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EARLY (SHORT TERM) SIDE-EFFECTS OF CHEMOTHERAPY IN PAEDATRIC SOLID MALIGNANCY

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ABSTRACT **Aim:** The aim of the study was to see early side effects that comprises acute which develop within 24 hours and delayed which develops after 24 hours and up to 6 - 8 weeks after chemotherapy treatment in pediatric solid malignancy. **Material & Methods:** The present cross-sectional study was conducted on 34 children aged up to 12 years and newly diagnosed pediatric solid cancer patients in the Department of Pediatric Surgery in Chacha Nehru Bal Chiktsalaya, New Delhi, India in between Nov 2018 to March 2020. **Results:** The males were 20 (58.8%) and females were 14 (41.2%) indicating slight male predominance in our present study. Majority of 8 (23.5%) children had neuroblastoma followed by Wilms' Tumor which were in 7 (20.6%) children, RMSwere in 5 (14.7%) , SCT were in 3 (8.8%) ; while Hepatoblastoma and Yolk Sac Tumor Of Rt. Ovary each were in 2 (5.9%) children. The result shows the age distribution of the studied children where the majority of children were 16 (47.1%) belonging to the age group 2-5 years, while 12 (35.3%) children were less than one year and only 6 (17.6%)children were greater than five years. **Conclusion:** The male children were 58.8% indicating the male predominance in our study. Wilms' Tumor was most frequent (25.0%) in age group 2- 5 years. Nausea, vomiting, alopecia, and constipation were the most frequently occurring side effects in almost all the regimen used.

KEYWORDS : Side effects, Chemotherapy

INTRODUCTION

Cancer is progressively becoming a cause of death of children aged between 1 to 14 years; also the likelihood of cancer has on an average increased up to 1.0% every year. 2 As an outcome, survival from the childhood cancers many of which were deadly in pre-chemotherapy era has increased dramatically from 20.0-30.0% in the 1960s to 62.0% in the 1970s (mortality of 4.5/1,00,000).[1] The current mortality of pediatric cancer is 2.6/1,00,000 and survival is 83.0%, which shows that the modern medicine may cure 4 out of 5 children with cancer. Guerney's et al. reported an average of 1.0% yearly increase in the occurrence of all the malignant neoplasms in children less than 15 years of age between 1974 and 1991. Although the mortality rates have dropped 50.0% since 1973, cancer is still the principal cause of the mortality by disease in children ages between one and fourteen.[2,3]. The overall occurrence of 38 to 124 per 1,00,000 children annually is lower than that in the developed world. Across the world, the yearly number of new cases of childhood cancer exceeds two lakhs and more than 80.0% of these are from the developing world. Seven out of ten children with cancer in countries which are resource-rich are cured with a five-year survival for certain cancer for example retinoblastoma, now 95.0%.[4,5]

In therapeutic doses vigorously dividing normal host cells like those in the bone marrow or mucosal epithelium are sensitive to the cytotoxic effects of anti-cancer drugs. Acute side effects common to several anticancer drugs include myelosuppression, nausea, vomiting, alopecia, oro-intestinal mucositis, liver function abnormalities, allergic oro-cutaneous reactions and local ulceration from hypodermic drug extravasation. These acute side-effects occur hour to weeks after a dose and are usually reversible. The myelosuppression caused by chemotherapy leads to lowering the immunity and thus revealing patient to high risk of developing various infections.[6] The aim of chemotherapy is to be as helpful as possible with bearable side effects, since the dose of the chemotherapy will be lethal to the cancer cells as well as to the normal cells. Incidence of specific side effects would vary according to the medications or chemotherapy used. So various parameters must be taken into the consideration to prevent, lessen and overcome these side effects.[7]

Thus, the aim of the study was to see early side effects that comprises acute which develop within 24 hours and delayed which develops after 24 hours and up to 6 - 8 weeks after chemotherapy treatment in pediatric solid malignancy.

MATERIALS AND METHODS

The present cross-sectional study was conducted on 34 children aged up to 12 years and newly diagnosed pediatric solid cancer patients in the Department of Pediatric Surgery in Chacha Nehru Bal Chiktsalaya, New Delhi, India in between Nov 2018 to March 2020. After clearance from the ethical committee of the institute and written informed consent were taken from all the guardians of children for participation in the study.

PRE-CHEMOTHERAPEUTIC WORK-UP

Inclusion Criteria

1. Age≤12 years.
2. Children with newly diagnosed solid malignancy for chemo-therapy.

Exclusion Criteria

1. Hematologic malignancy
2. Patient with congenital neutropenia
3. Medically unfit for chemotherapy

METHODOLOGY

All the patients were blindly examined by an expert Paediatric surgeon and thereafter routine examinations were done to do the analysis of the side effects of chemotherapy in pediatric solid malignancy developed on day 1, day 7, then on the next scheduled chemotherapeutic cycle followed up till 8 weeks.

Patient's history was taken (from their parents or themselves) using a confidential questionnaire formulated by us. The questionnaire included questions providing information on personal data, which were properly encoded. The clinical data given by patients were then complemented with information on the diagnosis of the disease, the treatment administered, adverse effects reported, and laboratory findings.

Procedure

Patients who were prescribed chemotherapy for the first time for specific pediatric solid malignancy were enrolled and observed on day 1, and day 7 and then on the next scheduled cycle followed up till 8 weeks post-chemotherapy treatment. The demographic data of patients enrolled were recorded, particularly white blood cell count, absolute neutrophil counts, hemoglobin, and platelet level. A record of chemotherapeutic drugs given and side effects i.e. biochemical,

hematological, and clinical were noted; level of severity of side effects were recorded according to guidelines prepared by modified Hartwig and Siegel scale. Every patient enrolled was receiving prophylactic anti-emetic and adequate hydration before starting chemotherapy.In case of febrile neutropenia, i.v antibiotics (hospital policy) along with injection Filgastrim (at a dose of 15*wt;s.c. od for 3 days was given, if ANC level does not increases then continue further) is given and one cycle of chemo was skipped . WHO criteria was used to define the nutritional assessment of studied children. All the clinical data based on the examination of the patient was collected from the patient's attendant without distressing them and their attendants.

Statistical Analysis

Microsoft Excel was used in creating the database and producing graphs, while the data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23 for Windows. A comparison between groups was done by the Chi-square test used for categorical variables and One-Way ANOVA for comparing the biochemical parameters at different follow-up. A P- value $p<0.05$ was considered significant for all the tests.

RESULTS

Table 1: Distribution Of The Studied Children On The Basis Of Gender And Type Of Malignancies

Gender	Frequency (n=34)	Percentage (%)
Male	20	58.8%
Female	14	41.2%
Type of Malignancies	Frequency (n=34)	Percentage (%)
Neuroblastoma	8	23.5%
Wilm's Tumor	7	20.6%
RMS	5	14.7%
SCT	3	8.8%
Hepatoblastoma	2	5.9%
Yolk Sac Tumor	2	5.9%
ltdysgerminoma of ovary	1	2.9%
Adenocarcinoma Colon	1	2.9%
Lt Testicular Tumor With Metastasis	1	2.9%
Ca Head of Pancreas	1	2.9%
Rhabdoid Tumor of Kidney(Rt)	1	2.9%
Infantile Fibro- sarcoma	1	2.9%
PNET	1	2.9%

The males were 20 (58.8%) and females were 14 (41.2%) indicating slight male predominance in our present study. Majority of 8 (23.5%) children had neuroblastoma followed by Wilms' Tumor which were in 7 (20.6%) children, RMSwere in 5 (14.7%), SCT were in 3 (8.8%); while Hepatoblastoma and Yolk Sac Tumor Of Rt. Ovary each were in 2 (5.9%) children.

Table 2: Distribution Of The Studied Children On The Basis Of Age And Further Distributed On The Basis Of Most Common Malignancy Found

Age Distri-bution	Total children		Only Neuro-blastoma children		Only Wilms' Tumor	
	Frequency (n=34)	%	N	%	N	%
≤ 1 Year	12	35.3%	5	41.7%%	2	16.7%
2- 5 Year	16	47.1%	3	18.8%	4	25.0%
> 5 Year	6	17.6%	0	0.0%	1	16.7%

The table shows the age distribution of the studied children where the majority of children were 16 (47.1%) belonging to the age group 2-5 years, while 12 (35.3%) children were less than one year and only 6 (17.6%)children were greater than five years. Neuroblastoma was most frequent in age group ≤ 1 year (41.7%) and Wilm's Tumor was most frequent in age group 2- 5 year (25.0%).

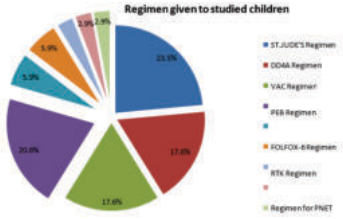

Fig. 1: Distribution Of Different Regimen Given In Studied Children

Majority of 8 (23.5%) children were given ST.JUDE'S Regimen followed by PEB regimen in 7 (20.6%) children, DD4A regimen were in 6 (17.6%) , and VAC regimen were also given in 6 (17.6%) children; while PLADO and FOLFOX-6 regimen each were in 2 (5.9%) children while RTK regimen, EE4A regimen, and VAC-I (Vincristine, Cyclophosphamide, Doxorubicin, Etoposide, Ifosfamide) were in only 1 (2.9%) in each category.

Table3: Distribution Of Studied Children On The Basis Of Clinical Side Effects And Regimen Given

Clinical Side effects	Regimen Given								
	ST.JUD E'S Regimen (n=8)	DD4A Regimen (n=6)	VAC Regimen (n=6)	PEB Regimen (n=7)	PLAD O Regimen (n=2)	FOLFO X-6 Regimen (n=2)	EE4A Regimen N (n = 1)	RTK Regimen (n=1)	Regime n for PNETn (n = 1)
Nausea	5 (62.5%)	3 (50.0%)	5 (83.3%)	5 (71.4%)	2 (100.0%)	1 (50.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Vomiting	5 (62.5%)	3(50.0%)	6 (100.0%)	6 (85.7%)	2 (100.0%)	2 (100.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Alopecia	6 (75.0%)	4 (66.7%)	6 (100.0%)	4 (57.1%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Constipatio n	6 (75.0%)	2 (33.3%)	1 (16.7%)	4 (57.1%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Anorexia	7 (87.5%)	4 (66.7%)	2 (33.3%)	6 (85.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Gastritis	4 (50.0%)	1 (16.7%)	2 (33.3%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Musculoskel etal Pain	4 (50.0%)	3 (50.0%)	4 (66.7%)	4 (57.1%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Fever	6 (75.0%)	3 (50.0%)	6 (100.0%)	6 (85.7%)	1 (50.0%)	2 (100.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Weakness	5 (62.5%)	2 (33.3%)	4 (66.7%)	4 (57.1%)	1 (50.0%)	1 (50.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Oral Ulceration	3 (37.5%)	0 (0.0%)	1 (16.7%)	3 (42.9%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Restlessness	2 (25.0%)	0 (0.0%)	2 (33.3%)	4 (57.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Diarrhea	3 (37.5%)	1 (16.7%)	2 (33.3%)	3 (42.9%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Headache	3 (37.5%)	1 (16.7%)	2 (33.3%)	4 (57.1%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Alt. Sensation	0 (0.0%)	1 (16.7%)	1 (16.7%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Neutropenia	3 (37.5%)	2 (33.3%)	5 (83.3%)	3 (42.9%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Abdominal Cramps	3 (37.5%)	1 (16.7%)	1 (16.7%)	4 (57.1%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)
Increased Breathing Efforts	4 (25.0%)	1 (16.7%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
Burning Micturition	1 (12.5%)	1 (16.7%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Skin Rashes	2 (25.0%)	1 (16.7%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ringing Ears	0 (0.0%)	1 (16.7%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1	0 (0.0%)

Hearing Loss	0 (0. 0%)	1 (16.7 %)	0 (0.0 %)	1 (14.3 %)	0 (0.0 %)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)

It was found that nausea, vomiting, alopecia, constipation were the most frequently occurring side effects in almost all the regimen used while hearing loss, skin rashes and burning micturition were the least occurring clinical side effects by the different regimen used.

Table 4: Distribution Of Severe Clinical Side Effects On The Basis Severity Of Grade

Severe Clinical Side effects	Total frequency of severe side effects	Grade-5	Grade-6	Grade-7
Nausea	2 (5.9%)	2 (100.0%)	0 (0.0%)	0 (0.0%)
Vomiting	3 (8.8/%)	3 (100.0%)	0 (0.0%)	0 (0.0%)
Alopecia	1 (2.9%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
Anorexia	1 (2.9%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal Pain	2 (5.9%)	2 (100.0%)	0 (0.0%)	0 (0.0%)
Fever	4 (11.8%)	3 (75.0%)	1 (25.0%)	0 (0.0%)
Weakness	2 (5.9%)	2(100.0%)	0 (0.0%)	0 (0.0%)
Neutropenia	13 (38.2%)	7 (53.8%)	4 (30.8%)	2 (15.4%)
Increased Breathing Efforts	1 (2.9%)	1(100.0%)	0 (0.0%)	0 (0.0%)
Ringing Ears	1 (2.9%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
Hearing Loss	1 (2.9%)	1 (100.0%)	0 (0.0%)	0 (0.0%)

Majority of the severe clinical side effects were shows the grade-5; while only neutropenia- 4 (30.8%) and fever-1 (25.0%) were in grade-6 and neutropenia -2 (15.4%) case in grade-7.

Table 5: Distribution Of Children On The Basis Of Outcome

Outcome	Frequency (n=34)	Percentage (%)
Succumbed	11	23.4%
Left study	1	2.9%
Alive up to study	22	64.7%

Out of 34 studied children 22 (64.7%) were alive and 11 (23.4%) were succumbed while one child left the study due to poor general condition. So the rate of mortality in presentstudy was 23.4%.

DISCUSSION

Cancer in children and adolescents are rare although the overall incidence of childhood cancer has been slowly increasing since 1975.[8] Worldwide, the annual number of new childhood cancer exceeds 200,000 and >80% of these are from the developing world.[1] Seven out of 10 children with cancer in the resource rich countries are cured, with 5-year survival rates for certain cancers such as Hodgkin's lymphoma and retinoblastoma approaching 95%.[9] Sharma PK et al[10] (2017) conducted a retrospective study on pediatric pharmaco- vigilance and reported the frequency of ADR increased with the number of medications. We did a prospective study to evaluate short-term side-effects post chemotherapy. The prospective nature of study avoids the bias of incomplete and missed records.

Surendiran A et al[11] (2010) used the modified Hartwig and Siegel scale to classify severity of adverse drug reaction as mild, moderate or severe with various levels according to factors like requirement for change in treatment, duration of hospital stay, and the disability produced by the adverse drug reaction. In our study the majority of children were in the age group 2-5 years {16 (47.1%)}, while 12 (35.3%) children were less than one year and only 6 (17.6%) children were greater than five year. Qureshi SS et al[12] (2018) and Sharma PK et al[10] (2017) also studied pediatric age group cases. Chemotherapy side-effects do not seem to have sex predilection. In present study the male children were 20(58.8%) and female 14(41.2%) with male:female ratio (M:F=1.4:1). The study conducted by Sharma PK et al[10] (2017) showed male predominance, while Sharma A et al[13] (2015) conducted study which showed female predominance. Sharma N et al[14] (2017) reported neuroblastoma as most common tumor in age group of 2–11 years (60%) followed by infants up to 23 months (27%), while in our study, it was most frequent in the age group ≤ 1 year (41.7%). In our study Wilms' tumor was most frequent in age group 2- 5 year (25.0%) which was consistent with Sharma N et al[14] (2017) who reported Wilms' tumor in 81.4% of children in the age group of 2–11 years.

In our study majority of the severe clinical side effects were in grade-5; while only Neutropenia-4 (30.8%) and Fever- 1 (25.0%) were in grade-6 and Neutropenia- 2 (15.4%) cases in grade-7. Hesketh PJ[15] in 2008 reported the incidence of chemotherapy-induced nausea & vomiting (CINV) as 25.0%–100.0%. Cyclophosphamide followed by cisplatin and 5-FU were the common agents responsible for CINV. In our study, 23 (67.6%) and 26 (76.5%) casesdeveloped nausea and vomiting respectively inspite of giving inj emeset prior to chemotherapy. Singh S et al[16] (2017) reported nausea and vomiting (Grade 2) in 47.0% of patients.

In our study 16 (47.1%) cases had constipation after chemotherapy. Abernethy AP et al46reported that constipation occured in 50.0–87.0% of advanced cancer patients. Yamagishi A et al47 and Anthony LB48 reported constipation as the third most common symptom in the patients receiving cytotoxic chemotherapy with an overall prevalence of 16.0%. Anorexia was seen in 21 (61.8%) cases in our study, while Hossein SA et al49 reported it in 29.0% cases. Out of 34 cases Oral Ulceration was found to be in 29.4% cases in the present study. Gandhi K et al20 (2017) reported that pediatric cancer patients going through chemotherapy had oral mucosal ulcer and mucositis as the most frequent side effects of chemotherapy. Zabernigg et al[17] conducted a study on cancer patients undergoing chemotherapy. They reported taste alterations in 69.9%, and a significant association was found between taste alterations and a change in patient's quality of life such as appetite and fatigue.

In the present study 47.1% cases observed neutropenia out of 34 studied cases which was almost half of the studied patients.Our findings were in accordance with Mohammed HB et al[18] who reported febrile neutropenia (fn) was common in the age group of 2–5 years 73 (54.0%). The rate of mortality in present study was 23.4% (11 succumed). Sharma N et al[14] (2017) studied 303 pediatric cancer patients and found that 33.9% went into remission, 35.64% were defaulters, 2.97% had stable disease, 2.31% had partial response, 3.96% were still on treatment, and 20.79% expired. In our study, one patient went LAMA, while rests are continuing their treatment.

CONCLUSION

The male children were 58.8% indicating the male predominance in our study. Wilms' Tumor was most frequent (25.0%) in age group 2- 5 years. Nausea, vomiting, alopecia, and constipation were the most frequently occurring side effects in almost all the regimen used. Neutropenia was the only severe side effect that occurs in almost all the regimens given. Majority of the severe clinical side effects was shown in grade-5; only Neutropenia shows in grade-6 and grade-7 also. Therefore it is an obligate matter for all clinicians to follow up all the cancer patients who receive chemotherapy in order to prevent or palliate any of these side effects which may appear. Moreover it is important to focus on research within this field in order to detect the proper ways which can help overcome these side effects.

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