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Clinical Study

Role of Enteral Hyperalimentation in the Management of Chemotherapy-Induced Neutropenia in Wilms Tumor

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Keywords
Cancer chemotherapy
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Abbreviations
ANC - Absolute neutrophil count
GCSF - Granulocyte colony-stimulating factor
RDA - Recorded daily dietary allowance
WT - Wilms tumor

Abstract

Introduction: *Chemotherapy of Wilms tumor (WT) often induces neutropenia. This study explores whether enteral hyperalimentation can reduce the incidence of chemotherapy-induced neutropenia and the need for granulocyte colony-stimulating factors (GCSF) in these patients.*

Methods: *Eight patients with WT were prospectively enrolled and were given enteral hyperalimentation. Anthropometric parameters, serum albumin levels, frequency and severity of neutropenic episodes, need for therapy postponement or dose reduction and the need for GCSF administration of these 8 patients were compared with that of 7 historic controls that were treated with the same chemotherapy protocol sans enteral hyperalimentation. Statistical analysis was done using Chi-square test.*

Results: *Enteral hyperalimentation was found to reduce the frequency of chemotherapy-induced neutropenia, especially the febrile neutropenia in WT. The requirement of GCSF was also less in the study group. However, these differences were not statistically significant. With enteral hyperalimentation there was no need for therapy postponement or dose reduction of chemotherapeutic drugs.*

Conclusion: *This single-centre, small sample-size study of WT failed to conclusively show any benefit of enteral hyperalimentation in reducing the frequency of neutropenia or the need for GCSF administration.*

INTRODUCTION

Chemotherapy of Wilms tumor (WT) often causes neutropenia by myelosuppression, which may be associated with fever, sepsis and rarely death. The usual management of chemotherapy-induced neutropenia includes postponement of therapy schedule or reduction in the dose of chemotherapy drug and administration of granulocyte colony-stimulating factor (GCSF). Postponement of schedule or reduction of drug dosage may compromise therapeutic intend and may lead to tumor relapse, whereas GCSF is known to cause significant long-term morbidity.[1] It is also known

that patients undergoing adjuvant chemotherapy suffer loss of appetite and hence eat inadequately and expose themselves to multiple adverse effects of malnutrition. We hypothesized that enteral hyperalimentation may reduce the incidence of neutropenia and hence the need for GCSF in these patients.

MATERIAL AND METHODS

This prospective interventional study was done in a tertiary-care hospital between December 2015 and September 2017. Due approval was obtained from the Institutional Ethics Committee. Patients aged 0-12 years presenting with low- and intermediate-risk WT (UK-CCSG protocol) of stages I to III were prospectively enrolled. Stage-III high-risk tumors, stage-IV disease and those with inferior vena cava thrombus extending beyond hepatic veins were excluded.

Prospectively enrolled 8 patients formed the study group (Group B) and they received enteral hyperalimentation. They were compared with 7 historic controls (Group A) who were treated by a similar chemotherapy protocol sans enteral hyper alimentation in the preceding year of this study.

Demographic data, clinical features and diagnostic work-up of these patients were recorded in a predesigned proforma. Nutritional status of each patient was assessed fortnightly from the outset of treatment. The parameters include weight, height, mid-arm circumference, triceps skin-fold thickness and serum albumin.

The weight of WT accounted for as much as 10-20% of the total body weight. Hence, to know the effect of hyperalimentation, we considered only the post-operative weight. Preoperative chemotherapy period was not considered for analysis.

All patients in the Group B were administered enteral hyperalimentation postoperatively. The recommended daily dietary allowance (RDA) of each patient was calculated according to the guidelines of the Indian Council of Medical Research (ICMR)[2] and hyperalimentation diet was defined as 1.2 times that of the RDA. Patients were encouraged to take the calculated diet orally as per their choice. When the total oral intake was less than 60% of the calculated amount, forced nasogastric tube feeding was employed. Hyperalimentation was temporarily withheld during the times of therapy-related vomiting or diarrhea. Children were sent home between the scheduled cycles of chemotherapy and their parents were encouraged to continue hyperalimentation at home as per the dietician chart. They were also taught the method of recording oral intake at home, so that calorie and protein content could be calculated by the dietician on their return for the next cycle of chemotherapy.

Nutritional assessment and blood counts were done fortnightly. Neutropenia episodes, if any were graded according to the Common Toxicity Criteria of the National Cancer Institute.[3] GCSF was administered when neutropenia was grade-2 or more. GCSF was given at a dose of 5µg/kg and the dose was increased if neutropenia persisted. GCSF was stopped when absolute neutrophil count (ANC) exceeded 1500 x 10^9/l. During episodes of febrile neutropenia, antibiotics (third-generation cephalosporins and aminoglycosides) were also administered.

Table 1. Grading of Neutropenia*

Grade	Absolute Neutrophil Count
Grade 0	≥ 2,000/mm^3
Grade 1	1,500 - 1,999/mm^3
Grade 2	1,000 - 1,499/mm^3
Grade 3	500 - 999/mm^3
Grade 4	<500/mm^3

* *As defined by the Common Toxicity Criteria of the US National Cancer Institute.*[3]

Primary outcomes were defined as the frequency of febrile neutropenia and the total dose of GCSF

required per kg body-weight during neutropenia treatment. Secondary outcomes were defined as the total delay in the completion of chemotherapy and the total reduction in the dosage of individual chemotherapy agents.

Statistical analysis of discrete data was done using Chi-square test with Yates correction. Statistical significance was set at P-value less than 0.05.

RESULTS

The subjects of the two groups were matched for age and stage of WT. In the Group B, 75% of the children needed nasogastric feeding on and off throughout their therapy, as they were unable to tolerate oral take because of vomiting and feed refusal.

Weight of patients with stage-2 and stage-3 WT increased after hyperalimentation; but it was not statistically significant. However, paradoxically, one patient of stage-1 in Group B had weight loss despite hyperalimentation. There was marginal improvement in mean triceps skin-fold thickness and mid-arm circumference in group B, while this data was not available for group A.

Neutropenia (with and without fever) occurred 19 and 16 times in the groups A and B respectively. There were no episodes of grade-4 neutropenia in the group B. (Fig. 1) Although the febrile neutropenia was more frequent in the group A (Fig. 2), it was not statistically significant (P=0.613).

In the group A, 4 of the 7 patients, needed GCSF during chemotherapy, whereas in the group B, 5 of the 8 patients needed GCSF. (χ2=0.1004; P=0.75) The total dose of GCSF required in the Group A was 500µg/kg, whereas it was 360µg/kg in the Group B; the difference was not statistically significant (P=0.11).

Chemotherapy had to be temporarily deferred for 4 and 2 weeks respectively in two patients of the Group A because of febrile neutropenia. In group B, none had to skip the therapy schedule. Two-third dose reduction of individual component of chemotherapy regimen was needed for 5weeks in one patient of the Group A. Dose reduction of 3mg/m^2 was needed for vincristine, 90µg/kg for actinomycin-D and 100mg/m^2 for adriamycin. Chemotherapy dose reduction was not needed in any of the patients of the group B.

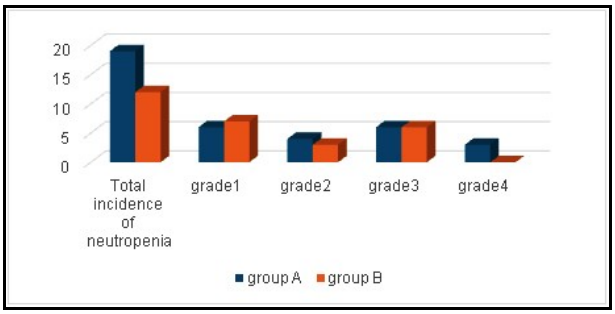

Fig 1. *Frequency of neutropenia.*

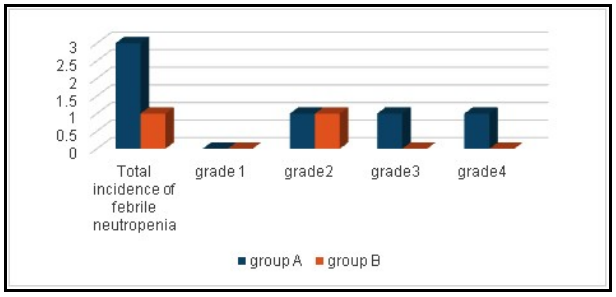

Fig 2. *Incidence of febrile neutropenia*

DISCUSSION

Impact of nutritional status on the outcome of cancer chemotherapy is a subject of much speculation, with limited evidence in the literature. Better nutritional status is presumed to be beneficial in two ways: firstly, by improving general immunity and secondly, by avoiding disruption of chemotherapy schedule from febrile neutropenia and low ANC. The present study was done to explore the effects of nutrition on chemotherapy-induced neutropenia.

Infectious complications are known to occur more frequently in malnourished children with cancer.

Several studies from low- and middle-income countries (LMIC) have shown a high prevalence of malnutrition at diagnosis and its adverse effect on the outcome of WT.[4,5]

In these children nutritional status can be improved by giving supplemental feeds through enteral or parenteral routes. Parenteral nutrition is associated with the risks of catheter infections, fluid-electrolyte imbalances and hepatopancreatic dysfunction.[6] Advantages of enteral feeding over parenteral route include prevention of bacterial translocation, preservation of normal flora, transit and histology of the gut, prevention of hyper-catabolic responses to stressful events and maintenance of gut immune function. Hence enteral nutrition is always preferable in terms of physiological response, local and systemic competence, quality of life, patient compliance and cost.[6,7] Nasogastric tube feeding can be a good option if oral acceptance is poor. Energy-enriched formula given through nasogastric tube feeding has been known to be effective in improving the nutritional status of children with cancer during the intensive phase of treatment.[8] Hyperalimentation is known to improve immune status, rate of wound healing and response to anti-neoplastic therapy.[9]

Israels et.al.[10] have noted grade-3 neutropenia in 59% of the WT and grade-4 neutropenia in 27% had grade-4 neutropenia. Grade-4 neutropenia occurred more commonly with 3-drug regimen than with 2-drug regimen (50% versus 15%). Nearly 60% of all patients and 85% of those receiving the 3-drug regimen had documented neutropenia of grade-3 or more. We also documented that 12 out of the 15 patients (80%) had a total of 35 episodes of neutropenia, of which 12 (34%) were of grade-3 and 8.6% were of grade-4. We observed less frequent neutropenic episodes in the patients receiving enteral hyperalimenta tion. Although grade-3 neutropenic episodes were equal in both the study group and historical controls, there were no episodes of serious grade-4 neutropenia in the group B. Disrupted therapy schedule and reduction in chemotherapy dosage was not needed in our patients who were given hyperalimentation. However, these differences did not reach the level of statistical significance, probably because of the small sample-size. A larger sample-size from multi centric study may provide the definitive answer in future.

CONCLUSION

This single-centre, small sample-size study failed to conclusively show the benefits of enteral hyper-alimentation in reducing the frequency of neutropenia or the need for GCSF administration in children receiving chemotherapy for WT.

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