Fermented Wheat Germ Extract Reduces Chemotherapy-Induced Febrile Neutropenia in Pediatric Cancer Patients

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Purpose: An open-label, matched-pair (by diagnosis, stage of disease, age, and gender) pilot clinical trial was conducted to test whether the combined administration of the medical nutriment MSC (Avemar) with cytotoxic drugs and the continued administration of MSC on its own help to reduce the incidence of treatment-related febrile neutropenia in children with solid cancers compared with the same treatments without MSC.

Methods: Between December 1998 and May 2002, 22 patients (11 pairs) were enrolled in this study. At baseline, the staging of the tumors was the same in each pair (mostly pTNM = T2N0M0), with the exception of two cases in which patients in the MSC group had worse prognoses (metastasis at baseline). There were no significant differences in the average age of the patients, the length of treatment time (MSC) or follow-up, the number of patients with central venous catheters, the number of chemotherapy cycles, the frequency of preventive counterneutropenic interventions, or the type and dosage of antibiotic and antipyretic therapy used in the two groups.

Results: During the treatment (follow-up) period, there was no progression of the malignant disease, whereas at end-point the number and frequency of febrile neutropenic events significantly differed between the two groups: 30 febrile neutropenic episodes (24.8%) in the MSC group versus 46 (43.4%) in the control group (Wilcoxon signed rank test, $P < 0.05$).

Conclusions: The continuous supplementation of anticancer therapies with the medical nutriment MSC helps to reduce the incidence of treatment-related febrile neutropenia in children with solid cancers.

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Cytotoxic therapy for pediatric malignancy is often associated with serious treatment-related complications. Among the sometimes life-threatening complications that occur, febrile neutropenia, infections, bacteremia, and general sepsis are still not uncommon.[1,2] MSC (code name) or Avemar (brand name), a medical nutriment invented by one of us (M.H.), is a standardized natural fermented wheat germ extract with potent in vitro anticancer effects.[3] It has recently been shown that this extract contributes to the delay of disease progression in melanoma patients[4] and to the prolongation of the progression-free and overall survival time of colorectal cancer patients.[5] It has also been reported that MSC supplementation improved quality of life and alleviated fatigue in patients with advanced lung cancer.[6] MSC has previously been shown to increase the regeneration of the hematopoietic system and thus to alleviate pathologic symptoms in irradiated or cyclophosphamide-treated mice,[7] as well as having been reported to have no toxicity in acute and subacute animal studies[8–10] and no disadvantageous interactions with the cytostatic drugs widely used in clinical practice.[11] As infections generally threaten children receiving immunosuppressive chemotherapy, the aim of the present open-label, matched-pair pilot clinical study was to test whether the simultaneous administration of MSC with chemotherapy, followed by the continued administration of MSC on its own, has any beneficial impact on the development of treatment-related febrile neutropenia in pediatric cancer patients.

METHODS

To be eligible for this matched-pair study (started in December 1998, closed in December 2003), patients had to have a histologically proven malignant disease, a WHO perfor-

mance status of 0, 1, or 2, adequate organ function, a life expectancy of at least 12 months, and a maximal age of 18 years. No restrictions were made regarding the time interval between diagnosis and enrollment in the study, but within pairs it had to be approximately the same. For patients who had previously undergone chemotherapy, the same schedule and the same number of previous treatment blocks had to be applied within pairs. All potentially eligible patients were asked if they preferred to take MSC and thus to be enrolled in the study. As a result, no direct randomization or stratification could be performed. Those who refused to take the preparation formed the control group. Matched pairs of patients were formed with the same histologic diagnosis, the same stage of tumor, and the same age and gender. Patients who could not be matched were excluded from the study.

Characteristics of the patients are shown in Table 1. At baseline, the staging of the tumors was the same in each pair (mostly pTNM = T2N0M0), with the exception of two cases in which the patients in the MSC group had worse prognoses (metastasis at baseline).

In addition to standard anticancer treatments, one patient in each pair received orally 6 g/m^2 MSC dissolved in water twice daily (12 g/m^2/d) uninterruptedly throughout the study (MSC group). The other patient received standard anticancer treatments on their own (control group).

The Regional Ethical Committee of the National Health Council approved the protocol, and all patients' representatives gave written informed consent before enrollment. All patients were evaluated at baseline, at the end of the first month, and every 3 months thereafter. Evaluation included a physical examination and assessment by imaging techniques (radiographic, ultrasonic, or magnetic resonance), laboratory tests (hematology, blood chemistry, and urinanalysis), and the collection of data for treatment-related toxicities. During the neutropenic periods, laboratory tests were carried out every day. A hemoglobin level below 80 g/L indicated a need for red blood cell (RBC) transfusion. Febrile neutropenia was defined as simultaneous cytopenic and febrile episodes (granulocytes < 0.5 g/L and a body temperature > 38°C). Preventive counterneutropenic interventions included RBC, platelet, and fresh-

TABLE 1. Patient Characteristics

Diagnosis, Chemotherapy, Patient Groups	Number of Patients	Male	Female	Age on Study, Years (mean, range)	Follow-Up (person-months)
Ewing sarcoma					
Carboplatin, dactinomycin, doxorubicin, epirubicin, etoposide, ifosfamide, vincristine					
MSC	4	1	3	13.3 (11–16)	172
Control	4	1	3	8.8 (7–13)	136
Cerebral PNET					
Carboplatin, cyclophosphamide, dactinomycin, doxorubicin, epirubicin, etoposide, ifosfamide, vincristine					
MSC	2	1	1	4 (3–5)	42
Control	2	1	1	12 (11–13)	44
Osteosarcoma					
Carboplatin, cisplatin, doxorubicin, ifosfamide, methotrexate					
MSC	3	1	2	15.3 (13–17)	129
Control	3	2	1	14.7 (11–18)	129
Hepatoblastoma					
Cisplatin, doxorubicin					
MSC	1		1	2	60
Control	1	1		2	60
Mesenchymal chondrosarcoma					
Cyclophosphamide, doxorubicin, etoposide, ifosfamide, vincristine					
MSC	1		1	12	50
Control	1		1	11	18
MSC (total)	11	3	8	11.0 (2–17)	453
Control (total)	11	5	6	10.6 (2–18)	387

frozen plasma transfusions and hematopoietic growth factor (filgrastim, molgramostim) treatment. All patients received the same type and dosage of antibiotic and antipyretic therapies during the febrile periods: an intravenous aminoglycoside plus an antipseudomonal β-lactam agent,[12,13] considered the standard of care in the United States,[14] and every 6 hours, 30 mg/kg body weight oral noraminophenazonum natrium mesylicum was administered.

The end-point of this study was to compare the incidence of febrile neutropenic events in the two groups. For this, the Wilcoxon signed rank test was used, with $P < 0.05$ indicating statistical significance. For other comparisons, the Mann-Whitney test, the *z*-test, and also the Wilcoxon signed rank test were applied.

RESULTS

Twenty-two randomly chosen patients (11 pairs) with histologically proven different pediatric malignant solid tumors were enrolled in this study between December 1998 and May 2002. All of them had been treated at the Oncology Unit of the Second Department of Pediatrics at the Semmelweis University in Budapest. The children had either a recent diagnosis of cancer or arrived for a routine check-up of their previously diagnosed and treated disease.

At baseline, there were no significant differences in the average age of the patients (11.0 vs. 10.6 years; Wilcoxon signed rank test: z = 0.306; $P = 0.759$) and the length of time of treatment (MSC) or follow-up (control) (453 vs. 387 person-months; Wilcoxon signed rank test: z = 1.643; $P = 0.100$) between the two groups. There was also no significant difference in the number of patients with central venous catheters (6 in the MSC group vs. 5 in the control group; *z*-test $P = 0.762$), thereby in the direct exposure to bloodstream infection between the two groups.

Altogether, the patients underwent 121 (MSC) versus 106 (control) chemotherapy cycles (no significant difference; Table 2). Similarly, there were no differences in the frequencies of the preventive counterneutropenic interventions (Table 3), nor in the type and dosage of antibiotic and antipyretic therapies applied.

During the treatment (follow-up) period, there was no recognizable progression of the malignant disease, whereas at end-point (Dec. 31, 2003), the number and frequency of febrile neutropenic events (the latter expressed as percentages of the total number of chemotherapy cycles) significantly differed between the two groups: 30 febrile neutropenic episodes (24.8%) in the MSC group versus 46 (43.4%) in the control group (Wilcoxon signed rank test: z = 2.090; $P = 0.037$) (see Table 2). The mean duration (days) of the febrile neutropenic episodes did not differ between the two groups, and there was only one pair with repetitive infections.

The overall white blood cell and lymphocyte counts analyzed daily during the neutropenic periods were significantly higher (i.e., closer to the normal values) in the MSC group (Table 4).

TABLE 2. End-Point Analysis

	MSC Group	Control Group	z Value	*P* Value
Number of patients	11	11	—	—
Total number of chemotherapy cycles (CC)	121	106	1.071	0.284*
Average number of CC per patient	11.0	9.6	1.027	0.304*
Total number of febrile neutropenic events (FNE)	30	46	—	—
Average number of FNE per patient	2.7	4.2	2.099	0.036†
Average duration of FNE (days)	6.1	8.9	1.606	0.108*
Frequency of FNE relating to CC	24.8%	43.4%	2.090	0.037†

*No significant difference.
†Significant difference.
Wilcoxon signed rank test.

The administration of the medical nutriment was safe. No serious adverse event (NCI-CTC grade 3 or 4) was reported.

DISCUSSION

Impairments of the cellular immune response and normal splenic functioning are direct consequences of the administration of more intensive and thus inevitably granulocytopenic, neutropenic, and myelosuppressive chemotherapeutic regimens.[15] Several modalities, such as different antibiotic schedules, some in combination with hematopoietic cytokines,[16] and the application of nutritional interventions,[17] have been tried to lower the incidence of febrile neutropenic and

TABLE 3. Preventive Counterneutropenic Interventions

	MSC Group		Control Group		WSRT
Intervention*	Mean	SD	Mean	SD	*P* Value
RBC	0.019	0.016	0.023	0.020	0.646 (NS)
Platelet	0.074	0.129	0.170	0.366	0.508 (NS)
FFP	0.0010	0.0027	0.0038	0.0059	0.237 (NS)
HGF	1.004	1.012	1.695	2.117	0.575 (NS)

RBC, red blood cell; FFP, fresh-frozen plasma; HGF, hematopoietic growth factor; WSRT, Wilcoxon signed rank test.
*RBC, platelet, and FFP transfusion values are expressed as IU/kg body weight/total chemotherapy cycles; HGF values are expressed as cycles/total chemotherapy cycles.

TABLE 4. Overall White Blood Cell, Granulocyte, and Lymphocyte Counts During Neutropenia

	MSC Group	Control Group	z-Value	*P* Value
Number of determinations	212	285	—	—
White blood cell				
Median	0.90	0.80	2.306	0.021†
Lower quartile	0.40	0.30		
Upper quartile	1.40	1.20		
Granulocyte				
Median	0.10	0.10	0.475	0.635*
Lower quartile	0.00	0.00		
Upper quartile	0.37	0.40		
Lymphocyte				
Median	0.70	0.50	3.817	<0.001†
Lower quartile	0.30	0.30		
Upper quartile	1.10	0.80		

*No significant difference.
†Significant difference.
Mann-Whitney test.

septic events. Despite these efforts, febrile neutropenia and septicemia remain significant causes of morbidity and mortality in children receiving myeloablative and cytopenic chemotherapies.[18]

An open-label comparative matched-pair pilot clinical trial was therefore conducted to test whether the combined administration of the medical nutriment MSC with cytotoxic drugs and the continued administration of MSC on its own would help to reduce the incidence of treatment-related febrile neutropenia in children with solid cancers compared with the same treatments without MSC.

This study has limitations. First, it was a pilot study; therefore, all results should be considered preliminary until subsequent studies confirm them. Second, it was not possible to use a blind design. Due to the well-balanced treatment arms in terms of the myelosuppressive therapies plus the counterneutropenic interventions, the fact that there were diverse disease groups did not compromise the findings.

The result of this preliminary study was surprisingly positive. While receiving the same chemotherapeutic burden and preventive counterneutropenic interventions, as well as antibiotics and antipyretics, patients in the MSC group developed significantly less febrile neutropenia than their control group counterparts.

The effect of MSC in regenerating the hematopoietic system of mice treated with cytotoxic and myeloablative therapies has already been mentioned.[7] The finding that the MSC group in our study had a significantly higher lymphocyte count than the control group correlates well with these previous experimental data. Further explanation for the reported positive clinical findings can be found in the immune-modulatory effect of the fermented wheat germ extract. In experiments with mice, orally administered MSC significantly increased both the blastic transformation of lymphocytes and, in thymectomized mice, the survival of skin grafts, thereby inducing normal immune responses in animals having an artificially impaired immune system.[19] It has been postulated that interleukin 1α (IL-1α) and IL-1β, also by the induction of hematopoietic growth factor IL-6, can restore the bone marrow from chemotherapy-induced injury.[20] MSC has been shown to upregulate the expression of IL-1α, IL-1β, IL-5, and IL-6 genes in myeloid cell cultures.[21] The ability of this medical nutriment to accelerate regeneration of the hematopoietic system, reconstruct healthy immune response, and increase hematopoietic interleukin gene expression may explain its possible febrile neutropenia-preventing effect in children receiving cytotoxic therapies.

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