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Original Article

Results of Vincristine, Cyclophosphamide and Topotecan Protocol in Refractory/Relapsed Pediatric Solid Tumors: A Single-center Experience

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ABSTRACT

Aim: Despite dramatic progress in the treatment of pediatric solid tumors in the last 3 decades, confronting a relapsed or refractory patient is still challenging. We report our experience of refractory/relapsed pediatric solid tumor patients treated with vincristin + topotecan + cyclophosphamide (VTC) as a salvage therapy.

Materials and Methods: Eleven refractory/relapsed patients (5 neuroblastoma, 4 Ewing's sarcoma, 1 rhabdomyosarcoma and 1 osteosarcoma) who were given VTC as a salvage therapy were evaluated. All of them were metastatic at diagnosis and received appropriate initial chemotherapy. VTC consisted of vincristin (1.5 mg/m^2 on day 1), cyclophosphamide (600 mg/m^2/day with mesna, on days 1 and 2) and topotecan (1 mg/m^2/day on days 1, 2 and 3).

Results: Eleven patients received a total of 53 courses of VTC with a median of 4 (range: 2-14). Median age at diagnosis was 12 years. One patient achieved complete response, 6 patients had stable disease, and 4 patients had progressive disease after 2 courses of VTC. The median survival duration was 28 months after diagnosis while it was 16 months after relapse. The median survival duration after first VTC was 5 months (2-21 months). Myelosuppression was the primary dose limiting toxicity.

Conclusion: We concluded that VTC has a clinically tolerable but non-satisfactory effect on relapsed/refractory solid tumors in children.

Keywords: Refractory solid tumors, salvage chemotherapy, VTC treatment

Introduction

Despite dramatic progress in the treatment of pediatric solid tumors in the last 3 decades, confronting a relapsed or refractory patient is still challenging. These children, almost invariably, receive multimodal therapy that consists of radiation, chemotherapy (CHEMO) and surgery making them "heavily pre-treated patients". As a result, further therapies become intolerable. At the same time, current salvage chemotherapies do not provide satisfying results yet. Thus, novel chemotherapy regimens are needed.

Topotecan (TOPO), a camptothecin analogue, produces DNA strand breaks by forming a ternary complex with DNA and topoisomerase 1 (1). After its first approval for use in the treatment of recurrent ovarian cancer in 1996, clinical trials assessing camptothecins against various types of cancer have gained speed (2). The role of camptothecins in combination CHEMO has been another debate topic since then. *In vitro* synergism of topotecan with alkylating agents was shown in various studies (3,4). Consequently, clinical studies evaluating a combination of TOPO with

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other antineoplastic agents [including cyclophosphamide (CYC)] against solid tumors has been in favor (5,6). The Children's Oncology Group conducted a phase 2, randomized comparison study of TOPO plus CYC versus TOPO alone in recurrent/refractory neuroblastoma (NBL) patients revealing significantly better progression free survival but not overall survival (7). Other recent studies, despite the considerably low toxicity profile of this combination, pointed to modest activity of TOPO+CYC and the need for better combinations (8-10).

Another chemotherapeutic agent, vincristine, is thought to have a synergistic effect when combined with other anticancer drugs (11). It is suggested for use with topotecan as well (12). Kebudi et al. (13) recently published their results of a vincristine, TOPO and CYC CHEMO protocol vincristin + topotecan + cyclophosphamide (VTC) in recurrent/progressive Ewing sarcoma (ES) patients.

In the light of this data, we opted to apply VTC as a salvage treatment protocol in refractory/relapsed pediatric solid tumor patients after 2008. Here, we report our experience of refractory/relapsed pediatric solid tumor patients treated with VTC as a salvage therapy.

Materials and Methods

Clinical and laboratory data of all refractory/relapsed pediatric solid tumor patients who had received VTC CHEMO protocol at Kocaeli University Clinic of Pediatric Oncology after 2008 were collected from the patients' database with the approval of the Local Ethics Committee. Eleven refractory/relapsed patients (5 NBL, 4 ES, 1 rhabdomyosarcoma and 1 osteosarcoma) who were given VTC as a salvage therapy were retrospectively evaluated. Informed consent for VTC treatment was obtained from all the patients/parents. VTC consisted of vincristin (1.5 mg/m^2 on day 1), CYC (600 mg/m^2/day with mesna, on days 1 and 2) and TOPO (1 mg/m^2/day on days 1, 2 and 3). VTC was given over a 2-night stay in hospital and the patients were discharged on the 3rd day of hospitalization. The courses were repeated every 21 days with adequate hematological values (absolute neutrophil count >1.000 mm^3, platelet count >100.000/mm^3). None of the patients received any other anti-cancer or investigational drugs during their VTC cycles. Physical examination and laboratory evaluation were both performed just before each cycle and also when it was required (during febrile neutropenia or before transfusion).

We recorded the patients' ages, genders, diagnoses, initial site and stage of tumor, other chemotherapies that were given prior/after VTC, data on the surgery and radiotherapy if there was any, time of relapse, presence of metastasis, status of the disease during the initiation of VTC (progression vs relapse), response after 2nd, 4th and 6th-10th VTC therapy course if available and the last status of the disease (remission/alive with disease/died of disease). The response to VTC was assessed via standard radiologic evaluations (computerized tomography, magnetic resonance imaging and ^{18}F-FDG PET/CT where available), and the following criteria were used: [complete response (CR), no evidence of disease for 4 or more weeks; partial response (PR), at least 50% decrease in all measurable lesions for 4 or more weeks; progressive disease (PD), at least 20% increase in the size of any lesions; stable disease (SD), absence of CR, PR or PD].

We provided supportive care whenever needed and also hydration, antiemetics (granisetron) and granulocyte colony stimulating factors (beginning 24 hours after the end of VTC, lenograstim) as standard treatment. We also recorded the number of febrile neutropenic attacks, days of extra hospitalization caused by febrile neutropenic attacks and demand for blood products (packed red blood cells and thrombocyte suspensions) from the beginning of the first VTC cycle to 1 month after the last VTC was given. Blood product transfusions were performed in our outpatient clinic.

Statistical Analysis

All signs and findings of toxicities were searched for and recorded from the database regarding the Common Terminology Criteria for Adverse Events v4.0 provided by the National Institute of Health.

No specific statistical analysis was used in the study as we only observed the response rate after VTC treatment. All data of the study were analyzed with Microsoft Excel, 2007.

Results

We detected 11 relapsed/refractory solid tumor patients treated with VTC at our institution between January 2008 and November 2014. The patient characteristics are shown in Table I. The median age at diagnosis was 12 years (range: 3.5-18 y). All eleven of the patients were metastatic at diagnosis and received appropriate initial CHEMO. All patients had surgical intervention but none had a complete tumor resection during the initial treatment. Ten of the patients received radiotherapy, the exception was the osteosarcoma patient (#7). All but 3 relapsed and these 3 patients (#4, #7 and #8) still had progressive disease despite ≥3rd line therapy given after diagnosis. Median time from first remission to relapse was 14 months (range: 5-36

Table I. Patient Characteristics

Patient	Age at diagnosis (years)	Gender	Diagnosis	Localization of primary disease	Metastasis	Initial CHEMO*	Primary site XRT	Time to relapse after first remission	Localisation of relapse	Relapse treatment before VTC
#1	5	M	Neuroblastoma	Right adrenal	Bone	TPOG	25 Gy	14 mon	Metastatic (Brain)	Ifosfamide+Carboplatin+Etoposide (ICE)
#2	14	M	Ewing sarcoma	Right iliac bone	Lungs	EVAIA	50.4 Gy	17 mon	Primary site	ICE
#3	12	F	Ewing sarcoma	Cervical vertebrae	Brain	EVAIA	48.6 Gy	17 mon	Metastatic (Brain)	Ifosfamide
#4	4.5	M	Neuroblastoma	Right adrenal	Lungs, bone, bone marrow	TPOG	25 Gy	no remission	N/A	ICE, Irinotecan + temozolamide
#5	3.5	F	Neuroblastoma	Left adrenal	Bone marrow	TPOG	25 Gy	8.5 mon	Primary site + Metastatic (lungs, bone)	none
#6	6	F	Neuroblastoma	Right adrenal	Bone, bone marrow	TPOG	25 Gy	10.5 mon	Primary site + Metastatic (bone marrow)	ICE
#7	18	M	Osteosarcoma	Left femur	Lungs	COG	none	no remission	N/A	Ifosfamide, Gemcitabine + docetaxel
#8	15.5	M	Ewing sarcoma	Left iliac bone	Lungs	EVAIA	45 Gy	no remission	N/A	ICE, Irinotecan + temozolamide, Gemcitabine+Docetaxel
#9	7	M	Neuroblastoma	Right adrenal	Bone, bone marrow	TPOG	25 Gy	36 mon	Metastatic (Bone, bone marrow)	ICE, Irinotecan+temozolamide
#10	14	F	Ewing sarcoma	6th right rib	Bone	EVAIA	54 Gy	12 mon	Primary site + Metastatic (lungs)	ICE
#11	14	M	Rhabdomyosarcoma	Left leg	Iliac lymph nodes	EVAIA	45 Gy	15 mon	Metastatic (lungs, bone)	none

CHEMO: Chemotherapy, XRT: Radiation therapy, ICE: Ice, compression, elevation, VTC: Vincristin + topotecan + cyclophosphamide, M: Male, F: Female, TPOG: Turkish Pediatric Oncology Group, EVAIA: IECESS Treatment Protocol, COG: Children Oncology Group Treatment Protocol, N/A: Not available

months). Only one patient (#2) had a relapse at the primary tumor site, the other 10 patients had either primary and metastatic tumors or only metastatic tumors.

The eleven patients received a total of 53 courses of VTC with a median of 4 (range: 2-14). One patient achieved CR, 6 patients had SD, and 4 patients had PD after 2 courses of VTC (Table II). None of the patients showed PR. One patient (#1) is alive and in CR while the other 10 patients died of either relapsed or progressive disease. The median survival duration was 28 months (range: 10-67 months) after diagnosis while it was 16 months (range: 2-49 months) after relapse. The median survival duration after the first VTC was 5 months (2-21 months). The patient (#1) with brain metastasis did not have surgery for metastasis but received whole brain radiotherapy (30 Gy in 10 fractions). Three NBL patients had undergone autologous stem cell transplantation with a high dose CHEMO (ASCT + HD) (#1 alive, #6 and #9 died of disease), but the other two NBL patients (#4 and #5) did not receive ASCT+HD as their parents refused. Also, one patient (#4) had 131-I-MIBG therapy. Four patients (#2, #8, #10 and #11) received palliative radiotherapy at local inoperable sites aiming to relieve pain. None of the patients had therapeutic surgery during their VTC cycles.

VTC was well tolerated. We observed hematologic toxicity to be frequent. Myelosuppression was the primary dose limiting toxicity. All patients developed grade 3-4 anemia in a total of 15 courses. There were 9 grade 3-4 thrombocytopenia episodes in 9 patients. There were 4 febrile neutropenic episodes in 3 patients, 2 of them were bacteremia, and all were managed by intravenous antibiotics administered in hospital. These episodes resulted in a total of 30 additional inpatient days. We did not encounter a non-hematological toxicity of 3 grade or over. There were no significant toxicities or deaths related to VTC. We did not need to reduce the VTC dose for any patient.

Discussion

There are many studies drawing attention to the relatively superior effect of the TOPO+CYC combination for the treatment of various types of recurrent/refractory pediatric solid tumors. Most of these studies have focused on NBL and ES patients (6-9). The Pediatric Oncology Group (POG) studied TOPO + CYC treatment in a heterogeneous group of recurrent/refractory pediatric solid tumors and demonstrated a better objective response rate (>10%) in rhabdomyosarcoma, NBL and ES patients in phase studies (5,14). Currently, we need to achieve better results and combining vincristine with TOPO + CYC appears to be a smart move as it is an M-phase specific chemotherapeutic and this leads to an expectation of an additional anti-cancer effect.

Our patient group consisted of mostly NBL and ES patients. Only 1 patient (#1) had CR and none had PR. The objective response rate (CR + PR) was 9% overall and it was 20% among the NBL group. Patient #1's relapse occurred in the brain and the other NBL patients had metastases in various places; in the lungs, bones, bone marrow and a recurrence of the tumor at the primary site. A recent report (15), assessing 8.369 pediatric NBL patients,

Table II. Study group response to VTC treatment

#	Number of VTC cycles	Response after 2nd VTC	Response after 4th VTC	Response after 6th-10th VTC	Follow-up time after first VTC	Overall follow-up time after diagnosis	Last status of patient
1	14	CR2	CR2	CR2	12 mon	29 mon	Alive
2	4	SD	PD	N/A	5 mon	38 mon	DOD
3	8	SD	SD	PD	9 mon	66 mon	DOD
4	2	PD	N/A	N/A	2 mon	10 mon	DOD
5	2	PD	N/A	N/A	2 mon	10.5 mon	DOD
6	2	PD	N/A	N/A	4 mon	13.5 mon	DOD
7	2	PD	N/A	N/A	3 mon	20 mon	DOD
8	4	SD	PD	N/A	14 mon	26 mon	DOD
9	4	SD	PD	N/A	3 mon	67 mon	DOD
10	6	SD	SD	PD	11 mon	28 mon	DOD
11	5	SD	PD	N/A	21mon	36 mon	DOD

VTC: Vincristin + topotecan + cyclophosphamide, CR: Complete response, PD: Progressive disease, SD: Stable disease, N/A: Not available, DOD: Died of disease

has shown important clinical and biological differences. We earlier speculated in another report (16) that the differentiation of NBL cells varies individually during disease progression causing differences in the response to treatment and clinical outcome. This divergence could also affect radiological and other laboratory results, as well. We believe the discrete clinical features of patient #1 are associated with his better response to VTC. Furthermore, topotecan is known to penetrate well into the central nervous system (17). In our study, overall objective response rates, both among all patients and only in the NBL group, are lower than POG's TOPO + CYC study group (5), stated as 67% in rhabdomyosarcoma, 46% in NBL, 35% in ES patients and 42% overall.

All ES patients had SD after 2 VTC cycles. We observed 2 of 4 ES patients (the other 2 progressed) to sustain SD for the first 4 VTC cycles but their disease also progressed after 6-8 cycles of VTC. Kebudi et al. (13) reported an objective response of 50% (2 patients CR, 5 patients PR) in their relapsed/progressive ES patient series (14 episodes in 13 patients) treated with VTC. In another study (8) of TOPO + CYC performed in 14 relapsed/progressive (3 metastatic at diagnosis) ES patients, 3 patients (2 with local relapse) showed PR (23%) while none had CR. Hunold et al. (6) reported "time to relapse" and "local therapy" as significant prognostic factors in their ES series (including both pediatric and adult patients) treated with TOPO + CYC.

All the studies mentioned above seem to have better response rates than ours. We do not deny the objective effects of both TOPO + CYC and VTC therapies, however, the relative low number of high stage patients in their cohorts may have resulted with inevitably biased response rates. Our patients mostly had early relapses (8 of 9 relapsed patients) and all were metastatic with high stage tumors. All these factors could be responsible for our patients' low objective response.

Study Limitations

The small sample size, heterogeneity of the diagnoses and retrospective design are the major limitations in our study.

Conclusion

We concluded that VTC has a clinically tolerable but non-satisfactory effect on refractory/relapsed solid tumors in children.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Informed consent for VTC treatment was obtained from all the patients/parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: U.D., F.Ç., M.K., Design: U.D., F.Ç., M.K., Data Collection or Processing: U.D., F.Ç., M.K., Analysis or Interpretation: U.D., F.Ç., M.K., Literature Search: U.D., F.Ç., M.K., Writing: U.D., F.Ç., M.K.

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