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A PROSPECTIVE STUDY ON THE DOSE DEPENDENCY OF CARDIOTOXICITY INDUCED BY MITOMYCIN C

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Since 1975 mitomycin C (MMC) has been suggested to be cardiotoxic, especially when combined with or given following doxorubicin. Data on dose dependency or incidence concerning this side effect were not known. We have initiated a prospective study to obtain some more data on these subjects. Forty-four MMC-treated patients were studied, 37 of them could be evaluated. All patients were studied by repeated physical examinations, chest X-rays, electro- and echocardiography and radionuclide left ventricular ejection fraction (EF) determinations. The results were evaluated per cumulative dose level. One of the patients developed cardiac failure after 30 mg m^{-2} MMC and only 150 mg m^{-2} doxorubicin. The cardiac failure was predicted by a drop in EF determined during a cold pressor test. None of the other patients developed clinical cardiotoxicity, nor did the studied parameters change. The literature on this subject was also reviewed. Based on the combined data from the present study and the literature, we suggest that MMC-related cardiotoxicity is dose dependent, occurring at cumulative dose levels of 30 mg m^{-2} or more, mainly in patients also (previously or simultaneously) treated with doxorubicin. The incidence is likely to be less than 10% even for this risk group.

Key words: **Mitamycin C, Cardiotoxicity, Ejection fraction, Echocardiography, Cold pressor test.**

INTRODUCTION

The cardiotoxic effects of anthracyclines are well known[1] but cardiotoxicity is rare for most of the other antineoplastic agents.

Mitomycin C (MMC) has been reported to be present in high concentrations in the guinea pig heart,[2] and causes haemorrhages in the endocardium and pericardium of dogs.[3] Mixed myocarditis with lysis of cardiac muscle leading to sclerosis and mutilation was observed in Wistar rats,[4] although Verwey *et al.*[5] did not find cardiac changes in this animal species. Monti *et al.*[6] failed to show significant inhibition of the myocardial contractility in guinea pigs, or enhancement of the doxorubicin-induced negative inotropic effect. Obviously animal data on MMC toxicity on the heart are still inconsistent. MMC-induced cardiotoxicity in man has also been suggested, but there are only a few data available.[7–12] Recently, MMC has been introduced into adjuvant chemotherapy for cervical and gastric cancer. Because of the objectives of adjuvant treatment, the incidence of serious side effects should be very low, therefore we need to know more on possible MMC-related cardiotoxicity. We have initiated a prospective study to obtain more data on this subject. We also reviewed the literature on this topic.

MATERIALS AND METHODS

Patients receiving MMC as a single agent or as a part of combination chemotherapy were eligible for the study, provided they did not have symptomatic cardiac disease. Forty-four patients entered the study. Seven of them could not be evaluated because of tumor-related early death. Of the 37 evaluable patients, 19 were females and 18 were males. Age ranged from 26 to 71 yr and the median performance score was 1, according to the WHO criteria. Thirteen patients had breast cancer, eight had gastric cancer, six prostatic cancer and ten had miscellaneous types of neoplasia. Sixteen patients received single agent MMC, 21 received MMC combined with cisplatin (2 patients) or doxorubicin (19 patients) with (10 patients) or without 5-FU. Five of the patients treated with single agent MMC had previously received cumulative doxorubicin doses of 150 mg m^{-2}, 200 mg m^{-2}, 250 mg m^{-2}, 470 mg m^{-2} and 550 mg m^{-2}, respectively. Pretreatment studies

included physical examination, chest film, standard 12 lead ECG, gated bloodpool radionuclide angiography, determining the left ventricular ejection fraction at rest (EF_{rest}) and during cardiac stress induced by cold application in the form of cold pressor test (EF_{CPT}), and echocardiography. The evaluated electrocardiographic parameters included rhythm, conduction times, frontal axis, ST-segment and T-wave abnormalities. Also, the sum of the absolute deflection (mm) of the QRS voltages in the six limb leads was calculated. Gated bloodpool scintigraphy and CPT were performed as previously reported.[13] Echocardiography was performed with an ATL MARK 300 with a 900 wide angle mechanical sector scanner (transducer: 2.25 mHz) and a HP 77 020 AC with a 90° wide angle phased-array scanner (transducer: 3.5 mHz). Images were obtained with the patient in a left lateral supine position. A two dimensional study (2DE) was performed by multiple parasternal long axis, short axis and apical 2, 3 and 4 chamber views. The 2DE images were only intended for the detection of regional wall motion abnormalities, valve abnormalities and pericardial effusion. Besides, a left parasternal M-mode recording was performed. This recording was considered evaluable if the endocardium of the intraventricular septum and the left ventricular posterior wall could be visualized optimally just below the level of the mitral valve. The left ventricular ejection time (LVET) was calculated from the aorta valve leaftlet motion. Also, left ventricular end-diastolic dimension (LVED), left ventricular end-systolic dimension (LVES), fractional shortening (FS%) and, if possible, circumferential fiber shortening ($VCFcirc.sec^{-1}$) were obtained. All tests were repeated before each subsequent administration of MMC and 2 months after discontinuation of MMC treatment.

RESULTS

Patients were considered evaluable for cardiac function if at least results of physical examination, chest film and EF_{test} were available.

Seven patients were not evaluable, all because of tumor-related early death. At the cumulative dose level of 1–10 mg m^{-2} MMC, 37 patients could be evaluated. At the cumulative dose of 11–20 mg m^{-2}, 27 patients were evaluable, at 21–30 mg m^{-2} 20, at 31–40 mg m^{-2} 13 and at 41·50 mg m^{-2} 7 patients. In the latter two groups there were six patients also receiving a cumulative dose of 240–360 mg m^{-2} of doxorubicin, which in itself may be cardiotoxic. Thirteen other patients only received cumulative doxorubicin doses of less than 200 mg m^{-2}, which can hardly be considered cardiotoxic.[1] One of the evaluable patients developed cardiac failure. This 72-year old male was treated for disseminated gastric cancer with 5-fluorouracil, doxorubicin and mitomycin C according to the regimen reported by MacDonald *et al.*[14] He was admitted to the hospital because of sudden appearance of progressive dyspnoea. Physical examination revealed moist basal rhales, while blood pressure was normal. The chest film showed cardiac enlargement as well as signs of redistribution, compatible with the signs of cardiac failure. At the time of cardiac failure, the patient had received cumulative doses of doxorubicin and MMC of 150 mg m^{-2} and 30 mg m^{-2} respectively, achieving a complete remission. The left ventricular failure was treated successfully with digoxine and furosemide. Antitumor therapy was continued with single agent 5-FU. After 5 months, recurrent disease was noted and antineoplastic treatment was discontinued. The patient died of tumor progression, 10 months after the diagnosis of left ventricular failure. Autopsy did not show serious sclerotic changes, nor severe myocardial changes. Serial EF_{rest} determinations were not predictive for cardiac failure in this patient, in contrast to EF_{CPT} (Table 1). Echocardiographic images were considered insufficient for evaluation in this particular patient.

None of the other evaluable patients developed clinical cardiac failure or changes in ejection fraction suggestive for subclinical cardiotoxicity. Values on EF determinations are given in Table 2. Patients were considered evaluable for electro- and echocardiography if a series of three or more studies were available, while pericardial effusion had to be absent throughout the study. Only 15 patients matched these criteria. Most of the failures to perform echocardiography were caused by patient failure to show up or by poor echocardiographic image quality. Out of the 17 patients for whom an adequate number of studies were available, four were considered non-evaluable because of insufficient image quality.

Table 1. Values of ejection fraction in the reported patient

	Ejection fraction (%)/heart rate (bpm)*			
Course	0	1	2	3†
EF_{rest}	69/71	54/69	57/80	61/87
EF_{CPT}	68/71	50/65	49/84	44/85

*bpm = beats per minute.
†Cardiac failure occurred shortly after course 3.

Table 2. Parameters of cardiac function (median ± 2 S.E.M.) during treatment with mitomycin C

Parameter	Normal value (range)	Before treatment (n = 37)	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)
EF_{rest}	45–70	58 ± 4	61 ± 6	62 ± 4	61 ± 4	58 ± 3	65 ± 6
EF_{CPT}	45–70	62 ± 5	61 ± 5	61 ± 6	61 ± 6	60 ± 5	67 ± 4

Therefore, only 13 patients could finally be evaluated for electro- and echocardiography. The available data are given in Table 3. There were no electrocardiographic changes or abnormalities in those patients, nor were there gross changes in echocardiographic parameters. Concerning the frequency of cardiotoxicity, the probability of frequency based on the results of this study are given in Table 4, as 95% confidence limits.

DISCUSSION

Although definitive histological evidence is lacking, perhaps because of reversibility of the myocardial changes as in the case of early doxorubicin cardiotoxicity, our patient developing cardiac failure after only 150 mg m^{-2} of DX and 30 mg m^{-2} of MMC, appears to add to previous postulations on the cardiotoxicity of MMC.

Suzuki *et al.*[7] were the first to suggest MMC cardiotoxicity in 15 patients treated with MMC as a single agent. Buzdar *et al.* reported 14 cases of congestive heart failure in patients treated with MMC.[8] All patients had been pretreated with doxorubicin (DX), as were nine similar patients in other reports.[9,11,12] Ganz *et al.*[10] reported a patient developing precordial pain shortly after administration of a combination of DX and MMC. The results of animal studies for cardiotoxicity are inconsistent.[2–6]

Table 3. Echo- and electrocardial parameters (median ± 2 S.E.M.) during treatment with mitomycin C

Dose level (mg m^{-2})	0	1–10	11–20	21–30
No. of patients	13	13	13	13
Heart rate (bpm)	81 ± 10	82 ± 11	88 ± 11	92 ± 13
LVED (mm)	42 ± 3	43 ± 3	43 ± 4	46 ± 5
LVES (mm)	28 ± 3	28 ± 4	28 ± 4	32 ± 5
LVET (msec)	280 ± 25	302 ± 26	280 ± 24	285 ± 28
FS (%)	34 ± 4	36 ± 5	35 ± 6	33 ± 7
VCF (circ. sec^{-1})	1.3 ± 0.4	1.3 ± 0.3	1.2 ± 0.3	1.3 ± 0.5
Amplitude (mm)*	33 ± 6	32 ± 6	32 ± 7	34 ± 10
PQ-time (sec)	0.15 ± 0.01	0.15 ± 0.01	0.15 ± 0.01	0.15 ± 0.01
QRS-time (sec)	0.08 ± 0.01	0.08 ± 0.01	0.09 ± 0.01	0.09 ± 0.02

*Total amplitude of QRS in leads, I, II, III, AVR, AVL and AVF.

Table 4. Probable frequency of cardiac toxicity related to mitomycin C in the studied patients

	Cumulative dose of MMC dose (mg m^{-2}) 1–10	11–20	21–30	31–40	41–50
No. of patients evaluated	37	27	20	13	7
Observed toxicity (no.)	0	0	1	0	0
Probable frequency (%)*	0–9	0–13	0–25	0–25	0–41

*95% confidence limits.

Nevertheless, human data suggest that MMC may be cardiotoxic especially when combined with DX. Even at low cumulative doses of DX, generally not considered to be cardiotoxic,[1] combination chemotherapy with DX and MMC, or single agent MMC treatment after discontinuation of DX administration, may induce cardiotoxicity. Studies done in Sprague–Dawley rats[15] indicate that MMC-enhanced oxygen radical formation in cardiac sarcoplasmic reticulum might exacerbate membrane damage caused by prior exposure to DX. The inability of cardiac mitochondria to activate MMC to its free radical, may explain why MMC, unlike DX, does not commonly produce cardiac toxicity by itself.

Literature data on the frequency of MMC cardiotoxicity can only be depicted from a total of 233 patients,[8,9,11,12] with 23 cases of cardiotoxicity, which would indicate a frequency of 10%. The actual frequency is likely to be much lower, because the majority of reports on trials with MMC do not mention this side effect. With the addition of our patient, there are 23 patients with reported cardiotoxicity for whom adequate data on cumulative MMC dose are available. The median cumulative dose is 60 mg m^{-2} (ranges from 20 to 80 mg m^{-2}). In the present study we did not observe any cardiotoxicity at a cumulative dose of less than 30 mg m^{-2}. Therefore we believe that MMC can be administered safely up to a cumulative dose of 30 mg m^{-2}. A chemotherapy regimen, in particular adjuvant treatments, applying total MMC doses of 30 mg m^{-2} or less, will not be a risk for the patient concerning the development of cardiotoxicity. However, treatment protocols applying higher cumulative doses, in particular if MMC is given combined with or following DX, should be considered as being potentially cardiotoxic.

The patient developing cardiotoxicity in the present prospective study, may be added to the reports on synergistic cardiotoxic effects of DX and MMC. EF_{CPT} appeared to be predictive in this patient, while the EF_{rest} was not, underlining the need for more sensitive techniques for detecting cardiotoxicity. EF during dynamic exercise appears to offer such a more sensitive technique, but in the great majority of cancer patients this test does not appear feasible. Although the true value of EF_{CPT} has yet to be determined, this technique has been shown to be feasible in cancer patients.[13] None of the other parameters, used in the present study, have indicated the presence of subclinical cardiotoxicity. On the contrary, it was impossible to perform or interpret echocardiography in the majority of our patients (55%). An adequate number of echocardiograms could only be obtained in 17 of our patients (45%). Thirty-two percent of the patients had echocardiographic signs of pericardial effusions, rendering them inevaluable for assessing FS and VCF. Of interest, this pericardial effusion was not detected by CT-scanning. Because of the low number of patients evaluable for echocardiography and the fact that the only patient developing cardiotoxicity was also not evaluable for echocardiography, we cannot draw a conclusion on the value of this technique for the detection of MMC cardiotoxicity. Besides, it appears useless to apply this technique routinely for the purpose of detecting cardiotoxicity in cancer patients because of the low number of 'echocardiogenic' patients, and the high frequency of pericardial effusion.

Finally, for the detection of pericardial effusion, echocardiography appears more sensitive than CT-scanning.

In conclusion, evidence is accumulating that MMC, especially when administered in combination with DX or following even low cumulative doses of DX, may induce cardiotoxicity. The frequency of this side effect appears to be low, while the available data suggest a dose dependency. The data indicate that MMC can be administered safely up to a cumulative dose of 30 mg m^{-2}, without intensive monitoring of the patient.

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