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TOPOTECAN PLUS CYCLOPHOSPHAMIDE AS A SALVAGE REGIMEN IN PATIENTS WITH RELAPSED/REFRACTORY PAEDIATRIC TYPE TUMORS

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ABSTRACT

AIM: To assess the antitumor activity and safety profile of topotecan plus cyclophosphamide regimen in patients with relapsed/refractory paediatric type tumors and to analyze the progression free survival (PFS) and overall survival (OS) of these patients. **MATERIALS AND METHODS:** The details of patients of recurrent paediatric type tumors, treated over a period of consecutive five years from 2014 to 2018, with topotecan and cyclophosphamide regimen, were analyzed retrospectively. The patients should have had already received at least a previous chemotherapy regimen and had either a disease progression or relapse before being considered for the TC regimen. **RESULTS:** A total of 51 patients (median age 12yrs with 39 males and 12 females) received the TC regimen. The median number of cycles was 3 (range, 2–8). The response rate was: CR 0%, PR 35.3%, and disease stabilization (SD) 21.6 %. The median duration of PR in the patients was 7m (range4m -34m) and the median duration of disease stabilization was 6m (range 4m -16m). The median PFS and OS were 4m and 8m respectively. **CONCLUSION:** Topotecan plus cyclophosphamide is a well tolerated regimen for recurrent/ refractory paediatric type tumors, both in paediatric and adult populations, showing a good response rate. But, the duration of response (PFS) and OS is dismal.

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INTRODUCTION

Paediatric type tumors like sarcomas and neuroblastomas are rare. Sarcomas arise from connective tissue which includes bone, cartilage, fat, muscle, vascular, etc. They are of many subtypes which are named based on the cell type of their origin [(1)]. There are sarcoma subtypes that are common in children compared to adults like rhabdomyosarcomas (RMS), desmoplastic small round cell tumors, osteosarcomas (OSS) and ewings sarcomas /primitive neuroectodermal tumors (ES/PNET). The survival of adolescent and young adult patients with soft tissue sarcomas is way behind those of children diagnosed with a similar tumor histologically. The modalities of treatment of these aggressive tumors are surgery and radiation along with a chemotherapy backbone.

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Despite current successful multimodal therapy, a substantial number of patients relapse and need effective salvage chemotherapy. There is a lack of specific subsequent treatment regimens available. This study assessed the chemotherapy strategy of administering topotecan and cyclophosphamide (TC) in children and adolescents with relapsing or refractory sarcomas and neuroblastomas. Topotecan is a camptothecin derivative that was shown to be active in pediatric malignancies. Cyclophosphamide has been part of many regimens found effective in paediatric and adult malignancies.

MATERIALS AND METHODS

The study was a retrospective analysis, where the details of patients of recurrent solid malignancies treated at a tertiary cancer center in western India over a period of consecutive five years from 2014 to 2018, with topotecan and cyclophosphamide regimen, was assessed. The sarcoma variants included ES/PNET, RMS, OSS, pleomorphic

sarcoma, synovial sarcoma along with neuroblastomas. All the patients had already received at least a previous chemotherapy regimen and had either a disease progression or relapse before being considered for the TC regimen. There were a few patients who received TC as a third or fourth subsequent regimen. All the patients had ECOG performance status 0-2 and measurable disease. A total of 51 patients received the regimen. The TC-regimen consisted of to potecan 0.75 mg/m2 and cyclophosphamide 250 mg/m2, day1 to 5, every 21 days. The primary objective of this investigation included progression free survival (PFS) and overall survival (OS). The secondary endpoint was the response assessment, which was according to Response Evaluation Criteria in Solid Tumors 1.1 (RECIST). Kaplan and Meier's analysis was used to estimate PFS and OS. An event for PFS was disease progression or death. Death due to any cause was an event for OS. Alive patients were censored at the time of the last follow-up or contact. Prognostic factors were tested by univariate and multivariate analysis. Chi-square test was used for univariate analysis and cox-regression was used for multivariate analysis. Tests were performed using SPSS version 25 statistical software. A P value of <0.05 was used to define statistical significance.

RESULTS

A total of 51 patients received the TC regimen during the study period. The patient's baseline characteristics are listed in Table 1. The median age of the patients was 12 years (range 1–48 years). Out of 51 patients, 39 (76.5%) were males and 12 (23.5%) were females. The common histological types treated were ES/PNET with 18 patients (35.3%) followed by neuroblastoma with 15 patients (29.4%). OSS constituted 12 patients (23.5%), four patients (7.8%) had RMS, and one patient (2%) each of synovial sarcoma and pleomorphic sarcoma. Most of the primary tumors were located on the trunk (n=28, 54.9 %) and extremities (n=19, 37.2 %). Majority of the patients(n=29, 56.9%), had a localized disease at initial presentation while rest (n=22, 43.1%)were metastatic. All the patients had already received a standard induction chemotherapy regimen according to their histological subtype, before being considered for TC regimen. The different induction regimens received were VAC/IE protocol [(2)] (n=15, 29.4%), OPEC[(3)] (n=14, 27.4%), MAP[(4)] (n=10, 19.6%), VACA[(5)] (n=3, 5.8%), P+A [(6)] (n=3, 5.8%), IRS IV[(7)] (n=4, 7.8%) and IA [(8)] (n=2, 3.9%). The majority of the patients had a disease progression or relapse in the form of metastatic disease (n=42, 82.3%) whereas a local progression was seen in 9 patients (17.6%). The median duration between the completion of the induction regimen and the 2nd line TC regimen was 5m (range 1m -81 m). The median number of cycles TC received was three (range2 - 8).Out of the total patients, 18 (35.3%) had a partial response(PR) to the TC regimen, 11 (21.6%)had a stable disease(SD) while 22 (43.1%) had a progressive disease(PD). The median duration of PR in the patients was 7m (range4m -34m) and the median duration of stable disease was 6m (range 4m -16m). No differences in the response probability were seen for the line of treatment (2nd-line vs higher, P=0.34), type of relapse (local vs systemic, P=0.66) as well as histology subtype (P=0.43) (Table 2). In this study, patients with ES/PNET and neuroblastoma have had the highest control rate during TC. The toxicity profile of the TC regimen included haematological and non-haematological. The various grade 3 and 4 toxicities of the TC regimen are summarized in Table 3. At least one episode of severe neutropenia occurred in 25%, thrombocytopenia in 23% and febrile illness in 13.7 % of patients. The other side effects included nausea/ vomiting in 21%, fatigue in 31%, diarrhea in 8% and dysphagia in 6%. Median follow-up time was 20 months from the first diagnosis (range 10m-88m) and 7 months since the start of TC therapy (range 2m-34m). Median PFS and overall survival from the start of TC were 4m and 8m, respectively (Figure 1 and Figure2). Different variables were assessed for having a significant impact on PFS and OS (Table 4). Of the various factors assessed by multivariate analysis, only the number of cycles of chemotherapy received had a significant impact on both PFS and OS. Age (</=12years, >12years) and treatment response (PR+SD, PD) had a significant impact on OS but not on PFS. Other factors like gender, histologic subtype, site of primary disease (trunk/extremity), presentation (local /metastatic), type of relapse (localized /metastatic), line of treatment and time of relapse(early<6m/later) had no significant impact on PFS or OS.

DISCUSSION

Blanchet *et al* [(9)] reviewed 15 patients with a median age of 31 years, with recurrent sarcomas receiving TC regimen. The overall response rate for RMS was 33%, EWS 0%, and other sarcomas 25%. The median time to progression was 2.5 months. Our study showed a better median PFS of 4 months but had a larger population of pediatric patients who are known to show a better treatment response. Hartmann *et al* [(10)] identified thirty-nine adult patients with paediatic type relapsed or refractory sarcomas. The median age was 28 years (18–58) with 14 females and 25 males. Median PFS and overall survival from the start of TC were 2.2 and 7.9 months. There was one confirmed CR (2.6 %), PR in 8 %, and 10 patients (26.3 %) had SD. In comparison, the present study had a better PR of 35.3% and a similar SD of 21.6%. Severe leukocytopenia and thrombocytopenia occurred in 44 (versus 27 in the present study) and 36 % (versus 23%), and infection in 27 % (versus 13.7%). Non-hematological side effects consisted mainly of diarrhea and dysphagia (3 % each), fatigue (6 %) and nausea/ vomiting (8 %).

Hunold *et al* [(11)] assessed fifty-four patients, having a diagnosis of ewings sarcoma, aged 3.2–49.5 (median: 17.4) years receiving TC following first (40 patients) or second (6 patients) relapse or progression under 1st line therapy. Sixteen patients (32.6%) showed PR, 13/49 (26.5%) had SD, 14/49 (28.6%) progressed. Overall survival after 1 year was 0.61 (95%-CI 0.47–0.74). Farhat *et al* [(12)] in a single institution analysis assessed 14 patients with Ewing sarcoma receiving TC at first relapse. The response was assessable in 13 patients and showed progressive disease in 6 (46%), stable disease in 4 (31%), and partial response in 3 (23%). So there was a response in 54% of patients whereas the response rate in our patients with Ewing's sarcoma was better (66%). Saylors RL. *et al* [(13)] assessed e 83 children with recurrent or refractory solid tumors. Responses (CR and PR) were seen in RMS (10 of 15 patients), ES (six of 17 patients), and neuroblastoma (six of 13 patient). PR was seen in two of 18 patients with osteosarcoma and in one patient with a Sertoli-Leydig cell tumor. Twenty-three patients had either minor responses or stable disease. The results were better in our present study.

Table 1. Patient's baseline characteristics

Patient characteristics	Number of patients	Percentage
Gender		
Male	39	76.5
Female	12	23.5
Histology		
PNET/ES	18	35.3
Neuroblastoma	15	29.4
Osteosarcoma	12	23.5
Rhabdomyosarcoma	4	7.8
Synovial sarcoma	1	2
Pleomorphic sarcoma	1	2
Primary tumor location		
Trunk	28	54.9
Extremities	19	37.2
Head and neck	4	7.8
Tumor spread at diagnosis		
Localized	29	56.9
Metastatic	22	43.1
Prior treatment modalities		
Chemotherapy	51	100
Surgery	36	70.6
Radiation	17	33.3
Chemotherapy protocols		
VAC/IE	15	29.4
OPEC	14	27.4
MAP protocol	10	19.6
VACA	3	5.8
P+A regimen	3	5.8
IRS IV protocol	4	7.8
IA regimen	2	3.9
TC regimen treatment line		
2^{nd} line	38	74.5
3^{rd} line	11	21.6
4^{th} line	2	3.9
Number of cycles		
Median	3	
Range	1 – 8	
Type of relapse		
Localized	9	17.6
Metastatic	42	82.3

Table 2. Response to TC regimen

Histology	CR/PR/SD	PD	Total
ES/PNET	12	6	18
Neuroblastoma	10	5	15
Osteosarcoma	4	8	12
RMS	2	2	4
Synovial sarcoma	1	0	1
Pleomorphic sarcoma	0	1	1
Total	29	22	51

Table 3. Patients' adverse event profile

Toxicity	Grade 3		Grade 4	
	Number	%	Number	%
Haematological				
Anemia	4	7.8	0	0
Leucopenia	10	19.6	4	7.8
Neutropenia	7	13.7	4	7.8
Thrombocytopenia	9	17.6	3	5.8
Febrile illness	3	5.8	4	7.8
Non – haematological				
Vomiting	11	21.5	0	0
Diarrhea	4	7.8	0	0
Fatigue	15	29.4	1	1.9
Dysphagia	3	5.8	0	0

Table 4. Prognostic variables for PFS and OS

Factor	PFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
Age (</=12, >12)	1.65 (0.66-4.14)	0.27	2.74 (1.02-7.35)	0.04
Gender	1.33 (0.58-3.04)	0.49	1.35 (0.54-3.36)	1.35
Histology	0.94 (0.67-1.32)	0.75	1.26 (0.87-1.81)	0.21
Site (Trunk/extremity)	0.86 (0.35-2.11)	0.75	0.67 (0.27-1.67)	0.40
Stage (localized/metastatic)	1.00 (0.46-2.14)	0.99	0.61 (0.25-1.51)	0.29
Relapse type (local/mets)	0.98 (0.38-2.50)	0.97	1.14 (0.41-3.12)	0.79
Treatment line (2^{nd}/other)	1.18 (0.51-2.72)	0.69	0.78 (0.31-1.96)	0.60
Time of relapse (early<6m/late)	0.95 (0.47-1.93)	0.90	1.30 (0.58-2.94)	0.52
No. of cycles	0.65 (0.49-0.86)	0.01	0.68 (0.50-0.92)	0.01
Treatment Response	2.23 (1.45-4.05)	0.90	2.05 (1.20-3.50)	0.01

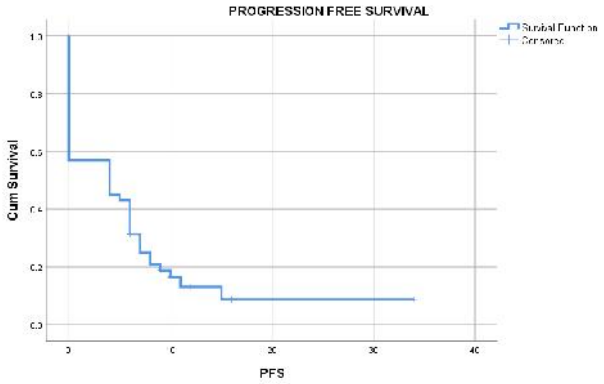

Figure 1. Kaplan Meier progression free survival curve

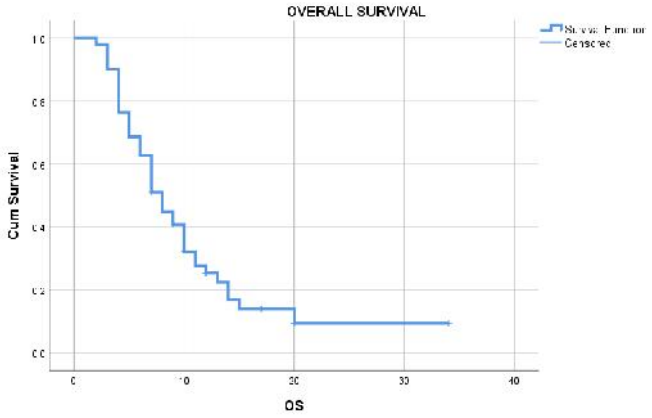

Figure 2. Kaplan Meier overall survival curve

Ashraf K *et al* [14] reviewed 27 children with neuroblastoma, in the first relapse, receiving TC regimen. Seventeen (63%) patients had an objective response. The response rate in our patients with neuroblastoma was in tune with this study (66% - 10 out of 15 patients). The median PFS was 1.2 years and the median OS was 2.3 years. Adult patients with chemosensitive paediatric sarcomas tend to have a less favorable outcome compared to children with similar histologies.

Our study had a majority of paediatric patients but still didn't have a significantly higher PFS or OS compared to this study receiving TC regimen in paediatric population. The number of cycles of chemotherapy received had a significant influence on PFS while the number of cycles, age, and response to treatment had a significant influence on OS. Other factors like age, gender, histology, primary site, etc. didn't influence the survival significantly. The limitation of our study is its retrospective nature and the small sample size.

CONCLUSION

Topotecan plus cyclophosphamide is a well tolerated regimen for recurrent sarcomas/neuroblastomas, both in paediatric and adult population showing a good response rate. But, the duration of response (PFS) and OS is dismal. Ongoing trials like the rEECur [15], may throw further light on better regimens in comparison with TC for recurrent paediatric type tumors.

Conflict of interest: None

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