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The Efficacy of Camptothecin Variants on Incidental Relapsed/Refractory Malignancies of Childhood

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ABSTRACT

In this study, we aimed to assessed the effect of camptothecin derivatives (irinotecan and topotecan) on median survival and disease-free survival and their effect on treatment responses in relapsed/refractory patients in real-life settings. In our study, we retrospectively evaluated patients under the age of 18 who were followed up in paediatric haematology clinics with the diagnosis of relapsed/refractory wilms tumour, neuroblastoma, osteosarcoma, ewing sarcoma and Medulloblasoma (MB) between 2017 and 2022. Patients who received irinotecan as salvage therapy were included in the study. A total of 71 patients from a single centre in Turkey were included in the study. All patients received at least 2 lines of treatment before relapse/refractoriness. Median overall survival times according to the response groups obtained with Campthotesin were statistically significant (p<0.001). Median overall survival times according to the permanent response groups were statistically significant (p<0.001). Median disease-free survival times according to the response groups obtained with campthotecin were statistically significant (p<0.001). Median disease-free survival times (months) according to the permanent response groups were statistically significant (p<0.001). According to the results of the multivariate Cox regression model, topotecan use (p=0.037) decreased mortality (p<0.001, -2 loglikelihood=338.33). The response obtained with PR (p=0.023) increased disease-free survival, while topotecan use (p=0.034) decreased disease-free survival (p<0.001). Response and survival analyses obtained with the effect of camptothecin derivatives on topoisomerase indicate that appropriate treatment regimens containing camptothecin derivatives can be used for these patients.

Keywords: Camptothecin; Relapsed/Refractory malignancies; Irinotecan; Topotecan

INTRODUCTION

Camptothecin (CT), a monoterpene indole alkaloid with strong anticancer effect, was produced by Monroe E. Wall in 1957. In 1985, its effect on DNA topoisomerase I enzyme was demonstrated and its semi-synthetic derivative irinotecan was confirmed for clinical utilize in Japan in 1994. Subsequently, irinotecan and topotecan were approved for clinical use in the USA in 1996. It shows its antitumoural effect by acting on DNA topoisomerase I enzyme. It is known to have a specific effect on S-phase. Topoisomerases are important enzymes that control DNA topology and play an active role in DNA replication, repair and transcription. Topoisomerase I causes a single chain break in DNA, the enzyme binds covalently to the end of the chain and an enzyme-DNA complex is formed. Camptothecin prevents the separation of the DNA-Topoisomerase enzyme complex and replication cannot continue. It causes the chain to break. When the other chain is broken by DNA polymerase, it causes cell death as a result of cell damage.

Irinotecan (IT) is a water-soluble, semi-synthetic derivative of camptothecin. Its active metabolite is SN-38 (7-ethyl-10-hydroxycamptothecin). Topotecan (TT) has increased solubility compared to camptothecin and 10-hydroxy camptothecin with the tertiary amine group added at position 9. It is the first topoisomerase I inhibitor approved by the Food and Drug Administration (FDA) in the USA after camptothecin. As a result of clinical trials, it has been observed that treatment with sustained release method is more effective than single and high dose drug administration. Wilms' Tumour (WT) accounts for 5.9% of all childhood malignant tumours and is the most common renal tumour in childhood. WT is most commonly seen in children between 1 and 5 years of age. It occurs equally in both genders. The prognosis of patients with WT is the most favourable among all solid tumours and has reached a survival rate of 85% in all cases. The 4-year survival in relapsed patients is between 50%-80%.

Osteosarcoma (OS) is a rare malignancy and is a primary malignant tumour of bone characterized by the production of osteoid or immature bone by malignant cells. Approximately 750 to 900 cases are diagnosed each year in the United States, 400 of which are in children and adolescents under 20 years of age. As in other bone malignancies, the principal treatment consists of adjuvant and neoadjuvant chemoterapy and radiotherapy. There is no guideline-guided survival analysis in osteosarcoma, but it is known that the majority of patients relapse within 10 years.
Neuroblastomas (NRB) are tumours that arise from primitive sympathetic ganglion cells and paragangliomas and cause catecholamine synthesis. Neuroblastomas originate from neuroblastic tumours in 97% of cases and exhibit a spectrum ranging from spontaneous remission to aggressive progression. Treatment consists of intensive multiple combination chemotherapies including doxorubicin, cyclophosphamide, a platinum drug and etoposide in addition to surgical treatment. The aim of treatment is to achieve at least partial remission and to treat metastatic disease, if any. In one study, 3-year EFS was 78% and OS was 91% in stage 4 patients, while EFS was 67% and OS was 87% in the unfavourable group. This indicates that other treatment options and modalities are needed for these patients. Approximately 20% of high-risk neuroblastoma patients are at risk of relapse or refractory disease. Approximately 40% of patients who have completed all standard chemotherapy will experience disease relapse [1].
Ewing Sarcoma (EWS) is a rare malignancy that occurs mostly as an undifferentiated primary bone tumour and more rarely in soft tissue. EWS has a peak incidence at two different ages, 10 years and 20 years. Approximately 70% of patients are under 20 years of age. It tends to involve lung, bone and bone marrow. While 5-year survival was 36% previously, it is now up to 56%.
Medulloblastoma (MB) is the most common brain tumour occurring in childhood and originates primarily in the cerebellum. Approximately 500 children in the USA are diagnosed with MB each year. There are usually 2 peak periods, 5 and 10 years of age. Approximately 70% of patients are diagnosed before the age of 20. It is caused by mutations in patched-1 (*PTCH1*) gene, tumour protein p53 (*TP53*) gene, Familial Adenomatous Polyposis (*FAP*) gene, Adenomatous Polyposis Coli (*APC*) genes which may predispose to malignancy in 5%-6% of patients. Among the most important factors determining MB survival is the stage of the disease at the time of diagnosis. While 5-year survival is 78% in early stage (M0-M1) disease, survival is 21% in advanced stage (M2-M3) disease [2].
In this retrospective study, we firstly wanted to present real-life data in Turkey. Treatment options standardized by guidelines for R/R WT, NRB, OS, EWS and MB patients are limited. Considering that these patients in the R/R group and their management are different from the use in primary care settings, we aimed to evaluate the effect of camptothecin derivatives (irinotecan and topotecan) on median survival and disease-free survival and their effect on treatment responses in R/R patients in real-life settings. We believe that the results of this study will provide important contributions to the literature in determining treatment options for R/R WT, NRB, OS, EWS and MB patients.

MATERIALS AND METHODS

Study participants

In our study, we retrospectively evaluated patients under the age of 18 who were followed up in paediatric haematology clinics with the diagnosis of R/R wilms tumour, ewind sarcoma, neuroblastoma, osteosarcoma and medulloblasoma between 2017 and 2022. Patients who received irinotecan as salvage therapy were included in the study. A total of 71 patients from a single centre in Turkey were included in the study. All patients received at least 2 lines of treatment before relapse/refractoriness. Regimens containing gemcitabine, docetaxel, ifosfamide, carboplastin, doxorubicin, epirubicin, vincristine, doxorubicin, cyclophosphamide, methotrexate and vinblastine were used before R/R disease [3].

Patients

A total of 76 patients were treated with either of the campthotecin analogues during the study period. Topotecan or irinotecan containing chemotehrapy protocols were used as salvage treatment agents.
Inclusion criteria for the study were:

- Patients under 18 years of age.
- Patients with relapsed/refractory wilms tumour, neurobasltoma, ewing sarcoma, osteosarcoma and medullablastoma.
- Patients receiving irinotecan or topotecan as salvage therapy.
- Patients who have not yet been treated with haematopoietic stem cell transplantation.

Inclusion criteria for the study were:

- Patients aged 18 years and over.
- Patients with wilms tumour, neurobasltoma, ewing sarcoma, osteosarcoma in remission.
- Patients receiving irinotecan or non-topotecan therapy as salvage treatment.

Wilms tumour, neurobasltoma, ewing sarcoma, osteosarcoma and medulloblastoma were diagnosed histopathologically. Staging was performed with Positron-Emission Tomography-Computerised Tomography (PET-CT) or Magnetic Resonance Imaging (MRI). Besides the demographic data of the patients, gender, age, histopathological diagnoses, follow-up time, time of CCR start, date of progression after CCR, number of chemotherapy protocols used before CCR, the status of patient at last visit and outcome were recorded. Response evaluation was made according to individual requirements. Patients without additional symptoms or clinical deterioration were evaluated with Positron-Emission Tomography-Computerized Tomography (PET-CT) or Magnetic Resonance Imaging (MRI) after 3 courses of CCR (first response evaluation). Patients who experienced new symptoms or clinical findings after start of BCR were accepted as clinical progression and assessed immediately. In case of clinical or radiological progression CCR was cessated. Follow-up time, time to progression and follow-up time after CCR were assessed [4].

Treatment

The chemotherapy protocols used are topotecan (1 mg/m^2/day 1-5 days, in every 21 days) combined with cyclophosphamide (200 mg/m^2/day 1-5 days and vincristine (1.5 mg m^2/day 1); irinotecan (150 mg/m^2/day 1, in every 21 days) combined with temozolomide 125 m^2/day 1-5 days and vincristin 1.5mg m^2/day 1; irinotecan (150 mg/m^2/days 1,14) combined with temozolomide 125 m^2/day 1-5 days and bevacizumab 10 mg/kg/days 1,14). This study was conducted in accordance with the principles of the declaration of Helsinki and approved by the scientific ethics committee of health sciences University faculty of medicine Adana City hospital [5].

Statistical method

Statistical analyses were performed using SPSS version 25.0 statistics for Windows (IBM, NY, USA). Descriptive data were expressed as mean ± SD for continuous variables and n and % for categorical variable. The method of Kaplan-Meier was used for the comparison of Cmtile obtained response, campthotecin types, permanent response and times of survival and disease-free survival times between disease groups. For various clinical factors, multivariate cox regression method on mortality risk and disease-free survival times are given. $p<0.05$ values were considered significant [6].

RESULTS AND DISCUSSION

There were a total of 71 patients in the study. Among all patients, 53.5% were male and the mean age was 11.05 ± 5.33 years. The mean follow-up period was 36.94 ± 23.81 months. Disease groups, progression, permanent response, mortality, response obtained from camptothecin and frequency analyses are shown in Table 1.

Table 1: Distribution of clinical information about the patients (n=71).

Demographic variables		**N**	**%**
Gender	Female	33	46.5
	Male	38	53.5
Disease groups	WT	8	11.3
	NRB	16	22.5
	OS	8	11,3
	EWS	15	21.1
	MB	24	33.8
Response obtained from camptothecin	CR	12	16.9
	PR	12	16.9
	SD	11	15.5
	PRD	36	50.7
Permanent response	Yes	14	19.7
	No	57	80.3
Mortality	Alive	18	25.4
	Ex	53	74.6
Progression	No	18	25.4
	Yes	53	74.6

Overall median survival (months) was 30.60 (95% CI: 25.24-35.95). 2-year survival was 67.5% and 5-year survival was 22.3%. Median overall survival times (months) according to disease groups did not show a statistically significant difference (p=0.711). In the group of the WT, 2-year survival was 75% and 5-year survival was 37.5%, in the neuroblastoma group, survival of 2-year was 55.6% and survival of 5-year was 16.7%, in the osteosarcoma group, survival of 2-year was 87.5% and survival of 5-year was 25%. In the Ewing sarcoma group, survival of 2-year was 66.7%, survival of 5-year was 17.8%, in the medullablastoma group, 2-year survival was 70.8%, 5-year survival was 23.3%. OS comparisons of patients are shown in Table 2 [7].

Table 2: Comparison of patients' OS times

Overall Survive (months)	**Median (%95 CI)**	**2 years survival %**	**5 years survival %**	**p**
Overall	30.60 (25.24-35.95)	67.5%	22.3%	
Disease groups				
WT	49.93 (3.50-96.36)	75.0%	37.5%	0.711
NRB	27.73 (16.06-39.40)	55.6%	16,7%	
OS	30.60 (26.62-34.57)	87.5%	25.0%	
EWS	28.76 (24.22-33.31)	66.7%	17.8%	
MB	34.06 (23.70-44.42)	70.8%	22.3%	
Cmtile obtained respons				
CR	-	100.0%	91.7%	<0.001
PR	25.13 (5.27-44.99)	58.3%	16.7%	
SD	38.63 (26.19-51.07)	90.9%	27.3%	
PRD	25.90 (21.81-29.99)	52.5%	0.0%	
Campthotecin types				
Irinotecan	25.90 (22.41-29.38)	58.3%	7.0%	0.035
Topotecan	31.13 (0.00-62.67)	62.7%	24.3%	

Irinotecan+topotecan	34.76 (26.98-42.54)	78.6%	30.6%	
Permanent response				
Yes	-	100.0%	92.3%	<0.001
No	27.46 (23.91-31.01)	59.5%	6.5%	

Median overall survival times (months) according to the response groups obtained with campthotesin were statistically significant (p<0.001). Median survival (months) in the Complete Respond (CR) group was not reached. Median survival (months) in the partial response (PR) group was 25.13 (95% CI: 5.27-44.99), median survival (months) in the Stable Disease (SD) group was 38.63 (95% CI: 26.19-51.07) and median survival (months) in the progressive disease (PRD) group was 25.90 (95% CI: 21.81-29.99). There was a statistically significant difference in median survival times between CR group and PR (p=0.001), SD (p=0.004) and PRD (p<0.001) groups, between PR group and PRD (p=0.045) groups and between SD group and PRD (p=0.019) groups. While survival of 2-year was 100% in CR group, survival of 5-year was 91.7%. In PR group, survival of 2-year was 58.3% and survival of 5-year was 16.7%. In the SD group, survival of 2-year was 90.9% and survival of 5-year was 27.3%. In the PRD group, survival of 2-year was 52.5% and survival of 5-year was 0%.

Median overall survival times (months) according to campthotecin types groups were statistically significant (p=0.035). Survival of median (months) in the irinotecan group was 25.90 (95% CI: 22.41-29.38), survival of median (months) in the topotecan group was 31.13 (95% CI: 0.00-62.67) and survival of median (months) in the irinotecan+topotecan group was 34.76 (95% CI: 26.98-42.54). A statistically significant difference was found between the irinotecan group and irinotecan+topotecan (p=0.015) groups in terms of median survival times. In the irinotecan group, survival of 2-year was 58.3% and survival of 5-year was 7%. In the topotecan group, survival of 2-year was 62.7% and survival of 5-year was 24.3%. In the Irinotecan+Topotecan group, survival of 2-year was 78.6% and survival of 5-year was 30.6% (Table 2).

Median overall survival times (months) according to the permanent response groups were statistically significant (p<0.001). Median survival (months) was not reached in the permanent response group and median survival (months) was 27.46 (95% CI: 23.91-31.01) in the non-permanent response group. In the group with permanent response, 2-year survival was 100% and 5-year survival was 92.3%. In the group without permanent response, 2-year survival was 59.5% and 5-year survival was 6.5% (Table 2) [8].

Progression Free Survival (PFS) comparisons of patients are shown in Table 3. Overall median disease-free survival (months) were 18.20 (95% CI: 14.16-22.23). Disease-free survival of 2-year was 36.5% and survival of 5-year was 24%. Median disease-free survival times (months) according to disease groups did not show a statistically significant difference (p=0.843). In the WT group, the 2-year disease-free survival was 50%, while the disease-free survival of 5-year was 37.5%. In the Nnı group, the disease-free survival of 2-year was 37.5%, while the disease-free survival of 5-year was 30%. In the osteosarcoma group, disease-free survival of 2-year was 37.5% and disease-free survival of 5-year was 12.5%. In the Ewn group, disease-free survival of 2-year was 26.7% and disease-free survival of 5-year was 20%. In the Sss group, disease-free survival of 2-year was 37.5% and disease-free survival of 5-year was 25% (Table 3).

Table 3: Progression-Free Survival (PFS) comparisons of patients.

Disease-free survival (months)	**Median (%95-CI)**	**2 years PFS %**	**5 years PFS %**	***p***
Overall	18.20 (14.16-22,23)	36.5%	24.0%	
Disease groups				
WT	18.50 (0.00-47.09)	50.0%	37.5%	0.843
NRB	16.00 (12.99-19.00)	37.5%	30.0%	
OS	13.76 (5.35-22.17)	37.5%	12.5%	
EWS	18.00 (14.00-21.95)	26.7%	20.0%	
MB	20.46 (13.06-27.86)	37.5%	25.0%	
Cmtile obtained response				
CR	-	100.0%	78.6%	<0.001
PR	15.36 (12.65-18.08)	25.0%	16.7%	
SD	13.76 (1.86-25.67)	27.3%	0.0%	
PRD	16.06 (13.66-18.46)	21.6%	4%	
Campthotecin types				
Irinotecan	15.56 (10.92-20.21)	29.2%	12,5%	0.155
Topotecan	23.60 (0.00-49.36)	46.8%	33,4%	
Irinotecan+topotecan	18.50 (16.55-20.44)	35.7%	28,1%	
Permanent response				
Yes	-	92.9%	82.5%	<0.001
No	16.00 (13.92-18.07)	22.6%	8.6%	

Median disease-free survival times (months) according to the response groups obtained with campthotecin were statistically significant (p<0.001). Median disease-free survival (months) was not reached in CR group. In PR group, median survival of disease-free (months) was 15.36 (95% CI: 12.65-18.08), in SD group median survival of disease-free (months) was 13.76 (95% CI: 1.86-25.67) and in PRD group median survival of disease-free (months) was 16.06 (95% CI: 13.66-18.46). A statistically significant difference was found between the CR group and PR (p=0.001), SD (p=0.002) and PRD (p<0.001) groups in terms of median disease-free survival time. In the CR group, disease-free survival of 2-year was 100% and disease-free survival of 5-year was 78.6%, while in the PR group, disease-free survival of 2-year was 25% and disease-free survival of 5-year was 16.7%. In the SD group, disease-free survival of 2-year was 27.3% and disease-free survival of 5-year was 0%. In

the PRD group, disease-free survival of 2-year was 21.6% and disease-free survival of 5-year was 4% (Table 3).
There was no statistically significant difference between camptothecin species groups in terms of median disease-free survival (months) (p=0.155). In the irinotecan group, disease-free survival of 2-year was 29.2% and disease-free survival of 5-year was 12.5%. In topotecan group, disease-free survival of 2-year was 46.8% and disease-free survival of 5-year was 33.4%. In the irinotecan+topotecan group, disease-free survival of 2-year was 35.7% and disease-free survival of 5-year was 28.1% (Table 3).
Median disease-free survival times (months) according to the permanent response groups were statistically significant (p<0.001). The median disease-free survival time (months) was not reached in the permanent response group, while the overall disease-free survival time (months) was 16.00 (95% CI: 13.92-18.07) in the non-permanent response group. In the group with permanent response, disease-free survival of 2-year was 92.9% and disease-free survival of 5-year was 82.5%. In the group without permanent response, disease-free survival of 2-year was 22.6% and disease-free survival of 5-year was 8.6% (Table 3).

Multivariate Cox regression results of parameters are shown in Table 4.

Table 4: Multivariate Cox regression results of parameters.

	OS		**PFS**	
	Multivariate		**Multivariate**	
	HR (95%CI)	**p**	**HR (95%CI)**	**p**
Cmtile obtained response (ref: CR)				
PR	4.205 (0.80-21.94)	0.088	6.36 (1.28-31.46)	0.023
SD	2.73 (0.48-15.29)	0.253	3.51 (0.65-18.90)	0.143
PRD	4.76 (0.93-24.35)	0.061	3.88 (0.82-18.16)	0.085
Campthotecin types (ref: Irrinotecan) Topotecan Irinotecan+topotecan Permanent response (ref: None)	0.45 (0.21-0.95) 0.46 (0.21-1.01)	0.037 0.051	0.45 (0.21-0.94) 0.68 (0.32-1.45)	 0.034 0.322
	p<0.001; -2 Log Likelihood=338.33		p<0.001; -2 Log Likelihood=352.70	

Campthotecin achieved response, campthotecin types and permanent response variables were statistically significant in terms of mortality risk and disease-free survival (p<0.05). These variables, which were found significant as a result of univariate analyses and multivariate Cox regression model. According to the results of the multivariate Cox regression model, topotecan use (HR:0.45; 95% CI: 0.21-0.95; p=0.037) decreased mortality (p<0.001, -2 loglikelihood=338.33). The response obtained with PR (HR:6.36;95%CI: 1.28-31.46; p=0.023) increased disease-free survival, while topotecan use (HR:0.45;95%CI: 0.21-0.94; p=0.034) decreased disease-free survival (p<0.001, -2 loglikelihood=352.70) (Table 4).

DISCUSSION

The lack of a proven salvage treatment option for patients with relapsed-refractory paediatric solid tumours such as wilms tumour, neuroblastoma, ewing sarcoma, osteosarcoma and medulloblasoma has been the most important factor determining survival in this disease group. In addition to the low remission rates obtained with various treatment regimens used, the duration of remission obtained and the short average survival time have led to the use of different salvage treatment options. In addition, relapsed refractory patients consist of patients who have been exposed to long-term cytopenia and infection due to both their disease and the chemotherapy they have previously received and are currently receiving. The aim for this patient group is treatment options that will prevent relapse, cause less toxicity and prolong survival. WT, OS, ES and NRB and MB patient groups consist of a population similar to the patient group documented in the literature in terms of age, gender, quality and number of previous chemotherapy regimens.
Patients with WT are in the good prognostic group among paediatric malignancies, but 5-year survival is 65%-75% even in stage 4 cases. The relapse rate in wilms' tumours is only approximately 15% even in patients with good risk group. An optimal salvage therapy for relapsed WT patients has not yet been clearly defined. Many different chemotherapy regimens (cyclophosphamide, ifosfamide, carboplatin, etoposide and cisplatin) have been use. The results of haematopoietic stem cell transplantation (HSCT) treatments are also not clearly known. The 4-year survival in relapsed patients varies between 50-80% in the literature. In a study using cyclophosphamide and carboplatin with surgery and radiotherapy as salvage treatment, 4-year EFS was 42% and OS was 48%. In our study, 2-year mean survival was 75% and 5-year survival was 37.5% in the WT relapse refractory patient group. Although disease-free survival of 2-year was 50%, disease-free survival of 5-year was 37.5%. Our findings are consistent with the literature and constitute an option for a sub-therapeutic salvage treatment in this disease group in which even the results of HSCT have not yet been demonstrated.
Surgical treatment is the mainstay of treatment for newly diagnosed OS patients and provides a significant survival advantage in combination with chemotherapy. However, there is still no standardized treatment regimen and approach for OS patients. Methotrexate plus doxorubicin and cisplatin (MAP) regimen is recommended by the American osteosarcoma study group. In the European osteosarcoma intergroup study, 1/3 of 565 relapsed osteosarcoma patients were given treatment and 5-year survival analyses showed that while survival in 2 years was 35%, it was 14% after 2 years. In our patient cohort, 2-year mean survival after irinotecan and topotecan based chemotherapy salvage regimens was 87.5% and mean survival of 5-year was 25%. While disease-free survival of 2-year was 37.5%, disease-free survival of 5-year was 12.5%, which was similar to the literature. Salvage therapy with camptothecin derivatives may be one of the treatment options for R/R OS patients.

Treatment of neuroblastoma patients consists of intensive multiple combination chemotherapies including doxorubicin, cyclophosphamide, a platinum drug and etoposide in addition to surgical treatment. In a study conducted in newly diagnosed NRB patients, 3-year EFS was 78% and OS was 91% in stage 4 patients, while EFS was 67% and OS was 87% in the unfavourable group. This indicates that other treatment options and modalities are needed for these patients. There is no standardised treatment regimen for relapsed or refractory disease and the options are very limited. Approximately 20% of high-risk neuroblastoma patients are at risk of relapse or refractory disease. Up to 40% of patients who have completed all standard chemotherapy will experience disease relapse. Despite autologous haematopoietic stem cell treatment and high-dose chemotherapy, only approximately 50% of high-risk patients have a chance of long survival. This rate is only 15% in patients who received prior aggressive treatment. In our study cohort of R/R Neuroblastoma patients, the mean survival of 2-year was 55.6% and the mean survival of 5-year was 16.7%. Disease-free survival of 2-year was 37.5% and disease-free survival of 5-year was 30%. These results are similar to previous studies and suggest that camptothecin derivatives can be used as salvage therapy especially for patients in the poor risk group and R/R patients.
With current treatment regimens in newly diagnosed ES patients, 5-year survival has increased from 36% previously to 56% today. In metastatic disease, there are studies adding the cyclophosphamide, doxorubicin, vincristine and Ifosfamide plus Etoposide (I/E) to this treatment. In the report presented by the European Ewing Tumour Groups, the late relapse rate in ES patients with 5-year survival was reported to be 13%. Survival in ES patients is very low after relapse and has been found to be only 15%-20%. In relapsed ES patients, high-dose ifosfamide or Irinotecan plus Temozolomide (IT) is used as salvage therapy. In relapsed/refractory EWS patients, 4 different chemotherapy regimens (high-dose ifosfamide, irinotecan plus temozolomide, topotecan plus temozolomide and gemcitabine plus docetaxel) were used. In addition, studies on carboplatin plus etoposide and targeted therapies (ifosfamide plus lenvatinib) are still ongoing. In our ES patients, mean survival of 2-year was 66.7% and mean survival of 5-year was 17.8%, disease-free survival of 2-year was 26.7% and disease-free survival of 5-year was 20%. It is known that survival rates are low in R/R ES patients, targeted therapies are promising, but camptothecin derivatives, which are currently available treatment options, are observed to increase response rates in this patient group [9].
A standardised treatment regimen for R/R MB patients has not yet been established. Regimens based on reoperation followed by RT and systemic chemotherapy is used. Systemic chemotherapy regimens usually consist of cisplatin, lomustine and vincristine cyclophosphamide. Consolidation treatment with autologous stem cell transplantation is another treatment option that is being used in patients who achieve remission after relapse. Prolonged disease-free survival in relapsed patients is observed only in 20%-25% of cases. In our patient cohort, 2-year survival analysis of R/R medulloblastoma was 70.8% and 5-year survival analysis was 22.3%. Our results were consistent with the literature. Both irinotecan and topotecan-containing salvage regimens may be among the limited salvage treatment options for this patient population.
Irinotecan is mainly used for carcinomas of the colon, while topotecan has been used primarily for ovarian cancers, although both drugs have TOP1 in their target similarly. The different indications were mostly determined empirically by clinical trials. In a previous study evaluating camptothecin analogues in neuroendocrine tumours, there was no statistical difference between irinotecan and topotecan-containing regimens on response to second-line therapy. Both irinotecan and topotecan have previously demonstrated efficacy in patients with ovarian ca and lung ca where mechanisms of resistance are involved. There was no statistical difference between topotecan-containing regimens and CEI (cisplatin, etoposide and irinotecan)-containing regimens in terms of survival advantage in patients with solid malignancies. We found no statistically significant difference between irinotecan and topotecan on survival in all patient groups. Our results were in parallel with the results of previous studies. Camptothecin derivatives may be used in combination therapies in MB, OS, EWS, WT and NRB patients due to their effects on topoisomerase in relapse refractory patients [10].
Our study has some limitations. Firstly, our study is based on retrospective analysis. The fact that the patient groups were not randomized one-to-one and there was no control group is another limitation. Although the low number of patients is another limitation, sufficient number of patient data was reached as single center data in terms of analysis.

CONCLUSION

Our study has several conclusions. First of all, relapses of WT, NRB, EWS, OS and MB, which are the most common malignancies of childhood, have a significant negative effect on survival if they are refractory. In addition, the lack of an optimal treatment option determined by guidelines for R/R patients constitutes an important problem for this patient group. Response and survival analyses obtained with the effect of camptothecin derivatives on topoisomerase indicate that appropriate treatment regimens containing camptothecin derivatives can be used for these patients. Especially for a patient population that has exhausted treatment options. Furthermore, the lack of differences between irinotecan or topotecan treatments increases the number of chemotearpy regimens with camptothecin derivatives. In 5 patient groups (WT, NRB, OS, EWS, MB), a 2-year median survival of 55.6% to 87.5% and a disease-free survival of 26.7% to 50% were achieved. Irinotecan and topotecan-containing regimens were effective on survival in patients who had received multiple lines of prior therapy in our relapsed refractory patient cohort. However, survival results and response evaluations are needed in multicentre, prospective studies with long-term follow-up protocols including control groups, randomised in terms of disease characteristics and previous treatment. Thus, appropriate treatment guidelines can be established for R/R patients.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests

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INFORMED CONSENT

The authors declare that the patients included in the study signed informed consent forms to use their medical information in the studies.

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