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Short communication

Gut protection by cyclophosphamide "priming" in patients receiving high-dose melphalan – effect of drug scheduling*

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Summary. A "priming" injection of cyclophosphamide (400 mg/m^2 given i.v. on day –7) has been shown to reduce intestinal permeability and thus gut toxicity in patients receiving high-dose melphalan. To determine the optimal timing for this injection, patients receiving 200 mg/m^2 melphalan with an autologous bone marrow transplant were randomly assigned to receive cyclophosphamide at 5, 7 or 9 days before the melphalan. The median percentage of [^{51}Cr]-ethylenediaminetetraacetic acid excretion was similar (9.1% vs 7.1% vs 7.7%, respectively), with equivalent duration of WHO grade 2–4 mucositis and diarrhoea being recorded for each group. Thus, the timing of the cyclophosphamide prime is not critical, and the priming injection may be given between 5 and 9 days prior to high-dose melphalan.

Introduction

High-dose melphalan (HDM) is given to patients suffering from myeloma as consolidation treatment to prolong their remission after induction chemotherapy. The use of melphalan is limited by gut toxicity, which manifests as mucositis and diarrhoea.

When given at a low dose, a wide variety of cytotoxic drugs can enhance recovery from radiation- or drug-induced bone marrow injury [3, 5]. Moreover, initial studies in mice and sheep have shown that a low priming dose of cyclophosphamide given at 2 and 7 days, respectively, before high-dose chemotherapy can reduce the gut toxicity associated with the procedure as compared with high-dose chemotherapy alone [6, 7]. Priming with cyclophosphamide at 7 days before HDM treatment has been the practice in our unit for many years and has become part of the treatment programme for patients suffering from myeloma [2, 10].

Difficulties in assessing gut damage in man have been overcome using a [^{51}Cr]-ethylenediaminetetraacetic acid (EDTA) absorption test for the measurement of intestinal permeability [8]. This test objectively confirmed that the administration of 400 mg/m^2 i.v. cyclophosphamide at 7 days prior to treatment with HDM significantly reduced intestinal permeability [9] (median [^{51}Cr]-EDTA excretion was 3.1% in patients receiving a cyclophosphamide prime as compared with 7.4% in those given the same dose of melphalan but no prime). However, the cyclophosphamide priming injection does not alter the timing of the maximal gut damage that occurs approximately 9 days following HDM treatment [9].

The timing for the priming injection used in this study was extrapolated from preliminary experiments in sheep. To determine the optimal timing for the cyclophosphamide prime, patients receiving 200 mg/m^2 HDM with an autologous bone marrow transplant (ABMT) were randomly assigned to receive cyclophosphamide at 9, 7 and 5 days prior to the HDM injection. A further three patients (two of whom had received HDM on a previous occasion) were given a cyclophosphamide priming injection 3 days prior to HDM, but the toxicity related to this regimen was so severe that no other patient received the priming injection on day –3. We have subsequently shown that gut toxicity is increased when HDM is given on two occasions [1]; therefore, a direct comparison cannot be made.

Patients and methods

Written informed consent was obtained from all patients who were due to receive HDM (200 mg/m^2) with ABMT. These patients were randomised to receive 400 mg/m^2 i.v. cyclophosphamide either 9, 7, or 5 days prior to the high-dose procedure.

A total of 47 patients agreed to take part in the study. Following randomisation, 15 subjects were excluded prior to the procedure; of

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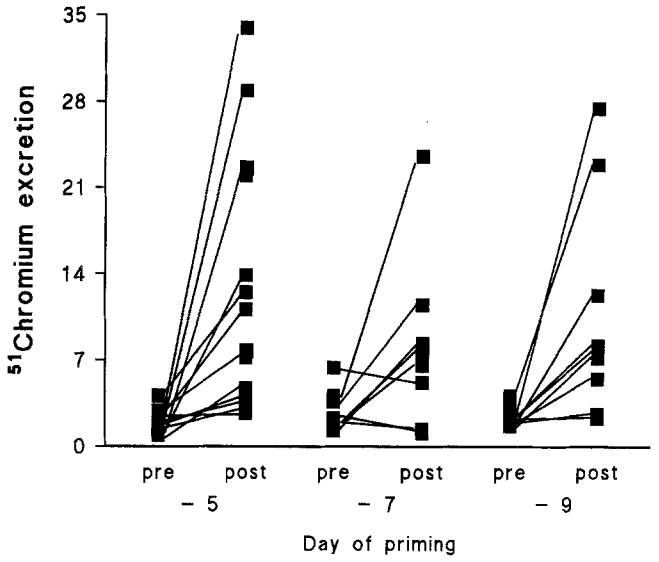

Fig. 1. Percentage of [^{51}Cr]-EDTA excretion at 9, 7 and 5 days prior to and 9 days after a cyclophosphamide priming injection in patients receiving HDM

these, 9 subsequently received only 140 mg/m^2 melphalan in the absence of ABMT and were therefore ineligible, 1 died prior to the procedure, 3 did not undergo the high-dose chemotherapy, 1 subsequently refused treatment for reasons of inconvenience and 1 did not accurately complete a 24-h urine collection.

No patient had received cytotoxic chemotherapy for at least 4 weeks prior to admission. Following an overnight fast the patients were asked to empty their bladders. Background activity was measured using a sample of this urine. At 9.00 a.m., 4 MBq [^{51}Cr]-EDTA (Amersham, Bucks; half-life, 27.7 days; sp. act., 37 MBq/10 ml^{-1}) was ingested by each subject, followed by 100 ml water. An aliquot of this solution was retained to serve as a standard. Patients were allowed to eat and drink freely 2 h later, and urine was collected for a total of 24 h. From each specimen of urine, 4-ml aliquots were removed, and the radioactivity was counted on a Kontron gamma counter for 10 min. The excretion of [^{51}Cr]-EDTA, expressed as a percentage, was calculated from the following formula:

$$\frac{\text{cpm urine}}{\text{cpm standard}} \times \frac{\text{weight of standard}}{\text{weight of dose}} \times \frac{\text{urine volume (ml)}}{\text{volume A diluted standard}} \times 100.$$

Creatinine clearance was calculated to estimate renal function. Cyclophosphamide (400 mg/m^2, i.v.) was given to 10, 9 and 13 patients on day –9, day –7 and day –5, respectively.

Patients were readmitted on day –1, and on day 0 they underwent bone marrow harvest while under general anaesthesia. Following appropriate hydration, 200 mg/m^2 melphalan was given according to the standard protocol [8], and the non-cryopreserved bone marrow was returned 12 h later. High-dose methylprednisolone (1.5 g daily) was given i.v. for 5 days, and all patients received prophylactic antifungal agents (1 ml oral nystatin qds, 10 mg oral amphotericin qds.), 400 mg oral cimetidine or 300 mg oral ranitidine daily, 300 mg oral allopurinol daily for 7 days, and anti-emetics as required. Antibiotics were commenced on day 5 and were changed as judged appropriate.

Previous data have indicated that the maximal increase in gut permeability occurs on about day 9 after HDM, and determinations of the percentage of [^{51}Cr]-EDTA excretion were therefore repeated at this time. Four patients vomited during the 24-h period and were not included in this part of the evaluation.

The toxicity of the HDM was assessed on a daily basis and graded according to WHO criteria. For the purposes of this study, only cases of mucositis and diarrhoea were recorded. The percentage of [^{51}Cr]-EDTA excretion in the three groups was compared using the Kruskal-Wallis test. The chi-square test with continuity correction was used to compare the numbers of patients in each group who developed severe mucositis and diarrhoea.

Results

The median percentage of [^{51}Cr]-EDTA excretion measured pre-treatment and at 9 days following high-dose chemotherapy is shown in Fig. 1. No significant difference was found between the groups either before or after chemotherapy or by comparing the change in the percentage of excretion (day –9: median, 7.7%; day –7: median, 7.1%; day –5: median, 9.1%). However, the range was wide.

Most patients experienced some degree of mucositis and diarrhoea. The duration of severe (grades 2 and 3/4) toxicity for each group is shown in Table 1. There was no significant difference between the groups in the number of patients who developed severe mucositis or diarrhoea.

Table 1. Gut toxicity following treatment with HDM

Day of cyclophosphamide prime	Total number of patients		Mucositis		Diarrhoea	
			Grade 2 (%)	Grade 3/4 (%	Grade 2 (%)	Grade 3/4 (%)
–5	13	Number of patients (%):	8 (61)	4 (31)	12 (92)	7 (54)
		Median duration in days (range):	4 (1–9)	11 (2–13)	2 (1–11)	6 (2–8)
–7	10	Number of patients (%):	6 (60)	1 (10)	7 (70)	2 (20)
		Median duration in days (range):	8 (2–13)	4	2 (1–4)	4 (1–7)
–9	10	Number of patients (%):	8 (80)	5 (50)	8 (80)	7 (70)
		Median duration in days (range):	4 (1–12)	6 (1–7)	2 (1–5)	6 (1–11)

Discussion

The use of [^{51}Cr]-EDTA for the measurement of intestinal permeability has previously been shown to be reproducible, and this was confirmed by the pre-treatment values obtained for this group of patients. Although the number of subjects in each group was small, the post-treatment intestinal permeability did not appear to be affected by the day on which the cyclophosphamide priming injection was given. Larger numbers would be needed to show a significant difference. However, in our earlier study, in which 16 patients were randomly assigned to receive HDM (200–220 mg/m^2 with ABMT, in the presence or absence of a cyclophosphamide prime on day –7), a statistically significant difference (p <0.01) was obtained in favour of the use of a priming injection [9].

The mechanism by which priming reduces intestinal damage is not known [4], but the procedure is clinically useful. We advocate that all patients receiving high-dose chemotherapy with melphalan should receive a cyclophosphamide priming injection at approximately 7 days prior to the high-dose procedure, but the exact timing is not critical and thus allows flexibility in the administration.

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References

1. Mansi JL, Viner C, Ellis E, Meldrum M, Milan S, Gore M, Cunningham D (pers. communication) Repeat administration of high dose melphalan in relapsed myeloma.
2. McElwain TJ, Selby PS, Gore ME, Viner C, Meldrum M, Millar BC, Malpas JS (1989) High dose chemotherapy and autologous bone marrow transplantation for myeloma. Eur J Haematol 43 [Suppl 51]: 152–156
3. Millar JL, Hudspith JN (1976) Sparing effect of cyclophosphamide (NSC-26271) pretreatment on animals lethally treated with alpha-irradiation. Cancer Treat Rep 60: 409–414
4. Millar JL, McElwain TJ (1985) The concept of priming. Eur J Cancer Clin Oncol 21: 1303–1305
5. Millar JL, Blackett NM, Hudspith BN (1978) Enhanced post-irradiation recovery of the haemopoietic system in animals pretreated with a variety of cytotoxic agents. Cell Tissue Kinet 11: 543–553
6. Millar JL, Phelps TA, Carter RL, McElwain TJ (1978) cyclophosphamide pretreatment reduces the toxic effect of high dose melphalan on intestinal epithelium in sheep. Eur J Cancer 14: 1283–1285
7. Millar JL, Hudspith BN, McElwain TJ, Phelps TA (1978) Effect of high-dose melphalan on marrow and intestinal epithelium in mice pretreated with cyclophosphamide. Br J Cancer 38: 137–142
8. Selby PJ, McElwain TJ, Crofts M, Lopes N, Mundy J (1984) ^{51}Cr EDTA test for intestinal permeability. Lancet II: 38
9. Selby PJ, Lopes N, Mundy J, Crofts M, Millar JL, McElwain TJ (1987) Cyclophosphamide priming reduces intestinal damage in man following high dose melphalan chemotherapy. Br J Cancer 55: 531–533
10. Selby PJ, McElwain TJ, Nandi AC, et al (1987) Multiple myeloma treated with high dose melphalan. Br J Haematol 66: 55–62