Clinical features of Ewing and chondrosarcoma

Maldegem, A.M. van

Chapter 4

Etoposide and carbo-or cisplatin combination therapy in refractory or relapsed Ewing sarcoma: a large retrospective study

Annemiek M. van Maldegem, Charlotte Benson, Piotr Rutkowski, Jean-Yves Blay, Henk van den Berg, Joanna Placzke, Meybrit Rasper, Ian Judson, Heribert Juergens, Uta Dirksen, Hans Gelderblom

Pediatr Blood Cancer 2015 Jan;62:40-44

Abstract

Introduction

Patients with Ewing sarcoma who develop refractory or relapsed disease have limited treatment options. In some sarcoma centres in Europe the combination of etoposide with carbo- or cisplatin is being used for these patients, however there are no published data available yet. Here we investigated the outcome of the combination treatment for patients with advanced Ewing sarcoma in progression after standard treatment.

Materials and methods

All patients diagnosed with Ewing sarcoma between 1980 and 2012 in one of 6 major sarcoma centres in Europe and treated with either carboplatin and etoposide or cisplatin and etoposide were included and data were retrospectively collected for analysis.

Results

A total of 107 patients enrolled in this study of which 61 received the combination of etoposide and carboplatin and 46 received etoposide and cisplatin. The median overall survival (OS) was 23 months for both patient groups and the 5-year OS was 24.5% for the patients who received carboplatin and etoposide and 20% for those who received cisplatin and etoposide. The progression free survival was better in patients treated with the combination of carboplatin and etoposide (14.5 versus 6.3 months p=0.023).

Conclusion

This is a retrospective study on the combination treatment of etoposide and carbo- or cisplatin in refractory Ewing sarcoma. The results justify exploring the combination in a prospective study with relapsed patients.

Introduction

Ewing sarcoma (EWS) is a rare disease with an annual incidence of approximately 3 per million new cases each year [1]. EWS affects mostly children and adolescents with a peak incidence at age fifteen [2]. It arises in bone and to a lesser extent in soft tissue with the most common primary sites being the pelvis and the long tubular bones. EWS is associated with chromosomal translocations involving the *EWS* gene on chromosome 22 and an ETS transcription factor gene, the commonest translocation, t(11;22)(q24;12), resulting in the EWS-FLI1 fusion protein [3]. For patients with localised disease 5 year survival rates have improved to 70% in the last decades [4, 5]. However, 25% of all patients present with metastatic disease, mostly to the lungs or bones. The survival rates for these patients are much lower, around 50% for patients with only lung metastases and around 20% for patients with bone metastases [6, 7]. Following relapse, the prognosis is poor with 5 year overall survival of 13% [8].

When patients develop relapsed or refractory disease with no local treatment options several palliative chemotherapy regimens are used. In some sarcoma centres in Europe these patients are treated with either the combination of carboplatin and etoposide (carbo-eto) or cisplatin and etoposide (cis-eto). Carboplatin and cisplatin belong to the group of platinum-based antineoplastic agents and generating several types of DNA damage that are difficult to repair and lead to cell death. Carboplatin has fewer side effects than cisplatin; however, in some tumour types, namely testis, the drug is considered to be less effective. Etoposide belongs to the topoisomerase inhibitor family and forms a complex with DNA and topoisomerase II enzyme thereby preventing re-ligation of DNA strands and causing them to break [9].

Because there is no published literature on the effect of the two agent combination of etoposide with a platinum-based antineoplastic agent for patients with relapsed or refractory Ewing sarcoma, we retrospectively collected the overall survival data of these patients who received the combination and also looked at possible prognostic factors for survival.

Materials and methods

Patient data were collected retrospectively from the archives of 5 sarcoma centres in Europe (Leiden University Medical Center, Leiden, the Netherlands; Royal Marsden Hospital, London, United Kingdom; Memorial Cancer Center, Warsaw, Poland; Emma Children's Hospital, Amsterdam, the Netherlands; Centre Leon Berard, Lyon, France;). The data for

the patients treated in Germany were collected from the sarcoma relapse registry (SAREZ) and the Ewing relapse registry of the cooperative Ewing sarcoma study group (CESS). All successive patients diagnosed with Ewing sarcoma between 1980 and 2012 were identified. From these a subpopulation was made for patients treated with either carbo-eto or cis-eto. These patients were included in the analysis and the following data were collected: patient identification number, gender, date of birth, date of first diagnosis, date of last contact or death, tumour location at onset, location of metastases, outcome of previous treatment lines, date of start carbo-eto or cis-eto treatment, number of treatment cycles, date of progression and major toxicity. Overall survival (OS) and progression free survival (PFS) was calculated using the Kaplan and Meier method and compared with the log-rank test.

Results

A total of 107 patients were treated with the carbo- or cisplatin and etoposide combination from 1980 until 2012 and all were enrolled in this study, 61 received carbo-eto, 46 received cis-eto. The characteristics of these patients are shown in Table 4.1. The treatment was given either weekly carboplatin or cisplatin on day 1 and etoposide on day 1–3 or 3-weekly carboplatin or cisplatin on day 1 and etoposide on day 1–2 or 3. The most common schedule for the carbo-eto patients was for the weekly treatment 120 mg/m^2 carboplatin and 100 mg/m^2 etoposide both given intravenously and for the 3-weekly regimen 200 mg/m^2 carboplatin and 100 mg/m^2 etoposide also given intravenously. For the cis-eto patients the most frequently used treatment regimen was for the weekly schedule 60 mg/m^2 cisplatin intravenously and 50 mg etoposide orally and for the 3-weekly regimen 50 mg/m^2 cisplatin intravenously and 150 mg/m^2 etoposide intravenously. Within the limitations of evaluating toxicity data in a retrospective study no cases of hearing loss or secondary cancers were reported, but there were 2 cases of renal insufficiency. However this data may be incomplete and toxicity was not always reported according to common toxicity data. The median OS calculated from start of treatment until death or last patient contact was 23 months for both patient groups (Figure 4.1). The PFS after start of the treatment is better in the patients treated with the combination of carbo-eto (mean = 14.5 months) than patients treated with cis-eto (mean = 6.3 months) (Figure 4.2). Of the patients in the carbo-eto group 68% were pretreated with etoposide, for the cis-eto group this was 75%. The response data are shown in Table 4.2, with 10 CR (31%), 7 PR (20%), 3 SD (8%) and 14 PD (40%) in the carbo-eto group and 4 CR (10%), 7 PR (19%), 10 SD (27%) and 16 PD (43%) for the cis-eto group. In the cis-eto group one patient received CR after pulmonary metastasectomy, the other patients in both groups received CR after only the combination treatment. This data was available for 90% of all patients. The patients

Table 4.1 Characteristics of the 61 patients with Ewing sarcoma who received etoposide and carboplatin treatment and 46 patients with Ewing sarcoma who received etoposide and cisplatin treatment between 1980 and 2012

Carboplatin + etoposide		Cisplatin + etoposide	
Male	41	Male	31
Female	20	Female	15
Age		Age	
Mean	20	Mean	25
Range	2–48	Range	5–46
Primary site		Primary site	
Pelvis	19	Pelvis	15
Vertebra	6	Rib	4
Scapula	2	Femur	3
Rib	15	Mediastinum	3
Femur	5	Retroperitoneal	2
Fibula	3	Bone	9
Skull	3	Foot	4
Chest wall	2	Scapula	1
Soft tissue	1	Humerus	1
Humerus	1	Mesenterium	1
Toe	1	Neck	1
Clavicle	2	Soft tissue	2
Axilla	1		
Site metastases		Site metastases	
Bone	3	Bone	5
Lung	13	Lung	17
Lung + bone	15	Lung + bone	2
Lung + bone + other	9	Lung + bone + other	2
Lung + other	4	Lung + other	2
Bone + other	6	Bone + other	1
Other	4	Other	7
Treatment line		Treatment line	
First	0	First*	5
Second	48	Second	21
Third	9	Third	9
Fourth	2	Fourth	2
Fifth	1	Fifth	4
Sixth	1	Unknown	5

Other = lymph nodes, bone marrow, mediastinum, liver, CNS, soft tissue, skin, peritoneal, pleura.
* Primary systemic treatment after surgery in patients with primary extensively metastatic disease.

in the carbo-eto group received an average of 3.1 treatment cycles (range 1–11 cycles), the patients in the cis-eto group received this treatment longer with a mean of 3.8 cycles (range 1–15 cycles). Concerning possible prognostic factors, we found that there was a better prognosis for patients with tumours of the extremities than in the axial skeleton in the carbo-eto group (p=0.012) (Figure 4.3). For the patients in the cis-eto group tumour

Table 4.2 Overview of studies for patients with refractory or relapsed Ewing sarcoma published in the last decade. For comparison we added the current study.

Author	Year published	Study type	Number of patients	Treatment	Outcome*	Main toxicity
El Weshi [21]	2004	Prospective	27	Etoposide 75 mg/m^2/day for 5 days Ifosfamide 1.2 mg/m^2/day for 5 days Cisplatin 20 mg/m^2/day for 5 days Q 3wks	1 CR (4%) 8 PR (30%) 9 SD (33%) PFS 6.6 months OS 8.1 months	19 grade IV granulocytopenia 15 grades III/IV thrombocytopenia
Whelan [22]	2004	Retrospective	39	Carboplatin AUC 6 for 1 day Etoposide 120 mg/m^2 for 3 days Cyclophosphamide 500–750 mg/m^2 for 2 days Q 3 wks	1 CR (2.5%) 9 PR (23%) PFS 10 weeks OS not reported	Haematological, leading to 56% dose reductions 16% grade III/IV infection 7% grade III/ IV mucositis
Hunold [23]	2006	Retrospective	54	Topotecan 0.75 mg/m^2/day, days 1–5 Cyclophosphamide 250 mg/m^2/day, days 1–5 Q 3 wks	16 PR (32.6%) 13 SD (26.5%) PFS not reported OS 61% at 1 year	4.4% grade III/IV infection 1 toxic death
Wagner [24]	2007	Retrospective	16	Temozolomide 100 mg/m^2/day on days 1–5 Irinotecan 10–20 mg/m^2/day on days 1–5 and 8–12 Q 3–4 wks	1 CR (6%) 3 PR (18.7%) PFS 30 weeks OS not reported	11% grade III/IV diarrhea
Ferrari [25]	2009	Prospective	37	Ifosfamide 15 g/m^2 over 5 days Q 3wks	2 CR (5.5%) 10 PR (27%) 11 SD (30%) PFS not reported OS 29% at 2 year	97% grade IV neutropenia 54% grade IV thrombocytopenia

Table 4.2 *Continued*

Author	Year published	Study type	Number of patients	Treatment	Outcome*	Main toxicity
Fox [10]	2012	Prospective	14	Gemcitabine 675 mg/m^2 days 1 and 8 Docetaxel 75 mg/m^2 day 8 Q 3wks	0 CR 2 PR (14%) PFS not reported OS not reported	Mostly haematological
Kebudi [26]	2013	Retrospective	13	Vincristine 1.5 mg/m^2 Cyclophosphamide 600 mg/m^2/day Topotecan 1 mg/m^2 Q 3 wks	2 CR (15%) 5 PR (38.5%) 2 SD (15%)	55% grade III/IV neutropenia 44% grade III/IV trombocytopenia
Raciborska [27]	2013	Retrospective	22	Vincristine 1.5 mg/m^2 day 1 Irinotecan 50 mg/m^2/day days 1–5 Temozolomide 125 mg/m^2/day days 1–5 Q 3 wks	5 CR (22.7%) 7 PR (32%) 3 SD (13.6%)	3 grade III/IV diarrhea 1 grade III/IV neutropenia 1 grade III/IV thrombocytopenia
Maldegem (this article)	2014	Retrospective	61	Carboplatin day 1 average 480 mg Etoposide day 1–3 average 300mg	11 CR (31%) 7 PR (20%) 3 SD (8.5%)	42% haematological 6% alopecia 6% mucositis#
			46	Cisplatin day 1 average 60 mg Etoposide dag 1–3 average 90 mg	4 CR (10%) 7 PR (19%) 10 SD (27%)	

OS, overall survival; PFS, progression free survival; CR, complete response; PR, partial response; SD, stable disease.
* Response, PFS and OS when documented.
# Data was not available for all patients, therefore these percentages are probably an underestimation of the real toxicity encountered.

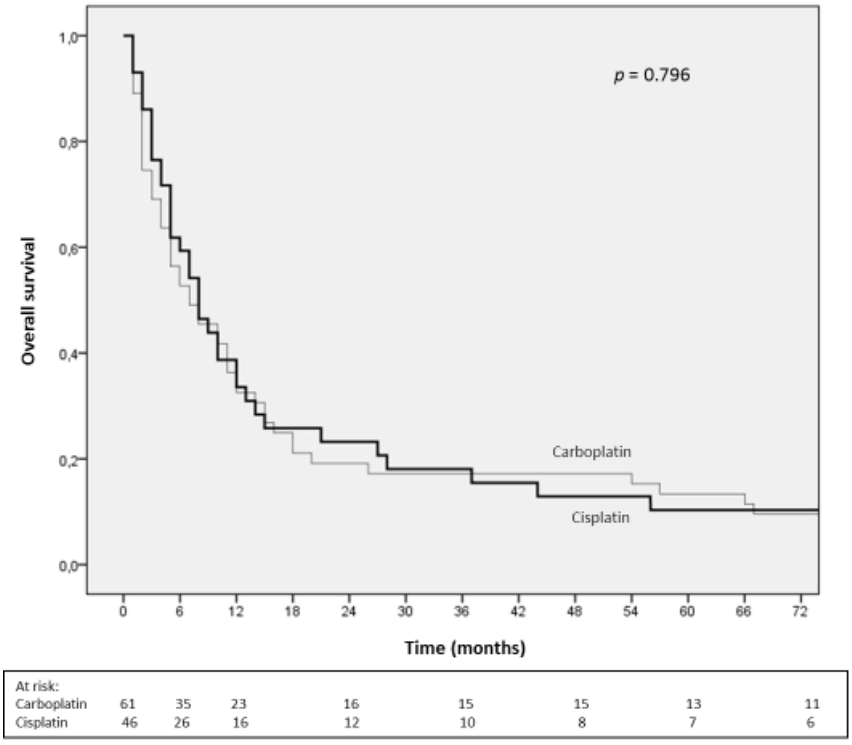

Figure 4.1 Overall survival calculated from start of carboplatin and etoposide or cisplatin and etoposide treatment till death or last patients contact.
The thin line is the carboplatin and etoposide group, the thick line is the cisplatin and etoposide group.

localisation was not significant in relation to OS (p=0.939). In the different age groups of children (1–15 years), adolescence and young adults (15–30 years) and adults (30 years and older) we found no difference in OS. In both groups response on previous treatment lines, gender, the localisation of metastases and metastases located in one versus multiple organs has no effect on OS. Toxicity data were only available for 33 patients (30%) and were mainly haematological (42%), alopecia (6%) and mucositis (6%), 36% of the patients had no grade II, III or IV toxicity. At the time of data collection a total of 12 patients were still alive, 6 in the carbo-eto group and 6 in the cis-eto group.

Discussion

For patients with Ewing sarcoma the standard treatment is surgery with or without radiotherapy combined with pre- and post-operative chemotherapy. However for patients who develop refractory or relapsed disease the treatment options are limited. In the last

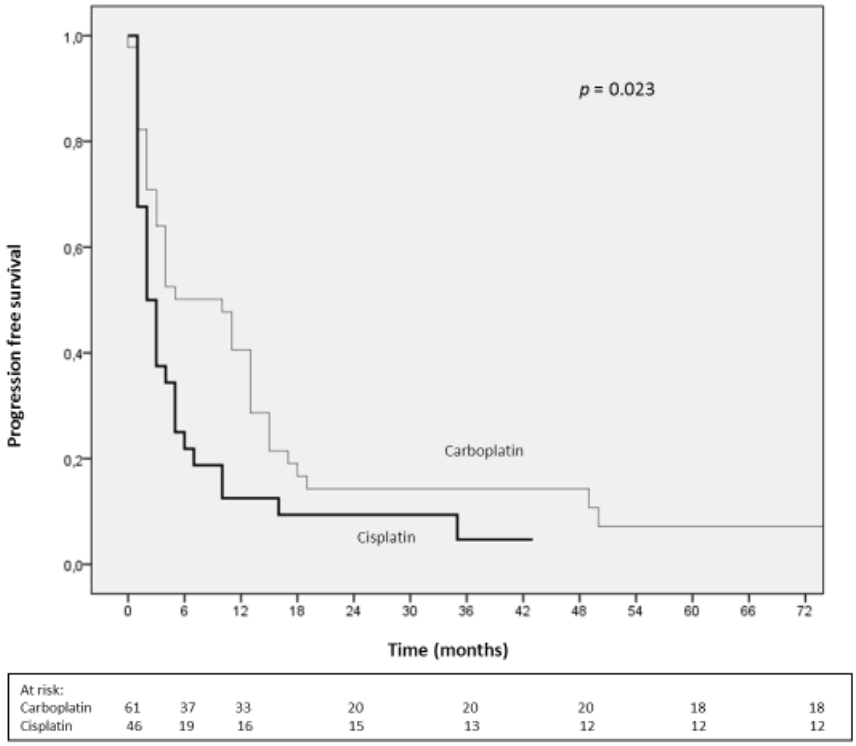

Figure 4.2 Progression free survival calculated from start of carboplatin and etoposide or cisplatin and etoposide treatment till disease progression.
The thin line is the carboplatin and etoposide group, the thick line is the cisplatin and etoposide group.

decade several studies have been published in which second line treatment options for advanced Ewing sarcoma were tested (Table 4.2). Generally there are 3 different commonly used schedules: the combination of irinotecan and temozolomide with diarrhea as the main toxicity, the combination of topotecan and cyclophosphamide with bone marrow toxicity, and high dose ifosfamide with known bone marrow and renal toxicity. The combination of docetaxel and gemcitabine is also used in some countries despite the fact that the published literature on this combination is scarce [10-13]. The response rate in these studies (CR and PR) ranges from 10 to 50% and PFS from 2 to 10 months. Another regimen that is sometimes used is ifosfamide, carboplatin and etoposide (ICE). A study was published in which recurrent or refractory sarcoma patients were treated with this combination [14]. The overall response rate was 51% with a median survival of 11.8 months. Due to the different ways of reporting the outcome it is difficult to compare the outcomes between these studies. Given our results with a response rate of 51%, a PFS of 14.5 months and OS of 23 months for the carbo-eto combination and a response

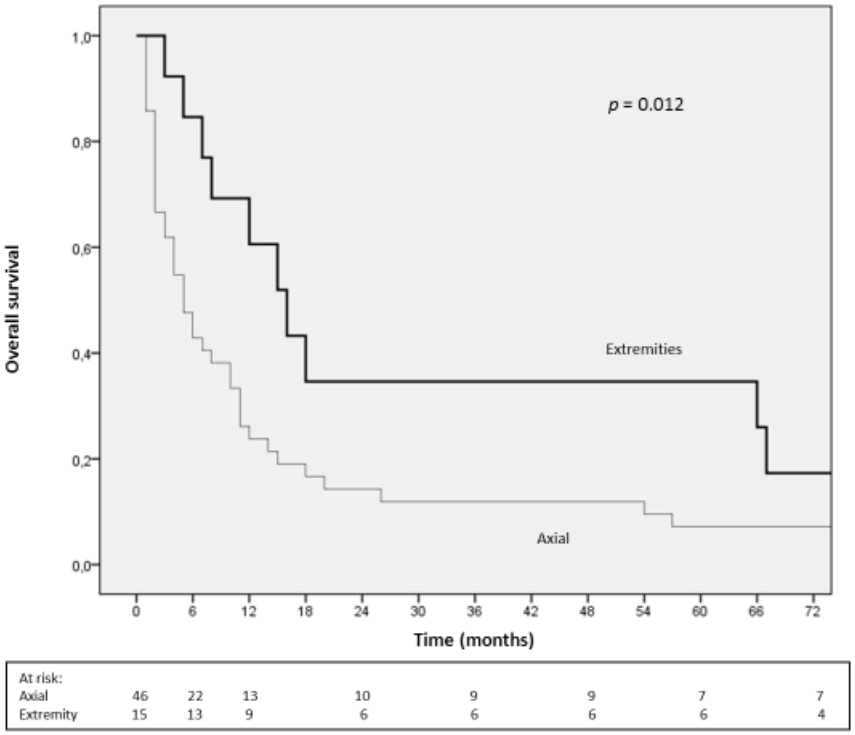

Figure 4.3 Overall survival for the patients who received carboplatin and etoposide treatment subdivided in the primary tumour location being either in the extremity or axial.
The thick line is the extremity group, the thin line is the axial group.

rate of 29%, a PFS of 6.3 months and a OS of 23 months for the cis-eto combination we conclude that the combination of a platinum with etoposide is a potential additional treatment option in this patient population. This is especially the case for the carboplatin combination for patients with impaired renal function, which is quite often the case in this heavily pretreated population. A prospective randomised multi-arm study for recurrent disease will be conducted within FP7 IEC project for Ewing sarcoma (rEECur-study).

The PFS for carbo-eto with a mean of 14.5 months is significantly better than the 6.3 months for the patients treated with cis-eto. But because of the retrospective nature of this study it is not possible to draw conclusions out of the comparison of the efficacy of these treatments. Patients that received carboplatin were treated on the weekly schedule with an average of 190 mg carboplatin and on the 3-weekly schedule with 630 mg, using the calculation of drug exposure relative to renal function giving an area under the curve (AUC) of 2.2 for carboplatin in the weekly schedule, and 7.5 on the 3-weekly schedule.

Comparing this to published reports, the dosages used are similar to other combination treatment regimens [15-19]. To make a comparison between the two treatment groups we also looked at the differences in side effects, but because this is a retrospective study the side effects of the patients were at the time not collected or scored in detail, as for instance by the common toxicity criteria and therefore comparison was not possible. These two platinum-based drugs have a lot of similar side effects, with two important differences namely the ototoxicity of cisplatin which occurs frequently (>10% [20]), and is experienced by the patients as a very severe side effect, and the nephrotoxicity of cisplatin, which is much greater than that of carboplatin. Another major difference between the two drugs is that carboplatin can be given on an outpatient basis while for high dosage cisplatin given in the 3-weekly schedule the patient has to stay overnight in the hospital, which together with the difference in toxicity may be a reason to prefer carboplatin instead of cisplatin. We found that in the carbo-eto group the OS for patients with a tumour located in the extremities is significantly better than for the patients with an axial located tumour, however this could be biased because of a different spread in tumour localisation as we see especially a lot of rib localization in the carbo-eto group, and could be by chance, again due to the retrospective nature of this study.

In conclusion, our results show, within the limitations of a retrospective study, that carboplatin and etoposide maybe is a good additional option for patients with recurrent metastatic Ewing sarcoma and worthy of investigation in a prospective trial with relapsed patients.

References

1. Cotterill S.J., Parker L., Malcolm A.J., et al. Incidence and survival for cancer in children and young adults in the North of England, 1968-1995: a report from the Northern Region Young Persons' Malignant Disease Registry. Br J Cancer. 2000;83:397-403.
2. Cotterill S.J., Ahrens S., Paulussen M., et al. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. J Clin Oncol. 2000;18:3108-3114.
3. Owen L.A., Kowalewski A.A., Lessnick S.L. EWS/FLI mediates transcriptional repression via NKX2.2 during oncogenic transformation in Ewing's sarcoma. PLoS One. 2008;3:e1965.
4. Jurgens H., Exner U., Gadner H., et al. Multidisciplinary treatment of primary Ewing's sarcoma of bone. A 6-year experience of a European Cooperative Trial. Cancer. 1988;61:23-32.
5. Granowetter L., Womer R., Devidas M., et al. Dose-intensified compared with standard chemotherapy for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study. J Clin Oncol. 2009;27:2536-2541.
6. Thacker M.M., Temple H.T., Scully S.P. Current treatment for Ewing's sarcoma. Expert Rev Anticancer Ther. 2005;5:319-331.
7. Rodriguez-Galindo C., Navid F., Liu T., et al. Prognostic factors for local and distant control in Ewing sarcoma family of tumors. Ann Oncol. 2008;19:814-820.
8. Stahl M., Ranft A., Paulussen M., et al. Risk of recurrence and survival after relapse in patients with Ewing sarcoma. Pediatr Blood Cancer. 2011;57:549-553.

9. Hande K.R. Etoposide: four decades of development of a topoisomerase II inhibitor. Eur J Cancer. 1998;34:1514-1521.
10. Fox E., Patel S., Wathen J.K., et al. Phase II study of sequential gemcitabine followed by docetaxel for recurrent Ewing sarcoma, osteosarcoma, or unresectable or locally recurrent chondrosarcoma: results of Sarcoma Alliance for Research Through Collaboration Study 003. Oncologist. 2012;17:321.
11. Mora J., Cruz C.O., Parareda A., de TC. Treatment of relapsed/refractory pediatric sarcomas with gemcitabine and docetaxel. J Pediatr Hematol Oncol 2009:31:723-729.
12. Navid F, Willert JR, McCarville MB, et al. Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma. Cancer. 2008;113:419-425.
13. Rapkin L., Qayed M., Brill P., et al. Gemcitabine and docetaxel (GEMDOX) for the treatment of relapsed and refractory pediatric sarcomas. Pediatr Blood Cancer. 2012:59:854-858.
14. Van WP, Angiolillo A, Krailo M, et al. Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the Children's Cancer Group (CCG) experience. Pediatr Blood Cancer. 2005;44:338-347.
15. Fu S., Hou M.M., Wheler J., et al. Exploratory study of carboplatin plus the copper-lowering agent trientine in patients with advanced malignancies. Invest New Drugs. 2013.
16. Takayama K., Inoue K., Tokunaga S., et al. Phase II study of concurrent thoracic radiotherapy in combination with weekly paclitaxel plus carboplatin in locally advanced non-small cell lung cancer: LOGIK0401. Cancer Chemother Pharmacol. 2013;72:1353-1359.
17. Twelves C., Chmielowska E., Havel L., et al. Randomised phase II study of axitinib or bevacizumab combined with paclitaxel/carboplatin as first-line therapy for patients with advanced non-small-cell lung cancer. Ann Oncol. 2014;25:132-138.
18. Wang L., Wu S., Ou G., et al. Randomized phase II study of concurrent cisplatin/etoposide or paclitaxel/carboplatin and thoracic radiotherapy in patients with stage III non-small cell lung cancer. Lung Cancer. 2012;77:89-96.
19. Yilmaz U., Polat G., Anar C., et al. Carboplatin plus etoposide for extensive stage small-cell lung cancer: an experience with AUC 6 doses of carboplatin. Indian J Cancer. 2011;48:454-459.
20. Bertolini P., Lassalle M., Mercier G., et al. Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. J Pediatr Hematol Oncol. 2004;26:649-655.
21. El W.A., Memon M., Raja M., et al. VIP (etoposide, ifosfamide, cisplatin) in adult patients with recurrent or refractory Ewing sarcoma family of tumors. Am J Clin Oncol. 2004;27:529-534.
22. Whelan J.S., McTiernan A., Kakouri E., et al. Carboplatin-based chemotherapy for refractory and recurrent Ewing's tumours. Pediatr Blood Cancer. 2004;43:237-242.
23. Hunold A., Weddeling N., Paulussen M., et al. Topotecan and cyclophosphamide in patients with refractory or relapsed Ewing tumors. Pediatr Blood Cancer. 2006;47:795-800.
24. Wagner L.M., McAllister N., Goldsby R.E., et al. Temozolomide and intravenous irinotecan for treatment of advanced Ewing sarcoma. Pediatr Blood Cancer. 2007;48:132-139.
25. Ferrari S., del Prever A.B., Palmerini E., et al. Response to high-dose ifosfamide in patients with advanced/recurrent Ewing sarcoma. Pediatr Blood Cancer. 2009;52:581-584.
26. Kebudi R., Cakir F.B., Gorgun O., et al. A modified protocol with vincristine, topotecan, and cyclophosphamide for recurrent/progressive ewing sarcoma family tumors. Pediatr Hematol Oncol. 2013;30:170-177.
27. Raciborska A., Bilska K., Drabko K., et al. Vincristine, irinotecan, and temozolomide in patients with relapsed and refractory Ewing sarcoma. Pediatr Blood Cancer. 2013;60:1621-1625.