to be less than* 10%. *Predictive laboratory test could not be indicated.*

INTRODUCTION

SINCE 1971 Mytomycin C (MMC), an antitumor antibiotic isolated from fermentation filtrates of *Streptomyces caespitosus*, is known to induce renal toxicity in man. Liu *et al.* [1] were the first to report this side effect. At present more than 150 cases have been reported [2]. Most often this renal toxicity is part of a hemolytic uremic syndrome (HUS), but also non-hemolytic renal failure and hemolysis without renal failure have been reported. These toxicities are almost always lethal.

At present MMC is more frequently included in studies on adjuvant chemotherapy, for example, in gastric and cervical cancer. The objectives of such treatment, being cure or improved survival, do not permit the development of potentially lethal side effects of the treatment applied. Data on frequence of occurrence and early detection possibilities of MMC-induced renal toxicity are not well-documented. In order to gain more knowledge on this subject, we initiated a prospective study with detailed monitoring of the patient during treatment with MMC. Also, the literature was reviewed.

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MATERIALS AND METHODS

Forty-four patients receiving MMC as a single agent or included in a combination regimen entered the study. Patient characteristics are given in Table 1. None of the patients had shown signs of hemolysis or renal function impairment during

Table 1. Patient characteristics

No. of patients entered:	44
No. of evaluable patients:	37
Sex:	
male	18
female	19
Age (years):	
median	57
range	26–71
Performance score (WHO):	
median	1
range	0–3
Tumor type:	
breast cancer	13
gastric cancer	8
prostatic cancer	6
miscellaneous	10
Treatment:	
MMC	16
MMC/Cisplatin	9
MMC/Doxorubicin	2
MMC/Doxorubicin/5-FU	10

the evolution of their disease, nor were such signs present before the start of the study.

All patients received MMC as an i.v. bolus, repeated every 4–8 weeks until tumor progression or finalizing of adjuvant chemotherapy. Two patients received doses of 6 mg/m^2, two received 8 mg/m^2 and 40 received doses of 10 mg/m^2. Prior to each subsequent administration of MMC, patients were monitored by physical examination, hematology screen including hemoglobin, reticulocyte count and white blood cell and platelet counts plus peripheral blood smear, haptoglobin, coagulation tests including cephaline time, thrombotest, fibrinogen and antithrombin III, serum and 24 hr urinalysis including sodium, potassium, calcium, phosphate, magnesium, albumin, creatinine and creatinine clearance. Also A_1- and B_2-microglobulin were determined in the urine. A final check-up was performed 2 months after the last administration of MMC, either if the drug had been given for advanced disease, or in an adjuvant chemotherapy setting. The urinary excretion values on electrolytes and A_1- and B_2-microglobulin were analyzed statistically by means of a Wilcoxon–Wilcox test.

RESULTS

Seven patients were inevaluable because of tumor-related early death. All remaining 37 patients were considered evaluable at the cumulative dose level of 1–10 mg/m^2, 27 patients at the dose level of 11–20 mg/m^2, 20 patients at 21–30 mg/m^2, 13 at 31–40 mg/m^2 and 7 at 41–50 mg/m^2. One of the 37 evaluable patients developed a hemolytic uremic syndrome. This was a 66-year-old male treated with single agent MMC because of an advanced cholangiocarcinoma. The patient was well until admission because of extreme tiredness. He had received a cumulative dose of MMC of 40 mg/m^2, and the last dose was administered 6 weeks before admission. Previously, laboratory tests had not revealed any abnormality. On admission there were no specific physical signs. Laboratory tests revealed a hemoglobin of 7.2 mmol/l (normal 8–10 mmol/l), WBC of 8.5 × 10^9/l with many fragmented white blood cells in the smear, platelet count of 90 × 10^9/l, nondetectable haptoglobin, normal coagulation tests, negative Coombs test, elevated serum creatinine of 145 μmol/l/m^2 (normal 30–80 μmol/l/m^2) serum lactate dehydrogenase 233 U/l (N < 175/U/l), bilirubin 13 μmol/l (N < 12), and proteinuria of 3 g/24 hr as well as 20–25 red blood cells per high power field in the urine.

Tests for circulating immune complexes or platelet auto-antibodies were not performed. The diagnosis of MMC-induced HUS was established. The patient refused any further treatment. He became anuric after 8 days and died at home 2 days later. Autopsy was not performed. In this patient the regular screening tests failed to predict the develpment of HUS. No other cases of HUS or renal toxicity were observed in this series. The most important parameters are given in Table 2. Serum creatinine levels did not change significantly. The high S.E.M. at a cumulative dose of 31–40 mg/m^2 is caused by the increase in creatinine in the reported patient.

There were no significant changes in creatinine clearance, nor in serum electrolytes. Additional coagulation tests changed neither. The excretion of electrolytes in the urine showed wide variations

Table 2. Changes in parameters for hemolysis and renal function (median ± 2 S.E.M.) during treatment with mitomycin C

Parameter	Normal value range	Before treatment	Cumulative MMC dose (mg/m^2) 1–10 (n = 37)	11–20 (n = 27)	21–30 (n = 20)	31–40 (n = 13)	41–50 (n = 7)
Haptoglobin (G/L)	0.3–2.0	2.5±0.38	2.2±0.4	2.1±0.5	2.1±0.5	1.8±0.6	1.8±0.8
Creatinine (μmol/l/m^2)	30–80	44±3	43±2	42±3	46±4	49±16	47±6
Creatinine Clearance (ml/min)	80–120	88±12	81±10	89±12	87±13	91±15	85±19
Sodium (mmol/l)	135–145	138±1	138±1	138±1	138±2	138±2	138±2
Potassium (mmol/l)	3.9–5.1	4.2±0.1	4.2±0.1	4.1±0.1	4.2±0.2	4.0±0.2	4.3±0.3
Calcium (mmol/l)	2.15–2.50	2.36±0.04	2.38±0.04	2.32±0.06	2.37±0.08	2.38±0.06	2.38±0.1
Phosphate (mmol/l)	0.80–1.30	1.07±0.06	1.06±0.05	1.05±0.08	1.07±0.07	1.03±0.10	1.11±0.12
Magnesium (mmol/l)	0.80–1.05	0.84±0.03	0.82±0.03	0.82±0.04	0.82±0.04	0.87±0.04	0.88±0.06

but all values were normal. The urinary excretion of A_1- and B_2-microglobulin also varied widely. Ranking of the results did not reveal significant changes. Except for the single patient with HUS, 6 additional patients developed erythrocyturia. In four of them this occurred during menses, urinary tract infection or introduction of a urinary catheter. One patient developed erythrocyturia after 10 mg/m^2 of MMC, coincided by proteinuria. There was no explanation for these symptoms, and they resolved spontaneously. No further MMC was administered to this patient.

Finally, one patient had erythrocyturia after 45 mg/m^2 of MMC, with red blood cell casts but without proteinuria or other signs. In this patient, MMC was discontinued because of tumor progression, the urinary changes disappearing spontaneously. The patient died 2 months later, without signs of renal impairment. The only case of HUS in this series developed after the administration of a cumulative dose of 40 mg/m^2 of MMC. In this study the overall frequency of HUS in 37 patients was 3%. If one considers only the subgroup of 13 patients who received a cumulative dose of more than 30 mg/m^2, the frequency was 7.7%.

DISCUSSION

This prospective study again suggests that MMC may induce HUS, as we observed one patient developing the syndrome after a cumulative dose of 40 mg/m^2. Most of the previous reports on this side effect [1–35] are case reports lacking data on the total numbers of patients treated. Data on the frequency of MMC-induced HUS or renal toxicity can only be derived from a few retrospective series [1, 3–10]. In those studies the frequency of renal toxicity caused by MMC varies from 2 to 25%. In a total of 965 patients treated, 85 developed renal toxicity. The mean incidence in those studies is 9%. Only three of those studies report on the relation of the frequency of renal toxicity and cumulative dose of MMC.

Ratanatharathorn *et al.* [3] retrospectively studied 171 patients receiving MMC/5-FU in a SWOG study. In 130 patients receiving less than 100 mg of MMC they observed 9 cases of renal toxicity (7%), while in 41 patients receiving more than 100 mg they observed 8 cases of renal toxicity (20%). Valavaara *et al.* [10] had similar findings in a retrospective analysis of 118 patients treated with MMC/Ftorafur. At a cumulative dose less than 50 mg/m^2 only 1 out of 63 patients developed toxicity (2%), while toxicity occurred in 4 out of 37 patients (11%) receiving a cumulative dose of 50–70 mg/m^2, and in 5 out of 18 patients (28%) receiving a cumulative dose of 70 mg/m^2 or more. Fielding *et al.* [8] observed 24 cases (8.5%) of HUS in 281 patients receiving two different combinations of chemotherapy including MMC as adjuvant treatment for gastric cancer. None of these complications occurred at a total dose of less than 1.2 mg/kg (equal to 40–50 mg/m^2). Interestingly, no complications of this kind occurred in a control group of 130 patients not receiving adjuvant chemotherapy, again suggesting that this side effect may be attributed to MMC. Data on cumulative dose could also be depicted from the case reports of 88 patients [1, 2, 4–7, 9, 11–34]. The median cumulative dose was 60 mg/m^2 (range 30–150 mg/m^2). None of those patients received less than 30 mg/m^2. Twenty-one received 30–50 mg/m^2, 21 50–70 mg/m^2 and 46 received a cumulative dose of more than 70 mg/m^2. These data indicate dose-dependency because one should keep in mind that the total number of treated patients will decrease as the cumulative dose level increases. The majority of reports on trials with MMC do not mention this side effect, possibly because most of the patients did not receive a high cumulative dose.

In our prospective study we only observed one case of HUS after a cumulative dose of MMC of 40 mg/m^2. Those literature data combined with our prospective data indicate that MMC can be administered safely up to a cumulative dose of 30 mg/m^2. Thus, treatments in particular on adjuvant chemotherapy, applying total MMC doses of 30 mg/m^2 or less, are not hazardous for the patient with respect to the development of severe renal toxicity. However, treatments applying higher cumulative doses, in particular if MMC is given as a part of combination chemotherapy, should be considered potentially nephrotoxic.

In case the dose of 30 mg/m^2 is exceeded, the availability of predictive signs would facilitate monitoring of the patient. Because we observed only one patient with renal toxicity in our study we cannot make a statement on possible predictive signs, although from the literature it is obvious that physicians should be alerted at the occurrence of proteinuria and microscopic hematuria as well as fragmented red blood cells in the blood smear.

All four patients with MMC-induced HUS previously seen at the Free University Hospital and the patient reported now, developed these signs, though in the latter patient they appeared only at the presence of a full-blown HUS. The other tests we performed in our prospective study did not indicate subclinical forms of renal toxicity or HUS.

Glomerular function did not change as shown by the values on serum creatinine and creatinine clearance. We did not observe tubular toxicity as indicated by the absence of changes in A_1- and B_2-microglobulin excretion. Both proteins can be used to detect tubular toxicity [36–38].

In the present study A_1-MG and B_2-MG excretion showed wide inter-individual fluctuations even if expressed as ratio to creatinine in the urine. In a Wilcoxon–Wilcox analysis the changes were not significant. For this reason we cannot suggest tubulotoxicity of MMC in man at the dose levels studied. This is in contrast with our findings in Wistar rats, but in the latter study other parameters such as *N*-acetyl-β glucosaminidase and alaninaminopeptidase were used [39]. In rats and mice MMC appears to be tubulotoxic [39–41].

In the present study, none of the serially-studied coagulation parameters changed during the observation period. In the patient developing a HUS, we did not find any evidence for intravascular coagulation. Besides, in two of our other HUS patients, adequate data were available to exclude intravascular coagulation. Thus, intravascular coagulation as the initial event in the development of MMC-induced HUS appears to be unlikely. On the other hand, aggravation of the syndrome after red cell transfusions has been suggested to be related to activation of intravascular clotting [2].

In conclusion, the MMC-induced HUS is dependent on the cumulative administered dose of MMC, occurring at doses higher than 30 mg/m^2. MMC can be administered safely up to this dose level, without intensive monitoring of the patient. However, at higher doses the drug should be considered to be potentially nephrotoxic and requires adequate monitoring, especially when given in combination chemotherapy.

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