Eur J Cancer, Vol. 28A, No. 12, pp. 1974–1976, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Unexpected Prolonged Myelosuppression After Mitomycin, Mitoxantrone and Methotrexate

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28 patients (26 with breast cancer and 2 with colon cancer) received mitomycin, mitoxantrone and methotrexate (MMM). Half the patients had grade III–IV leukopenia and 29% had grade III–IV thrombocytopenia. The median time of recovery to WHO grade 0 was 62 and 128 days, respectively. Thrombocytopenia and leukopenia were more frequent and longer lasting after the three-drug part of the therapy, which suggests a critical role for mitomycin in this toxicity.
Eur J Cancer, Vol. 28A, No. 12, pp. 1974–1976, 1992.

INTRODUCTION

THE COMBINATION of methotrexate, mitoxantrone and mitomycin (MMM) has been reported as safe and effective in advanced breast cancer [1]. Originally, haematological toxicity was reported to be mild [1, 2, 3] without any WHO grade III–IV toxicity in chemotherapy naive patients [4]. In subsequent small series with the same regimen, leukopenia and thrombocytopenia caused treatment delays and discontinuations [5, 6]. In reports comparing the MMM regimen with other chemotherapy regimens, the rate of dose reductions and delays as well as degree of cytopenia was equal to that caused by the cyclophosphamide methrotrexate 5-fluorouracil (CMF) regimen [7, 8] but higher than that caused by the vincristine doxorubicin cyclophosphamide (VAC) regimen [9, 10].

The unexpected occurrence in our patients of prolonged myelosuppression associated with this chemotherapy regimen prompted us to analyse the myelotoxicity experienced by 28 patients who had received MMM chemotherapy.

PATIENTS AND METHODS

Patients

The study population consisted of 28 patients (26 females with breast cancer and 2 males with colon cancer) treated and subsequently followed up at the Department of Radiotherapy and Oncology of Helsinki University Central Hospital between December 1987 and October 1990. Altogether, the data on 141 chemotherapy courses was analysed. The inclusion criterion was histologically proven, disseminated malignancy treated with at least the initial dose of MMM therapy. Mean age of the patients was 57 years (range, 38–72). All patients had previously received other chemotherapeutic drugs and 26 patients had also received radiotherapy. The median duration of previous chemotherapy was 11 months (range, 1–22).

Treatment and toxicity assessment

The MMM regimen consisted of methotrexate (35 mg/m^2) and mitoxantrone (8 mg/m^2 every 3 weeks, and mitomycin (8 mg/m^2) every 6 weeks [1].

Laboratory tests, including haemoglobin, white blood cell count and platelets, were performed before each treatment cycle and also at the time of the expected nadir (days 7–14 after chemotherapy). If grade III–IV leukopenia or thrombocytopenia was detected, laboratory tests were performed at least every second day until recovery. The degree of toxicity was coded according to the WHO criteria [11].

Statistical methods

For calculation of the duration of cytopenias, product limit survival analysis was performed using the BMDP IL program. Graphic presentations of the platelet and leucocyte counts during treatment cycles were constructed using 10- and 3-day sliding averages, respectively.

RESULTS

Dose intensity

The mean dose intensity during the first cycle was as follows: mitomycin 0.80, mitoxantrone 0.85 and methotrexate 0.98. Including all cycles, the dose intensity was slightly lower: mitomycin 0.78, mitoxantrone 0.79 and methotrexate 0.97. The mean time interval between the chemotherapy cycles was 24.6 days.

Responses

In 3 of the 21 evaluable patients with metastatic breast cancer, and objective response was detected. A stabilisation of disease was seen in 3 patients, whereas 15 had progressive disease. The median time to progression after the start of MMM was 2 months (range, 1–12 months). Neither of the 2 colon cancer patients showed any response to the MMM regimen.

Haematological toxicity

Myelosuppression was the major side effect. The initial leucocyte and platelet counts were at acceptable levels (leucocyte median 4.8, range 2.3–8.4; platelet median 237, range 102–394). During the therapy, 29% of the patients experienced WHO grade III leukopenia and 21% grade IV leukopenia. The proportion of patients experiencing grade III or IV platelet toxicity was 15 and 14%, respectively. The time intervals and frequencies of recovery from grade IV or III leukopenia and thrombocytopenia episodes to grade II–0 are given in Table 1. Following the three-drug part of the regimen, both leukopenia and thrombocytopenia were longer lasting. Figure 1 presents the sliding average of platelet count after each part of the regimen.

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Revised 19 Feb. 1992; accepted 4 Mar. 1992.

Table 1. Recovery from WHO grade III–IV myelotoxicity following two parts of MMM regimen

	No. of episodes	Time to recovery (median, days)	Time to recovery (range, days)	No. of episodes failing to recovery
Leucocytes				
Recovery to grade II, all cycles	52	8	1– 39	0
following MMM	34	9	1– 39	0
following MM	18	7	2– 20	0
Recovery to grade I, all cycles	52	24	5–111	4
following MMM	34	31	5–111	2
following MM	18	14	5– 82	2
Recovery to grade 0, all cycles	52	62	5–252	6
following MMM	34	72	5–252	4
following MM	18	36	5–174	2
Thrombocytes				
Recovery to grade II, all cycles	16	8	3– 28	2
following MMM	11	8	3– 28	1
following MM	5	6	6– 7	1
Recovery to grade I, all cycles	16	32	5–128	7
following MMM	11	32	5–128	3
following MM	5	10	10	4
Recovery to grade 0, all cycles	16	128	5–128	12
following MMM	11	128	5–128	7
following MM	5	—	—	5

Infections and transfusions

Following the 141 chemotherapy administrations, 7 patients out of 28 (25%) experienced 11 febrile neutropenia episodes requiring hospitalisation. None of these resulted in fatalities.

7 patients received platelet transfusions. The mean number of infused units was 14 (range 8–32).

DISCUSSION

MMM has been advocated as an efficient and tolerable chemotherapy regimen for metastatic breast cancer. We analysed the haematological toxicity experienced by 28 patients receiving MMM therapy. The patients studied were heavily pretreated.

Many of our patients experienced considerable haematological toxicity. Leukopenia grade III–IV was seen in half of the patients and thrombocytopenia grade III–IV in 29%. The striking feature of the thrombocytopenia was its long duration. The majority (75%) of grade III–IV thrombocytopenia episodes failed to recover to normal values. In a concomitant trial with the 5-fluorouracil epirubicin cyclophosphamide (FEC) regimen in our institution ($n=128$) only minimal thrombocytopenia was seen, whereas 32% of those patients experienced grade III–IV leukopenia [12, Blomqvist C., personal communication].

The dose intensity of mitomycin and mitoxantrone was below 0.8, and the mean delay in chemotherapy cycles exceeded 3 days. It is probable that the observed toxicities would have been more severe if the dose intensity and cycle length were not modified. Since earlier publications on the MMM regimen do not report the dose intensity, direct comparison with the toxicity

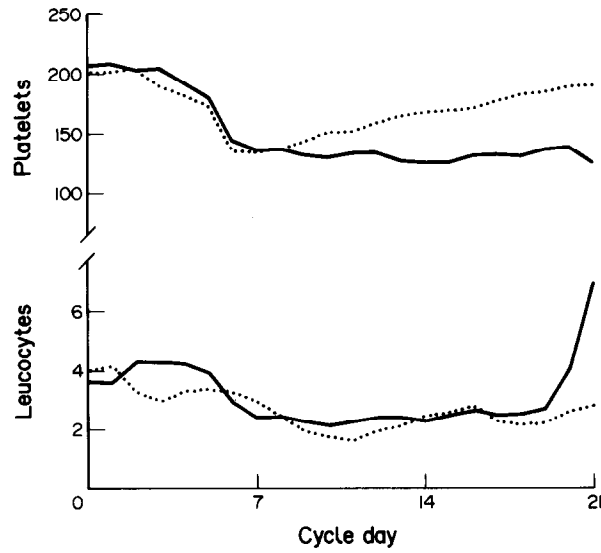

Fig. 1. Platelet and leucocyte counts (× 10⁹/l) during all MMM chemotherapy cycles. 3 week periods following three-drug (solid lines) and two-drug (dashed lines) dosages presented separately.

seen in our patients is not feasible. Since previous studies on the MMM regimen have mainly included chemotherapy-naive patients, the severity of haematological toxicity may partly be attributed to the previously administered chemo- and radiotherapy courses having caused a decrease in marrow capacity. The pretreatment leucocyte and platelet counts fell, however, mainly within normal ranges.

The occurrence of leucocyte toxicity, and particularly prolonged thrombocytopenia following the three-drug part of the therapy, suggests that mitomycin-C might play a remarkable role in such toxicity. The role of mitomycin in haematological toxicity has also been displayed in a randomised trial comparing the two parts, MMM and MM, given alone [13].

Although the MMM regimen was otherwise well tolerated, its use as a second-line treatment seems to be associated with relatively frequent occurrence of severe prolonged myelosuppression.

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Acknowledgements—We thank Sari Toukonummi for encouragement and support.

Eur J Cancer, Vol. 28A, No. 12, pp. 1976–1981, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Uroepithelial and Nephrotubular Toxicity in Patients Receiving Ifosfamide/Mesna: Measurement of Urinary *N*-Acetyl-β-D-glucosaminidase and β-2-Microglobulin

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The effect of three ifosfamide/mesna regimens on urinary *N*-acetyl-β-D-glucosaminidase (NAG) activity and β-2-microglobulin (β_2M) was studied. All regimens produced significant increases in these urinary proteins, indicating nephrotubular damage. In regimen A ($n = 15$), plasma nitrobenzylpyridine (NBP) alkylating activity area under the curve (AUC) on day 1 correlated with the percentage increase above baseline of maximum urinary NAG activity ($r^2 = 0.538$, $P = 0.0022$) and maximum β_2M concentration ($r^2 = 0.413$, $P = 0.0097$). In regimen B ($n = 5$), plasma NBP alkylating activity AUC correlated with the percentage increase above baseline of maximum NAG activity ($r^2 = 0.843$, $P = 0.03$) and β_2M ($r^2 = 0.78$, $P = 0.046$). In these two regimens the renal exposure to ifosfamide metabolites correlated with the increases in urinary NAG and β_2M. The relation of these urinary protein abnormalities to longer term effects on renal function with different ifosfamide/mesna schedules requires further study.
Eur J Cancer, Vol. 28A, No. 12, pp. 1976–1981, 1992.

INTRODUCTION

IFOSFAMIDE IS an effective antineoplastic agent and has a toxicity profile typical of oxazaphosphorine alkylating agents [1, 2]. When first used as chemotherapy in the early 1970s the dose-limiting side-effect of ifosfamide was haemorrhagic cystitis. This was reported in 18–40% of courses [3, 4] and was attributed to acrolein and possibly other ifosfamide metabolites [5, 6]. The co-administration of thiol compounds, e.g. mesna (sodium-2-mercaptoethane sulphonate) with ifosfamide has substantially reduced the frequency of ifosfamide-induced haemorrhagic cystitis [7–11].

The administration of high-dose ifosfamide as a bolus or by short infusion has been associated with severe renal toxicity, despite concomitant mesna administration [12–16]. The optimal mesna regimen and duration of therapy for different ifosfamide regimens has yet to be determined. A lower frequency of nephrotoxicity was noted if ifosfamide/mesna was administered by fractionated doses rather than by bolus, or mesna given as a continuous infusion [9]. Studies in children have shown significant reductions in glomerular filtration rate (GFR) following ifosfamide/mesna chemotherapy [14, 15]. Researchers treating children with fractionated 5-day ifosfamide/mesna in combination chemotherapy have reported the development of significant subclinical renal tubular damage despite mesna administration [17, 18]. In these studies there was no evidence of permanent renal impairment, even after several courses of chemotherapy [18].

The objectives of our observational study were to quantify the changes in urine content of *N*-acetyl-β-D-glucosaminidase (NAG) and β-2-microglobulin (β_2M) produced by different ifosfamide/mesna regimens. We intended to correlate these changes in urinary proteins with the degree of haematuria and with the pharmacokinetic parameters of ifosfamide (or ifosfamide metabolites). We studied three ifosfamide/mesna

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Revised 3 Feb. 1992; accepted 3 Mar. 1992.