Review Article

Mitomycin C-induced hemolytic uremic syndrome. Six case reports and review of the literature on renal, pulmonary and cardiac side effects of the drug

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\section*{Summary}

Six new cases of mitomycin C (MMC)-induced hemolytic uremic syndrome are reported and the literature on renal-, pulmonary- and cardiotoxicity of the drug is reviewed. The number of reports concerning these side effects is still increasing. The incidence of all three side effects will be below 10\%, while there appears to be a dose-dependency, with toxicity mainly occurring at cumulative doses of 20–30 mg/m\textsuperscript{2} or more. Toxicity often develops very sudden and the mortality rate especially of HUS is very high despite supportive care. The pathogenesis of toxicity is still unknown, although for HUS there are indications for a role of circulating immune complexes. The pulmonary toxicity can often be treated by corticosteroids, while the left ventricular cardiac failure can be treated with diuretics. The possible role of oxygen radicals in the development of MMC side effects is mentioned.

\section*{Introduction}

Since the last decade it has become well known that mitomycin C (MMC), an antitumor antibiotic isolated from Streptomyces caespitosus, induces renal-, pulmonary- and cardiotoxicity in man. The first reports on these side effects were published between 1971 and 1978 [43,49,63] and since then additional data have been rapidly accumulating. Unfortunately, all three types of toxicity appear to be unpredictable [69], while the mortality rate varies from 25\% for cardio- and pulmonary toxicity, to 95\% for renal toxicity [68,69]. Cardiotoxicity is expressed by left ventricular failure, pulmonary toxicity by interstitial pneumonitis, while renal toxicity most often is expressed as a hemolytic uremic syndrome (HUS), although renal failure or microangiopathic hemolytic anemia may also occur as single side effect. We presently report 6 new cases of HUS induced by MMC. Also an extensive review

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TABLE I
Patient characteristics.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
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</thead>
<tbody>
<tr>
<td>Cumulative dose of MMC (mg/m²)</td>
<td>MMC</td>
<td>MMC</td>
<td>BEMP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>MMC</td>
<td>BEMP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>FAM&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Anemia</td>
<td>+</td>
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<td>Thrombocytopenia</td>
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<td>+</td>
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<td>−</td>
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<td>+</td>
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<tr>
<td>Fragmentocytes</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Proteinuria</td>
<td>+</td>
<td>+</td>
<td>ND&lt;sup&gt;c&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Erythrocyturia (RBC/HPF)</td>
<td>20–25</td>
<td>ND&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10–15</td>
<td>10–15</td>
<td>20–25</td>
<td>15–20</td>
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<tr>
<td>Serum creatinine (µmol/l)</td>
<td>145</td>
<td>273</td>
<td>446</td>
<td>149</td>
<td>430</td>
<td>185</td>
</tr>
<tr>
<td>Latency period (wks)</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Survival</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>8</td>
<td>3</td>
<td>2</td>
</tr>
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</table>

<sup>a</sup> BEMP, Bleomycine/vindesine/MMC/cisplatin.
<sup>b</sup> FAM, 5-fluorouracil/Adriamycin/MMC.
<sup>c</sup> ND, not done.

of the literature on renal-, pulmonary- and cardiac side effects of the drug will be given.

Case reports (Table I)

**Patient A**, a 66-year-old male, was treated with MMC 10 mg/m² i.v. every 6 weeks because of an advanced cholangiocarcinoma, achieving a stable disease. He was free of symptoms until admission because of general fatigue, 6 weeks after the last administration of MMC. The cumulative dose then was 40 mg/m². As a part of a study protocol this patient underwent frequent laboratory tests until 2 weeks before admission, which did not reveal any abnormality. However, on admission hemoglobin was 7.2 mmol/l (normal: 8–10 mmol/l), WBC was 8.5 × 10⁹/l with fragmented red blood cells in the smear, platelets were 90 × 10⁹/l (normal > 120 × 10⁹/l).

Haptoglobin could not be detected, coagulation tests were normal, Coombs test negative, serum creatinine elevated 145 µmol/l (normal < 100 µmol/l), serum lactate dehydrogenase (SLDH) 233 U/l (normal < 175 U/l), bilirubin 13 µmol/l (normal < 12 µmol/l).

Urinalysis showed a proteinuria of 3 g/24 h and 20–25 red blood cells per high power field.

A MMC-induced HUS was diagnosed. The patient refused any further treatment and died at home 10 days later, having become anuric shortly before. Autopsy was not performed.

**Patient B**, a 50-year-old male, underwent a rectum amputation followed by 1 year of adjuvant i.v. 5-fluorouracil (5-FU) because of rectal cancer, Astler-Collar stage C₂, 3 years before. In 1981 liver metastases were found and treatment with MMC 7.5 mg/m² was initiated. Hematology screen and renal function were normal. In July 1982 anemia was noted. The cumulative dose of MMC had been 75 mg/m². Hemoglobin was 5.0 mmol/l, WBC 4.6 × 10⁹/l with fragmented red blood cells in the smear (Fig. 1), platelets were 60 × 10⁹/l and serum creatinine 273 µmol/l.

Some weeks later the patient was admitted because of acute dyspnea. Blood pressure appeared to be 240/130 mmHg and there were moist rhales at the base of both lungs. Laboratory tests included hemoglobin 3.3 mmol/l, WBC 5.1 × 10⁹/l with lots of fragmented red blood cells in the smear, platelets 36 × 10⁹/l, serum creatinine 615 µmol/l, bilirubin normal, SLDH > 600 U/l. Coagulation tests were
normal. No urinalysis nor haptoglobin determination was done. The chest-film was consistent with signs of left ventricular failure. Despite intensive treatment the patient died after several hours. At autopsy glomerulosclerosis (Fig. 2) with deposition of fibrinoid material and tubuli with protein casts were noted, consistent with changes of HUS. Also an interstitial lung fibrosis was found (Fig. 3).

Patient C was a 30-year-old female with squamous cell cervical cancer previously treated with irradiation. She was known to have auto-antibodies against erythrocytes without active signs of hemolysis. In August 1984 lung metastases were found and she started treatment with bleomycin, vindesine, cisplatin and MMC (8 mg/m² i.v. per cycle). Two weeks after the second cycle hemoglobin suddenly dropped to 3.0 mmol/l, WBC 12.8 × 10⁹/l with fragmented red blood cells in the smear, platelets 35 × 10⁹/l, serum creatinine 446 µmol/l, bilirubin 76 µmol/l, SLDH 292 U/l, haptoglobin non-detectable, while urinalysis revealed proteinuria and microscopic hematuria. A MMC-induced HUS was suggested. After red cell transfusions deterioration of all laboratory parameters was noted. Shortly after the patient died of peritonitis caused by perforation of the small intestine.

Patient D was a 65-year-old female with advanced breast cancer. She had extensively been pretreated with 5-FU, doxorubicin, cyclophosphamide, methotrexate and vincristine. Because of progressive disease single agent MMC treatment (10 mg/m² for 6 weeks) was initiated, achieving a stable disease. Six weeks after the last MMC administration (cumulative dose 47.5 mg/m²) an asymptomatic anemia was noted. Laboratory findings were hemoglobin 5.1 mmol/l, normal WBC and platelet counts but a lot of fragmented red cells in the blood smear, serum creatinine 149 µmol/l, creatinine clearance 26 ml/min, SLDH 223 U/l, no detectable haptoglobin, negative Coombs test, and proteinuria and microscopic hematuria at urinalysis. A MMC-induced HUS was presumed. No red blood cell transfusions were given. After a 2-month period of continuous low-grade hemolysis the
patient died due to tumor progression. Autopsy showed similar renal changes as in patient B.

Patient E was a 54-year-old female with disseminated squamous cell cervical cancer, treated with vindesine, bleomycin, cisplatin and MMC (6–8 mg/m² per alternating cycle), achieving a complete remission. Four weeks after the last administration of MMC (cumulative dose 40 mg/m²) the patient was admitted because of severe anemia. At admission blood pressure was normal, but moist rhales were found in both lungs. Hemoglobin was 4.0 mmol/l, WBC $6.0 \times 10^9$/l with fragmented red blood cells in the smear, platelets $41 \times 10^9$/l, SLDH 324 U/l, serum creatinine 430 µmol/l, bilirubin normal, haptoglobin non-detectable, Coombs test negative and bone marrow unremarkable. Coagulation tests were normal. Urinalysis showed proteinuria and microscopic hematuria. The chest-film revealed interstitial changes and edema, while the radionuclide left ventriculography showed an ejection fraction of 73% (normal > 45%). Despite intensive supportive care the patient died of progressive renal- and respiratory failure 3 weeks later. Autopsy was not performed.

Patient F, a 50-year-old male, was treated with 5-FU, doxorubicin and MMC for advanced pancreatic cancer, achieving a stable disease. Five weeks after the last administration of MMC (cumulative dose 40 mg/m²) a red blood cell transfusion was given when hemoglobin was 6.0 mmol/l. Two weeks later he was admitted to the hospital because of severe anemia. Except for pallor, physical examination did not show abnormalities.

Laboratory findings included: hemoglobin 2.9 mmol/l, platelets $54 \times 10^9$/l, WBC $7.6 \times 10^9$/l, with many fragmented red blood cells in the smear, serum creatinine 185 µmol/l, creatinine clearance 58 ml/min, no detectable haptoglobin, negative Coombs test, elevated SLDH and serum bilirubin, increased percentage of the Clq binding-assay (32%) suggesting the presence of circulating immune complexes, proteinuria and microscopic hematuria. Coagulation tests were unremarkable. The chest-film showed pulmonary edema, while a radionuclide determined left ventricular ejection fraction was 55%, suggesting a non-cardial origin of the pulmonary edema.

The patient was treated with repeated red cell transfusions and plasmapheresis, resulting in normalisation of the Clq level, but not decreasing hemolysis nor improving renal function. A short trial with captopril medication and fluid administration did not improve renal function either. Finally, the patient became oliguric and died. No autopsy was performed.

Discussion

Renal toxicity

All patients reported in this paper had laboratory findings suggestive of, or histology confirming HUS, presumably caused by MMC. Renal disease induced by MMC in animals was already reported in the early sixties. The drug caused tubular necrosis in monkeys [53], tubular changes in mice [40,47] and hemorrhages in the renal cortex in dogs [53]. Also in Wistar rats laboratory changes suggestive of tubular damage have been found [69]. The first report on renal side effects of MMC in man was published by Liu et al. in 1971 [43]. Up to now 163 cases have been reported [3–5,7,10,12,14,18,20,24,26–28,31–34,36,38,39,41,45,46,51,52,54–58,60–62,65,68,72,74].

Clinically, the syndrome is often compatible with HUS, but also renal failure without hemolysis as well as microangiopathic hemolytic anemia (MAHA) without renal failure have been reported. Usually the patient presents with proteinuria, microscopic hematuria, anemia and thrombocytopenia (Table 1).

In case of hemolysis the Coombs test is always negative. The HUS is often coincided by non-cardiogenic alveolar edema, as was the case in patients B, E and F. Sometimes renal side effects and pulmonary side effects coexist, as was proven at autopsy in patient B. The renal side effects have a latency period of 0–8 months after the last administered dose of MMC, and are most of the time unpredictable [69] as in all of our patients. However, there are instances in which the hemolysis precedes renal failure for 1–2 months. All published patients
had an adenocarcinoma, several in complete remission.

In a retrospective literature study the incidence of MMC renal toxicity was found to be 9% in a total of 965 studied patients [69]. There also appears to be a dose dependency, with toxicity only occurring at cumulative doses of 30 mg/m² or more [69].

The possibility exists that the incidence actually is higher because in some rapidly progressive cases the patient may be suspected to die of tumor progression while in fact they had a HUS. In our patient B the diagnosis was only made at autopsy. While in animals MMC renal toxicity appears to be tubular, the pathologic changes in man are mainly glomerular. Basement membrane thickening, small infarcts, fibrin deposition in glomerular capillaries and tubular protein casts are found [24,27,32,43,51,55,68], just as in HUS due to other causes.

More specific for MMC-induced HUS are bizarre giant glomerular nuclear forms and degenerated nuclei, without specific immunofluorescence patterns. The causal role of circulating tumor cells [6,44] in MMC-induced HUS is still debatable, because most of the patients are found to be free of a clinically detectable tumor, as was patient E. In several patients circulating immune complexes and/or platelet auto-antibodies were found [10,68,74] as in our patient F. Cross-reaction of such circulating immune complexes to tumor antigen was shown by Zimmerman et al. [74]. They suggest that reduction of the tumor by chemotherapy might decrease a pre-existing state of antigen excess, thus permitting the formation of soluble antigenantibody complexes. In blood vessels such immune complexes can accumulate, inducing local vascular injury and initiating deposition of platelets and fibrin leading to a clinical HUS. In this situation HUS may even appear after disappearance of the tumor.

Plasmapheresis can reduce the immune complex level, but often does not lead to clinical improvement [10] (patient F). This might indicate that histological changes are often irreversible at the time of the appearance of clinical symptoms. In patient C the presence of erythrocyte autoantibodies was known before the start of MMC treatment. She developed HUS after an unusual low cumulative dose of the drug. Whether such a pre-existing state of subclinical auto-immune disease enhances the risk of MMC-induced HUS is not known.

Other possible pathogenetic factors might be local fibrin deposition preceded by the release of thromboplastin from tumor or red blood cells [6,11,29] or by a deficiency of a not yet specified plasma factor [35,59]. The hemolysis might then be caused by fragmentation of red blood cells on fibrin strands [38] or by contact with tumor emboli [6,44].

Up to now the treatment results of MMC-induced HUS have been disappointing. Red blood cell transfusions often aggravate the hemolysis [10,24,34,66,68], which was also noticed in our patients C, E and F. It has been suggested [1] that activation of intravascular clotting is responsible for this phenomenon. Because of previous observations we did not apply red cell transfusions in patient D. Attempts to control renal side effects with aspirin [38,56], dipyridamole [34,41], steroids [26,34,38,56] and cyproheptadine [38] were unsuccessful. In a limited number of patients heparin may lead to recovery of anemia [27] but not of renal failure. Plasmapheresis has been advocated for removal of circulating immune complexes and for substitution of a (suggested) deficient plasma factor required for clotting inhibition [24]. Indeed in some patients hemolysis decreased, but renal function did not improve [24,56]. In our patient F the circulating immune complexes disappeared while he was on plasmapheresis but neither hemolysis nor renal function improved.

In the majority of treated patients plasmapheresis had similar failures. If renal failure is progressive, hemodialysis may be considered. Despite hemodialysis most of those patients will die. However, there are several reports on surviving patients, most of whom require chronic hemodialysis [12,24,26]. Only two patients had partial recovery of renal function, permitting discontinuation of hemodialysis [12,68].

In one of them administration of captopril because of inappropriately high renin secretion facil-
initiated the administration of fluids which was suggested to have contributed to recovery of renal function [68]. However, in our patient F captopril was ineffective. Hug et al. [31] treated a patient with cyclophosphamide because of its effect in immunological dysregulation. Their patient had a short temporary improvement of hemolysis and renal function. This type of treatment merits further attention.

**Pulmonary toxicity**

Since the first report on MMC-induced pulmonary toxicity a total of 50 patients has been reported [2,3,5,9,17,18,22,23,25,37,39,45,48–50,71,73]. This pulmonary side effect should be distinguished from the alveolar edema that sometimes accompanies HUS from MMC, while also both types of toxicity may coincide as in patient B. Pulmonary toxicity had not been reported in animal studies. The incidence of pulmonary toxicity was 7% in a retrospective literature survey, while toxicity only occurred at cumulative doses of 30 mg/m² or more [69]. As for renal toxicity the actual incidence may be higher because of undiagnosed cases, thought to die of tumor progression. Also toxicity incidence appears to increase if the interval between treatment cycles is shortened [17].

In contrast to the renal toxicity of MMC in man, there appears to be no latency period for the development of pulmonary toxicity. Most patients presented with dry cough and progressive dyspnea while on MMC treatment. Fine basilar rales may be noted on physical examination. The chest-film shows bilateral diffuse interstitial reticular infiltrates, at times associated with fine nodularity. Infrequently reported pulmonary function tests indicated hypoxia and abnormal diffusion in those patients.

At histology one observes a diffuse alveolar septal edema, deposition of collagen, minimal infiltration of mononuclear cells and hyperplasia of type II alveolar lining cells [2,9,18,23,25,49,50,73]. Besides, muscular proliferation of the arterial wall and venous intimal fibrosis may occur. These changes closely resemble those of early stages of bleomycin-induced pulmonary toxicity.

The pathogenesis of MMC pulmonary toxicity is still unknown. Sometimes the pulmonary changes disappear after discontinuation of MMC treatment, but often progression occurs despite discontinuation of MMC administration. In the latter patients treatment with high doses of corticosteroids is frequently successful [5,23,25,37,39,49,73]. Most of the time steroids have to be given only temporarily, but some patients require maintenance treatment. A few patients have died of progressive respiratory failure despite extensive supportive care.

**Cardiotoxicity**

In the last decade 30 patients with cardiotoxicity attributed to MMC have been reported [8,13,17,21,63,69,70]. These patients developed left ventricular cardiac failure. In animals MMC causes peri- and endocardial hemorrhages in dogs [53] and mixed myocarditis with cardiac muscle lysis and sclerosis in Wistar rats [42], although another study in the same animal species was negative [69].

Also, no inhibition of contractility nor enhancement of the doxorubicin induced negative inotropic effect in guinea pigs could be found. Thus, although the results of animal studies are inconsistent, they do suggest that MMC may be potentially cardiotoxic, while the human data suggest synergism of doxorubicin and MMC concerning cardiotoxicity. Even at low cumulative doxorubicin doses, generally considered not to be cardiotoxic [30], combination chemotherapy consisting of doxorubicin plus MMC, or single agent MMC treatment after discontinuation of doxorubicin treatment, may induce cardiotoxicity in man.

In addition, Doroshow [16] observed that, in Sprague-Dawley rats, MMC enhanced oxygen radical formation in cardiac sarcoplasmic reticulum might exacerbate membrane damage caused by prior exposure to doxorubicin. The inability of cardiac mitochondria to activate MMC to its free radical, may explain why MMC does not commonly produce cardiac toxicity by itself. Indeed, the number of reported patients is low. However, the inci-
dence of MMC cardiotoxicity may approximate 10% in patients also exposed to doxorubicin [69].
Patients with toxicity can often be treated with diuretics and cardiotoxic drugs.

The serious side effects of MMC all occur in well oxygenated organs. Under preferably anaerobic conditions microsomal NADPH dependent reduction of MMC to the semiquinone radical with subsequent reduction to the hydroquinone takes place [15,69], finally inducing binding to DNA. However, under aerobic conditions the semiquinone radical is oxidized to the parent compound with the formation of superoxide radicals [67]. These radicals are known to be very toxic, and one may speculate whether they contribute to the serious side effects of MMC.

References


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