New ways to optimize breast cancer treatment

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Prevention of febrile leucopenia after chemotherapy in high risk breast cancer patients: no difference between granulocyte-colony stimulating growth factor or ciprofloxacin + amphotericin B

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Summary

In a prospective randomized trial, 40 stage IV breast cancer patients undergoing intermediate high-dose chemotherapy (cyclophosphamide, 5-fluorouracil plus epirubicin or methotrexate), received either recombinant human G-CSF (rhG-CSF, group I) or ciprofloxacin and amphotericin B (CAB, group II) for prevention of febrile leucopenia (FL). In group I, seven of 18 patients developed FL (after 10/108 courses); in II: seven of 22 patients (7/98 courses) (p=N.S). Median hospitalization duration and costs were not different. RhG-CSF was 6.6 times more expensive per course than CAB. In conclusion, prophylactic CAB has similar efficacy as rhG-CSF in this setting, and is more cost-effective.

Introduction

Bacterial and fungal infection is a considerable cause of death in cancer patients, and chemotherapy related leucopenia, is associated with substantial febrile morbidity[1]. Prophylactic haematopoietic growth factors are used to reduce the incidence of FL, by shortening the duration of neutropenia[2,3]. Reducing the number of potential pathogens by means of prophylactic antibiotics and anti-mycotic agents, was also shown to lower the risk of febrile morbidity[4]. However, no prospective study to compare the efficacy of prophylactic haematopoietic growth factor or prophylactic antibiotics and anti-mycotics in preventing FL has been performed. The aim of this study was to evaluate the efficacy of prophylactic rhG-CSF or CAB, in patients with metastatic breast cancer treated with intermediate high-dose chemotherapy, in a prospective randomized clinical trial.

Patients and methods

Patients: chemotherapy naive patients ≤ 65 years of age, with metastatic breast cancer were treated with a chemotherapy scheme consisting of 3 courses of intravenous (IV) cyclophosphamide, epirubicin and 5-fluorouracil (5-FU) on day 1 (dosage 1,500, 80 and 1,500 or 1,000 mg/m^2 respectively). 5-FU dose-reduction was introduced for the latter 18 patients (see: discussion). These courses were followed by 3 courses of IV cyclophosphamide and 5-FU on day 1 (dosage 1,500 and 600 mg/m^2) and IV methotrexate on day 2 (1,500 mg/m^2). Informed consent was obtained according to local procedures. Courses were administered with an interval of 3 weeks.

Prophylactic treatment: prior to chemotherapy, patients were randomized to group I or II. Group I received rhG-CSF (lenograstim, Rhône-Poulenc Rorer Nederland BV, Amstelveen, The Netherlands) 263 μg subcutaneously once daily, on days 3 to 12. Group II received oral ciprofloxacin (ciproxin, Bayer Nederland BV, Mijdrecht, The Netherlands) 2 times 250 mg daily, and oral amphotericin B suspension (fungizone, Bristol-Myers Squibb BV, Woerden, The Netherlands) 100 mg/mL, 4 times 5 mL daily; both on days 3 to 17. Leucocyte counts were tested prior to the courses and once, between days 10 to 14 after start of the course.

Febrile leucopenia (FL): was defined as a leucocyte count <1.0.10^9/L (grade IV according to WHO toxicity scale[5]), combined with fever (temperature >38.5°C), and was followed by hospitalization and standard analyses of possible infectious foci. Treatment was started with IV broad spectrum antibiotics containing cefuroxim and aminoglycosides, and adjusted if necessary when a particular focus was found. Leucocyte counts were monitored daily. During hospitalization, rhG-CSF was continued in group I, whereas in

group II the ciprofloxacin was stopped, while the

amphotericin B was continued. Hospitalized patients from group II switched to the use of rhG-CSF during later courses according to protocol, based on prophylaxis guidelines after prior FL[6]. Patients were discharged when temperature had normalized (< 37.5°C) for at least 24 hours, and when leucocyte count was above $1.0.10^9$/L. No chemotherapy was administered during FL.

Cost analyses: *of* h*ospitalization*: were performed based on data by Vellenga et al.[7], regarding costs in our hospital for one day of treatment of FL on a regular oncology ward ($364) and additional costs per hospitalization (diagnostics etcetera, $590). Costs of antibiotic treatment during hospitalization were calculated for both groups. *Prophylaxis*: costs of CAB and rhG-CSF were based on whole sale prices.

Statistics: analyses were performed using the chi-square test with continuity correction according to Yates (incidence hospitalization for FL, grade IV leucopenia and FL), or the Mann-Whitney U-test (hospitalization duration and costs). Only p-values ≤0.05 were considered significant.

Results

A total of 40 patients were randomized. Patients' characteristics and metastatic sites are reflected in table 1. Group I consisted of 18 patients, receiving a total of 108 analyzed courses. Group II consisted of 22 patients receiving a total of 98 analyzed courses. Not included in the analyses were 23 courses from 7 patients from group II, who switched to rhG-CSF. Of these 7 patients, 3 patients stopped, due to disease progression or death of disease, after having received a total of 9 courses; therefore 11 more courses were not administered and not included in the analyses.

Hospitalization for FL: in group I, 7/18 patients were hospitalized after 10/108 courses for FL; in group II, 7/22 patients after 7/980 courses (p=N.S.). Prior to 5-FU dose-reduction, seven of nine patients (group I) and six of 13 (group II) suffered from FL (after 54 and 49 courses respectively, p=N.S.). After 5-FU dose-reduction for the last 18 patients studied, FL declined equally in both groups (I: 0/9 patients; II: 1/9). As shown in the Figure, FL occurred mainly after the first three courses. Median hospitalization duration was 6 days (range 5-9) for group I, and 7 days (range 5-10) for group II (p=N.S.). No course was delayed due to FL.

Grade IV leucopenia and FL: in group I, 22/108 courses were followed by grade IV leucopenia; in group II, 41 of 98 (20 vs. 42%, $p<0.0025$). In group I, grade IV leucopenia was followed by fever in 10/22 courses; in group II, seven of 41 (45 vs. 17%, $p<0.025$).

Cost analyses: *for hospitalization*: no difference was found between both groups regarding regular oncological care and additional costs (group I: median $2,774 per hospitalization, range $2,410-$3,866; group II: median $3,138, range $2,410-$4,230). Also costs of antibiotic treatment per hospitalization were comparable (group I: median

$332, range $40-$734; group II: median $439, range $108-$594). *Prophylaxis*: the costs of the prophylactic rhG-CSF were 6.6 times higher than CAB ($1,085 per course vs $164).

Discussion

In this study, the efficacy of prevention of FL by rhG-CSF or CAB was evaluated, in patients with metastatic breast cancer treated with intermediate high-dose chemotherapy, in a prospective randomized clinical trial. The results show no difference of the incidence of hospitalization due to FL in the two groups, whereas in the group receiving CAB, a larger number of patients appeared to be at risk for developing fever with a significantly higher incidence of grade IV leucopenia. Although the reduction of 5-FU dosage during the study clearly affected the overall incidence of FL (which was the objective, as the incidence of FL was considered unethically high), no difference in FL between groups was induced.

In a retrospective study, prophylaxis of FL with either rhG-CSF or ciprofloxacin was equally beneficial in patients with paclitaxel induced leucopenia compared to a historical control group[8]; however, no randomized prospective study addressing this issue was performed previously. From the study presented here, prophylactic CAB may be considered to be a reasonable alternative for rhG-CSF (standard in patients at high risk for FL[6]). The cost aspect adds to the attraction of this alternative. Placebo-controlled assessment of prophylactic antibiotic and anti-mycotic agents will be useful in future studies, preferably in patients with grade IV leucopenia (thus possibly reducing the risk of development of resistant organisms).

Concluding, prophylactic CAB appears to be an effective and attractive alternative for rhG-CSF in preventing febrile leucopenia in high risk patients, but future placebo-controlled studies will have to further support this.

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Table 1: **Patients' characteristics**

Characteristic		group I	group II
Age (years)	median	39	42
	range	28-50	29-51
Metastases	single	8	14
	multiple	10	8
Metastatic sites			
	supraclavicular LN	10	10
	bone marrow	4	5
	liver	4	4
	lungs	2	3
	pos. bone scan	9	7
	skin	1	3

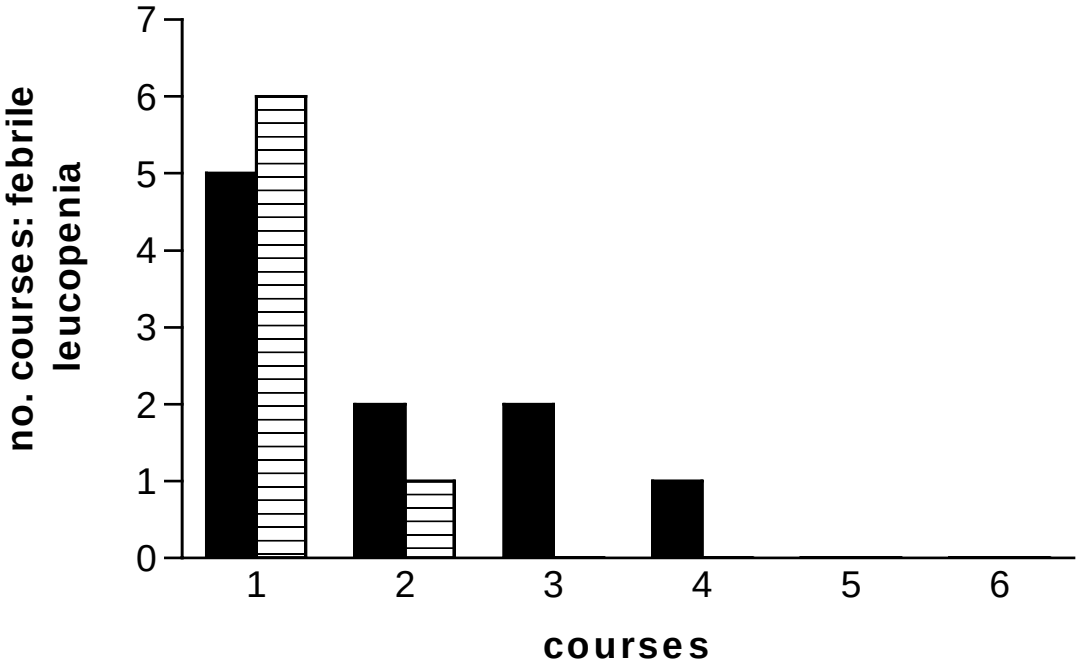

Figure: 1

Incidence of courses followed by febrile leucopenia.

X-axis: consecutive courses; Y-axis: number of courses followed by febrile leucopenia (black bar: group I, rhG-CSF; hatched bar: group II, CAB).

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