Retrospective studies in mesenchymal tumours: clinical implications for the future

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Single centre experience with ifosfamide monotherapy as second line treatment of recurrent/ metastatic osteosarcoma

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Abstract

Background

The effectiveness of second-line palliative chemotherapy in patients with recurrent/metastatic osteosarcoma is not well defined. Several small studies (6-19 patients) have reported on ifosfamide as second-line treatment. In this study we report our single centre experience, with second-line ifosfamide monotherapy in patients treated for recurrent/metastatic osteosarcoma.

Methods

Of all osteosarcoma patients treated with ifosfamide from 1978 until 2017 a chart review was conducted. Until 1997 a 5 gram/m^2 regimen was used and from 1997 onwards 9 gram/m^2 regimen was used. Overall survival (OS) from start of ifosfamide was the primary end point. Progression free survival (PFS) from start of treatment was also studied. To assess difference in survival between groups the log rank test was applied. To investigate the effect of ifosfamide dose and WHO performance status (PS) a Cox proportional hazard regression model was estimated.

Results

Sixty-two patients were selected with recurrent/metastatic osteosarcoma treated with second-line ifosfamide monotherapy (26 dose of 5 gram/m^2 and 36 9 gram/m^2). OS was significantly better in univariate analysis for 9 gram/m^2 compared to 5 gram/m^2 (10.9 (95% confidence interval (95%CI) 9.3–12.6) vs. 6.7 months (95%CI 5.9-7.6) respectively) and for PS (median OS PS 0: 13.0 months (95%CI 2.3-23.8), PS 1 8.2 months (95%CI 5.4-11.1) PS$\geq$2 6.2 months (95%CI 2.2-10.3) and unknown 5.4 months (95%CI 2.2-8.5). In multivariate analysis only PS showed a significant difference. No difference in PFS was found between 5 and 9 gram/m^2 ifosfamide treatment or PS.

Conclusion

This study suggests that ifosfamide is an effective second-line treatment for patients with recurrent/metastatic osteosarcoma.

Introduction

Osteosarcoma is the most common primary bone malignancy, but remains a rare tumour affecting predominantly adolescents and patients of advanced age. Primary treatment of high-grade osteosarcoma in case of local disease or local disease with pulmonary metastases is perioperative chemotherapy combined with surgery. The 3-year event free survival is approximately 60-70%.[1-4] Current first line treatment in most of the Western world is combination chemotherapy consisting of methotrexate, doxorubicin and cisplatin. The EURAMOS study tried to improve cure rate in patients with a poor pathological response to the first cycles of chemotherapy by the addition of ifosfamide and etoposide to the perioperative regimen of methotrexate, doxorubicin and cisplatin, but this study failed to reach its primary endpoint.[5] At present, more than 40% of all osteosarcoma patients continue to develop local recurrent or distant metastatic disease after primary treatment. These patients may still be cured when recurrence or metastases are limited and amenable to surgery.[6,7]

When cure is no longer possible, different palliative chemotherapeutic regimens are available, e.g. ifosfamide, etoposide, ifosfamide/etoposide and gemcitabine/docetaxel.[8-14] These treatment regimens were studied in small, single arm, studies and case series. No randomized phase II or III trials are available. Reported outcomes of these treatments are poor with response rates of 17% for gemcitabine/docetaxel, one out of eight patients for etoposide, and a higher response rate of 48-59% for ifosfamide/etoposide, but as first line treatment.[8-11] Progression free survival (PFS) for gemcitabine/docetaxel was 3.5 months.[11] Ifosfamide as second line treatment was studied in several small studies (between 6 and 19 patients per study) studying varying ifosfamide doses, ranging from 5 gram/m^2 in one day to a total of 14 gram/m^2 continuously over 7 days.[12-15] None of these studies reported the overall survival (OS) and/or PFS. Overall response rates varied between 24% and 44%.

A retrospective analysis of 7 Children's Oncology Group studies, all with inactive drugs (according to the study criteria), by Lagmay *et al.* showed an event free survival (which is usually called PFS) of 12% at 4 months, which can be used as reference for new single arm studies.[16] In a recently published small randomised phase II study, including 43 patients, regorafenib was shown to have an 8 weeks PFS of 65% versus 0% for the placebo group.[17]

This study reports the Leiden University Medical Center experience with ifosfamide monotherapy as palliative treatment in patients with osteosarcoma. It also studies (to the authors knowledge for the first time in literature) whether the currently used dose of 9 gram/m^2 over 3 days continuously is better than the previously used 5 gram/m^2 as bolus infusion.

Methods

Patients

From our hospital cancer registry all patients treated palliatively with ifosfamide monotherapy for an osteosarcoma were selected. Sixty-two patients were identified, of which 2 were excluded (1 was actually a salivary gland tumour and 1 was a uterine leiomyosarcoma treated as osteosarcoma). Three additional patients had the outdated diagnosis malignant fibrous histiocytoma (MFH). All three patients with so-called malignant fibrous histiocytoma of bone had pathology review before study entry by an expert bone tumour pathologist (JVMGB). For two patients osteoid deposition by tumour cells was focally observed and the diagnosis was changed to high grade osteosarcoma, and these two patients were included. The third patient was diagnosed with undifferentiated pleomorphic sarcoma after revision and was excluded. Patients were grouped based on their actual primary ifosfamide dose being $\leq$6 grams/m^2 (hereafter called intended dose 5 gram/m^2) or >6 grams/m^2 (called intended dose 9 gram/m^2). In our reference centre ifosfamide 9 gram/m^2 was introduced in 1997. Before 1997, 5 gram/m^2 was used. The cut-off of 6 gram/m^2 was chosen because this cut-off takes into account a little overdosing in the 5 gram/m^2 dosed patients and a small dose reduction in patients with an intended dose of 9 gram/m^2.

For all of these patients a chart review was conducted. Data was collected on age and sex, date of primary diagnosis, primary localization, histological subtype, primary treatment, primary intend of treatment (palliative or curative), metastases at diagnosis, localization of metastases at diagnosis, date of recurrence, date of start ifosfamide, planned dose of ifosfamide, actual primary dose of ifosfamide given, number of cycles of ifosfamide, given dose of ifosfamide, dates of response evaluation, outcomes of response evaluations and treatment after progression on ifosfamide.

Endpoints

The primary endpoint was OS, calculated as the time between start of ifosfamide and death. Secondary endpoints were PFS, calculated as time between start of ifosfamide and first documented progression and overall response rate, *i.e.* complete remission, partial remission, stable disease and progressive disease according to RECIST 1.1 or in case of only clinical evaluation clinical benefit. Covariates studied were histological subtype, WHO performance status (PS) at start of ifosfamide treatment and time between primary diagnosis and start of ifosfamide treatment. Toxicity was graded according to the NCI CTCAE version 4.0.

Statistics

Statistical analysis was performed with IBM Statistical Package for Social Sciences (SPSS) Statistics 24. Categorical data were summarized by frequencies and percentages, continuous variables were summarized by median and overall range. These were

presented according to the two different groups. The characteristics were compared with χ^2-test for categorical variables and a Mann-Whitney U test for the continuous variables. A χ^2-test was used to compare response rates between the two treatment groups. Kaplan Meier's methodology was used to estimate OS and PFS. Univariate and multivariate Cox proportional hazard regression model was estimated to investigate the effect of prognostic factors on OS and PFS.

To compare with existing literature, 8 weeks and 3 months PFS and 9- and 12-months OS were estimated by using Kaplan Meier's methodology.

The Medical Ethics Committee provided us a waiver for informed consent (registration number C14.167).

Results

Patients

In total, 62 patients treated with palliative ifosfamide treatment for osteosarcoma were identified from our hospital cancer registry. Thirty-six patients had a primary intended dose of 9 gram/m^2 ifosfamide and the other 26 had an intended dose of 5 gram/m^2. Table 1 shows the characteristics of the included patients. Patients with an intended dose of 9 gram/m^2 were older (30.0 (17-70) years vs. 22.5 (15-56) years), received more radiotherapy before start of ifosfamide and received more cycles of ifosfamide treatment (median 3 vs 4 cycles). As expected, mean cycle dose and cumulative dose of ifosfamide was higher in patients with an intended dose of 9 gram/m^2. Only, 1 patient (9 gram/m^2) was pretreated with a regimen containing ifosfamide. (Supplementary table 2) More patients were treated with chemotherapy or other treatment options after the end of ifosfamide in the dose 9 gram/m^2 group (21 vs 12 patients). (Supplementary table 4 and 5)

Table 1: baseline characteristics

	Ifosfamide		
	Intended dose of 5 gram/m2 N=26	**Intended dose 9 gram/m2 N=36**	**P**
Age (in years, median, range)	22.5 (15-56)	30.0 (17-70)	0.031
Male	18 (69%)	20 (56%)	0.275
Primary localization			0.593
Lower extremity	21 (81%)	26 (72%)	
Upper extremity	4 (15%)	4 (11%)	
Pelvis	1 (4%)	4 (11%)	
Thorax		1 (3%)	
Head		1 (3%)	
WHO Performance status			0.306
0	5 (33%)	18 (51%)	
1	6 (40%)	11 (31%)	
2	3 (20%)	4 (11%)	
3	1 (7%)	2 (6%)	
Subtotal	15	35	
Unknown	11 (42%)	1 (3%)	
Grade			0.344
High	24 (92%)	35 (97%)	
Intermediate/low	1 (4%)	1 (3%)	
Unknown[a]	1 (4%)		
Metastases			0.395
Local recurrence only	1 (4%)	1 (3%)	
Pulmonary only	14 (54%)	24 (67%)	
Both pulmonary and primary localisation	1 (4%)	1 (3%)	
Other	10 (48%)	10 (28%)	

Table 1: Continued.

	Ifosfamide		
	Intended dose of 5 gram/m2 N=26	**Intended dose 9 gram/m2 N=36**	**P**
Number of previous lines of chemotherapy			0.072
0		1 (3%)	
1	21 (81%)	34 (94%)	
2	5 (19%)	1 (3%)	
Previous surgery	23 (89%)	29 (81%)	0.404
Previous radiotherapy	1 (4%)	10 (28%)	0.018
Number of cycles Median (range)	3 (1-16)	4 (1-13)	0.059
Mean dose/cycle (range)	4.9 gram/m2 (3.6-6.1)	8.3 gram/m2 (5.6-9.6)	Not calculated[b]
Cumulative dose (range)	18.0 gram/m2 (5.0-92.7)	40.5 gram/m2 (6.7-110.5)	Not calculated[b]
Histologic subtype			0.257
Conventional	16 (62%)	27 (75%)	
Other[c]	10 (38%)	9 (25%)	

[a] Treated as high grade. [b] Mean dose/cycle and cumulative dose were not statistically compared because these were the subject of our study. [c] See also supplementary table 1.

Overall survival

Median OS was 9.1 months (95%CI 7.8 – 10.4) after start of ifosfamide (this is also the median follow-up of the patients because all patients died).(Figure 1A) The OS was significantly different between the intended dose of 5 gram/m^2 and 9 gram/m^2 (*P*=0.046). For the intended dose of 5 gram/m^2 the median OS was 6.7 months (95%CI 5.9-7.6) versus 10.9 months (95%CI 9.3 – 12.6) for the intended dose of 9 gram/m^2.(Figure 1B) The OS was also significantly different between PS 0, 1 and ≥2 (*P*=0.012) with a median OS for PS 0 of 13.0 months (95%CI 2.3-23.8), PS 1 8.2 months (95%CI 5.4-11.1) PS ≥2 6.2 months (95%CI 2.2-10.3) and PS unknown 5.4 months (95%CI 2.2-8.5).(Figure 1C). In multivariate analysis only PS was statistically significant associated to OS. (Table 2) The 9- and 12-month OS were estimated to compare with other studies. (Table 3)

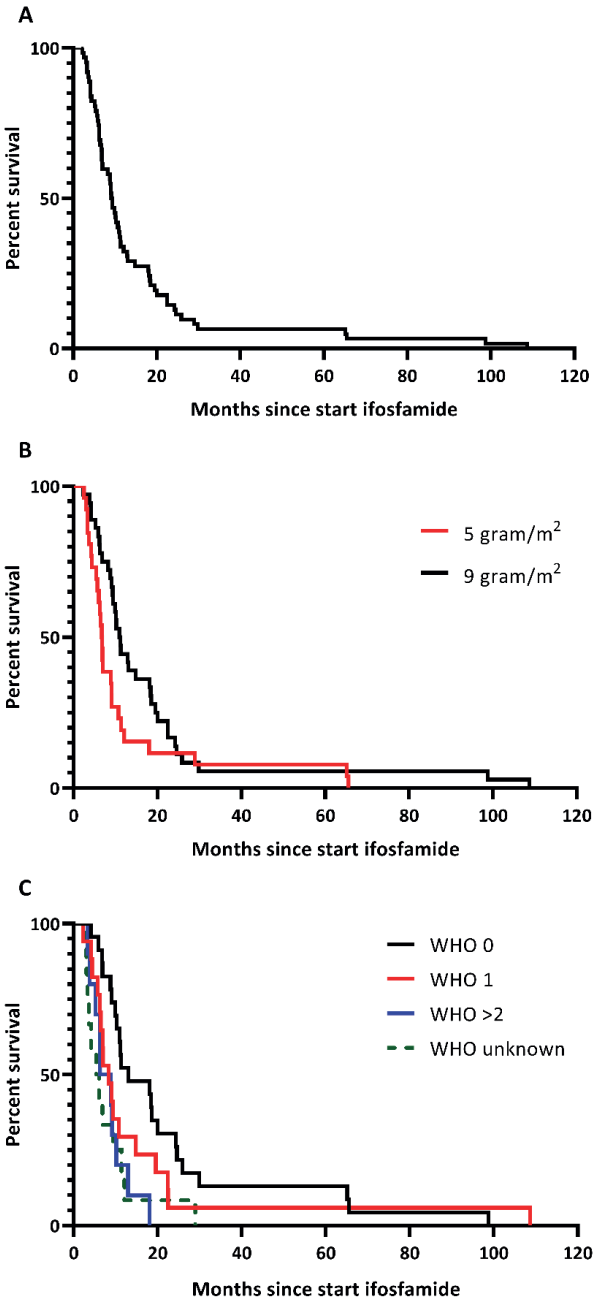

Figure 1: Overall survival, A all patients, B split based on dose, C split based on WHO performance score

Table 2 Multivariate analysis for prognostic factors for overall survival

		Overall survival	
		Adjusted hazard ratio	**P-value**
WHO performance score	**0**	1.00	0.016 (df=3)
	1	1.54 (0.81-2.93)	
	≥2	2.74 (1.26-5.97)	
	Unknown	2.70 (1.32-5.52)	

Progression free survival

The overall median PFS was 2.6 months (95%CI 2.2-3.0) after start of ifosfamide.(Figure 2A) The PFS showed a trend towards a better PFS for patients treated with an intended dose of 9 gram/m^2.(*P*=0.098) (Figure 2B) For the intended dose of 5 gram/m^2 the median PFS was 2.1 months (95%CI 1.3-2.9) versus 3.8 months (95%CI 2.2-5.4) for the intended dose of 9 gram/m^2.(Figure 2B) The PFS did not differ between the WHO performance states.(Figure 2C) The results of multivariate analysis resembled the univariate analysis. The 8 weeks and 3 months PFS were estimated to compare with other studies. (Table 3)

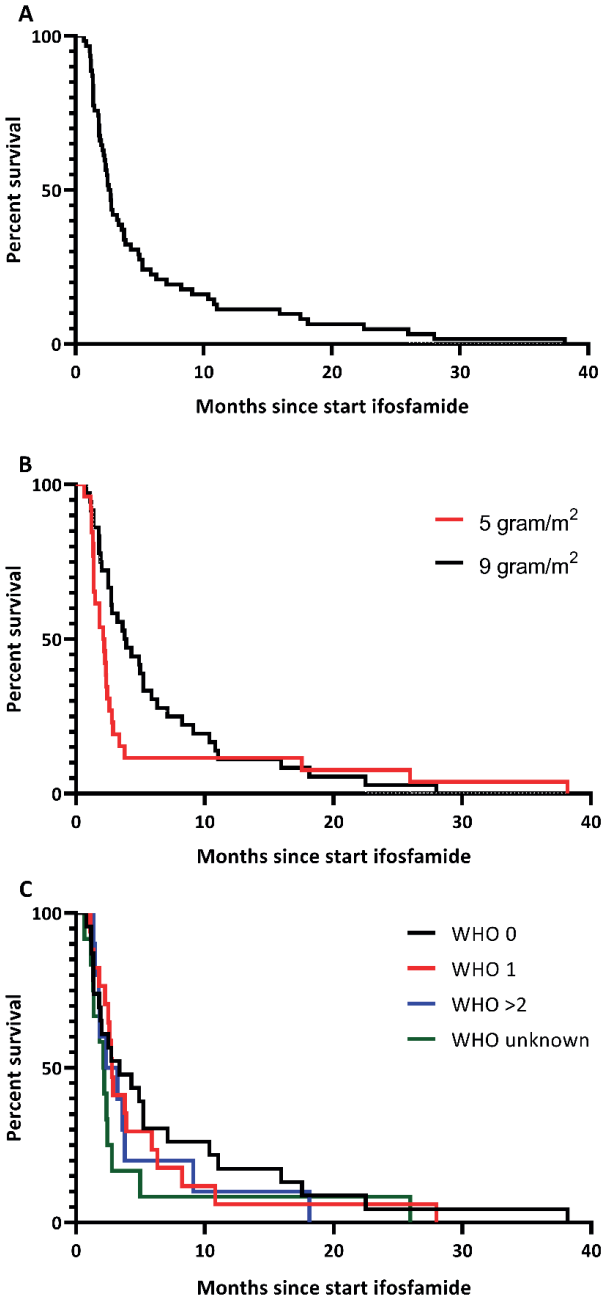

Figure 2: Progression free survival, A all patients, B split based on dose, C split based on WHO performance score

Table 3 Overall survival and progression free survival percentages at specific time points

	Intended dose 5 gram/m2	Intended dose 9 gram/m2
Overall survival 9 months	35% (95%CI 17 – 52)	69% (95%CI 52 – 82)
Overall survival 12 months	19% (95%CI 7 – 36)	44% (95%CI 28 – 60)
Progression free survival 8 weeks	54% (95%CI 33 – 71)	78% (95%CI 60 - 88)
Progression free survival 4 months	12% (95%CI 3 - 27)	44% (95%CI 28 – 60)

Overall response rate

Best overall responses are reported in table 4. Significant more patients had at least stable disease (78% vs 42%) when treated with ifosfamide 9 gram/m^2(*P*=0.005). Overall response rate did not differ significantly (36% vs 25%, p=0.27).

Table 4 Best overall response

		Best response				Total
		CR/PR/ clinical benefit	**SD**	**PD**	**Not evaluable**	
Intended dose	**5 gram/ m²**	6 (23%)	5 (19%)	15 (58%)	0 (0%)	26 (100%)
	9 gram/ m²	13 (36%)	15 (42%)	7 (19%)	1 (3%)	36 (100%)
Total		19 (31%)	20 (32%)	22 (35%)	1 (2%)	62 (100%)

Toxicity

As this is a retrospective study, toxicity was based on the reported toxicity in both the medical and nursing charts. This data is available in the supplementary data, table 5.

Discussion

This study is the largest study reporting the outcomes of ifosfamide monotherapy in the palliative treatment of osteosarcoma patients. Until now, only small studies with 6 to 19 patients reported outcome for patients treated with ifosfamide monotherapy. It shows that PS is an important prognostic factor for overall survival of osteosarcoma, but it was unfortunately not possible to detect a significant difference between 9 gram/m^2 and 5 gram/m^2.

To our knowledge, this is the first study to report both OS and PFS of patients treated with second line or later line ifosfamide chemotherapy for locally advanced or metastatic osteosarcoma. The overall response rate in this study (intended dose 5 gram/m^2 23% and 9 gram/m^2 36%) is comparable to earlier reports on ifosfamide monotherapy in these patients.[12-15,18] Additionally, in an ASCO 2015 abstract, results of ifosfamide 15 gram/m^2 continuously over 5 days were reported.[18] The overall response percentage was 22%, OS at 1 year was 60% and PFS at 6 months was 53%. Compared to these data, our study reports probably a lower 1 year OS and 6 months PFS in a patient population with worse PS and older age, but their results were not yet published.[18] In the French REGOBONE study, a placebo group was included with an 8 weeks PFS of 0% and in the regorafenib arm 65%.[17] In our study, ifosfamide showed an 8 week PFS of 54% (95%CI 33 – 71) for 5 gram/m^2 and 78% (95%CI 60 - 88) for 9 gram/m^2, suggesting a higher PFS for ifosfamide 9 gram/m^2 compared to regorafenib. The 4 month PFS of ifosfamide 9 gram/m^2 also compares favourably to the 4 months PFS defined in the retrospective study of the COG (44% (95%CI 28 – 60) vs. 12% (95% CI 6 – 19).[16] Also, an increase in clinical benefit rate is shown, when comparing 5 gram/m2 to 9 gram/m2.

One of the important results of this study is the prognostic impact of PS. This was already shown for some other tumours, e.g. soft tissue sarcoma.[19]

This study is limited by its retrospective character, the long study period and no routine monitoring interval of CT scan. All patients underwent CT scan at least each 2-3 cycles. We did an effort to report the toxicity of ifosfamide therapy, but this is probably an underestimation of the real toxicity and is probably also biased. The toxicity of ifosfamide monotherapy is well known. The long study period and the different time periods the study groups were treated in (5 gram/m^2 until 1997 and 9 gram/m^2 from 1997 until now) hamper the study because supportive care has improved during the years and this could cause a difference in OS. Also, the improvements in imaging could result in an earlier diagnosis of recurrent disease and thereby a suggested improvement in OS. Although in univariate analysis overall survival was better for 9 gram/m^2 and there was a trend towards a better PFS for patients treated with 9 gram/m^2, no significant impact of the dose on OS was found in multivariate analysis. This study is still underpowered because of the still small number of patients included, but also other causes are present. At baseline, there were differences in the number of pretreated patients between both groups (higher number of patients with 2 lines of chemotherapy in the 5 gram/m^2 group). This could have an impact on the results in several ways: selecting for patients with a more indolent disease and a more chemosensitive tumour or creating more chemoresistant tumours. It is not possible to determine what the most dominant effect is. Also, PS was slightly imbalanced at baseline, favouring the 9 gram/m^2 group, which could improve the OS in this patient group. Due to the still small patient group it is not possible to distinguish the effect of PS and ifosfamide dose. Although being the largest series, the small number of patients did not allow us to detect differences in for example

histologic subtypes of osteosarcoma. Lastly, we could not compare the outcomes of ifosfamide treatment to an untreated patient cohort of the Leiden University Medical Center. Although an untreated patient group exists, most of these patients had a reason why they were not treated and the comparison would result in a biased study. However, we did compare the data with the placebo arm of the REGOBONE study and with the retrospective study of the COG, showing that ifosfamide is an effective treatment (as reported above).[16,17]

This is the largest study until now, reporting data on OS and PFS of ifosfamide monotherapy as palliative treatment of osteosarcoma. This study suggests that ifosfamide is an effective second line treatment for patients with recurrent osteosarcoma.

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Conflicts of interest
The authors have declared no conflicts of interest.

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Supplementary material

Supplementary table 1: Osteosarcoma subtype

	Ifosfamide	
	Intended dose 5 gram/m² N=26	**Intended dose 9 gram/m² N=36**
Osteosarcoma subtype		
Conventional	16 (62%)	27 (75%)
Teleangiectatic	5 (19%)	1 (3%)
Small cell	1 (4%)	0 (0%)
Chondroblastic	4 (15%)	5 (14%)
Extraskeletal	0 (0%)	3 (8%)

Supplementary table 2: Pretreatment

	Intended dose 5 gram/m² N=26	**Intended dose 9 gram/m² N=36**
Pretreatment 1		
Doxorubicin/cisplatin	20 (77%)	27 (75%)
Doxorubicin/cisplatin/MTX	5 (15%)	6 (17%)
Doxorubicin/cisplatin/ ifosfamide/MTX*	1 (4%)	0
MTX/vincristin/doxorubicin	1 (4%)	0
Doxorubicin	0	2 (6%)
No treatment	0	1 (3%)
Pretreatment 2		
Doxorubicin/cisplatin	2	1
Doxorubicin	1	0
Iproplatin	1	0
MTX	1	1
No treatment	21	34

* Patient received only one cycle of this treatment

Supplementary table 3: Post ifosfamide treatment

	Intended dose 5 gram/m² N=26	Intended dose 9 gram/m² N=36
None	14	15
MTX < 1 gram/m2	7	2
MTX > 1 gram/m2		3
Radiotherapy	6	13
Metastasectomy	1	3
Caelyx	1	
Low dose doxorubicin	1	1
Iproplatin	1	
Carboplatin/etoposide		3
VEGF inhibition		4
EGFR inhibition		1
Docetaxel		1
Other systemic treatment, mainly phase I		4
Embolization/ Radiofrequency ablation		2

Supplementary table 4: Number of post ifosfamide treatment

	Intended dose 5 gram/m² N=26	Intended dose 9 gram/m² N=36
0	14	15
1	7	10
2	4	7
>2	1	4

Supplementary table 5: Toxicity (NCI CTCAE grade 3-5)

	Intended dose 5 gram/m² N=26	**Intended dose 9 gram/m² N=36**
No reported grade 3-5 toxicity	**18 (69%)**	**13 (36%)**
Febrile neutropenia	1 (4%)	7 (19%)
Neutropenia	3 (12%)	7 (19%)
Anaemia		3 (8%)
Vomiting	3 (12%)	
Nausea		5 (14%)
Syncope	1 (4%)	
Encephalopathy		3 (8%)
Hypophosphatemia		1 (3%)
Constipation		1 (3%)
Mucositis		1 (3%)
Anorexia		1 (3%)
Acute kidney injury		2 (6%)
Dehydration		1 (3%)