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Phase II study of gemcitabine combined with oxaliplatin in relapsed or refractory paediatric solid malignancies: An innovative therapy for children with Cancer European Consortium Study ☆

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ABSTRACT

Aim: To assess objective response rates after 4 cycles of gemcitabine in combination with oxaliplatin in children and adolescents with relapsed or refractory solid tumours.
Methods: This multicentre, non-randomised Phase II study included five strata: neuroblastoma, osteosarcoma, medulloblastoma and other CNS tumours strata with two-stage Simon designs and a miscellaneous, extra-cranial solid tumour stratum with descriptive design. Eligibility criteria included: age 6 months to 21 years; measurable, relapsed or

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refractory solid malignancy; no more than one previous salvage therapy. Gemcitabine was administered intravenously at 1000 mg/m^2 over 100 min followed by oxaliplatin at 100 mg/m^2 over 120 min on Day 1 of a 14-d cycle. Tumour response was assessed every 4 cycles according to WHO criteria.

Results: Ninety-three out of 95 patients enrolled in 25 centres received treatment: 12 neuroblastoma; 12 osteosarcoma; 14 medulloblastoma; 13 other CNS tumours and 42 miscellaneous non-CNS solid tumours. Median age was 11.7 years (range, 1.3–20.8 years). Tumour control (CR + PR + SD) at 4 cycles was obtained in 30/93 evaluable patients (32.3%; 95% confidence interval (CI), 22.9–42.7%), including four PR: 1/12 patients with osteosarcoma, 1/12 with medulloblastoma, 1/12 with rhabdomyosarcoma and 1/4 with other sarcoma. Five out of 12 eligible patients with neuroblastoma experienced stable disease. During a total of 481 treatment cycles (median 4, range 1–24 per patient), the most common treatment-related toxicities were haematologic (leukopenia, neutropenia, thrombocytopenia) and neurological (dysesthesia, paresthesia).

Concluding statement: The gemcitabine–oxaliplatin combination administered in a bi-weekly schedule has acceptable safety profile with limited activity in children with relapsed or refractory solid tumours.

1. Introduction

Despite significant improvements have been achieved in the overall survival of children with a malignancy, cancer remains the commonest disease-related cause of death in children over 1 year of age. New therapies are still needed, in order to reduce both the mortality and the morbidity associated with treatments.

The nucleoside analogue gemcitabine (2′,2′-difluoro-2′-deoxycytidine, Gemzar®) is approved as a single agent in pancreatic cancer and in combination in non-small cell lung, ovarian and breast cancer. Responses to gemcitabine have been observed in early phase studies in children with acute lymphoblastic leukaemia[1] and pancreatic cancer,[2] with disease stabilisation in osteosarcoma, neuroblastoma, Ewing's sarcoma, rhabdomyosarcoma and other soft-tissue sarcoma.[2,3] These findings suggest its potential role within a combination therapy, particularly for sarcomas.

Oxaliplatin (Eloxatin®), a diaminocyclohexane (DACH)-platinum compound, is active through the formation of DNA-adducts which are not recognised by mismatch repair complexes. Its particular toxicity profile, predominantly reversible sensory neuropathy without nephro- and oto-toxicity,[4] may allow platinum dose intensification. Activity has been observed in colon and ovarian cancer and germ cell tumours, and oxaliplatin is licensed for use in combination with fluorouracil in treatment of advanced colorectal cancer. In children, partial responses were observed in heavily pretreated children with osteosarcoma, neuroblastoma,[5] medulloblastoma[6] and ependymoma.[7]

Based on preclinical studies showing enhanced antiproliferative effects of gemcitabine when combined with oxaliplatin,[8] numerous clinical studies have evaluated the gemcitabine–oxaliplatin combination (GEMOX) in adult solid tumours, including a phase III trial in pancreatic cancer.[9] Schedules and drug doses have varied; the commonest being gemcitabine over 30 or 100 min on Days 1 and 8 and oxaliplatin as a 2-h infusion on Day 1 or 8 of a 21-d cycle.[9–22] Bi-weekly schedules with gemcitabine on Day 1 and oxaliplatin on Day 1 or 2 of a 14-d cycle have also been evaluated.[9,21,22]

The maximum tolerated dose (MTD) for GEMOX in adult phase I studies exceeded the recommended single agent dose for gemcitabine, and since a dose-response effect was not established,[23,24] the investigators recommended using both drugs at full doses, i.e. gemcitabine at 1200–1400 mg/m^2 on Days 1 and 8 and oxaliplatin at 130 mg/m^2 on Day 1 or 8 of a 21-d cycle. In the bi-weekly treatment cycle, no dose-limiting toxicity was observed with gemcitabine doses of 800–1500 mg/m^2 by 30-min infusion followed by oxaliplatin 70–100 mg/m^2 on Day 1, but in hepatocellular carcinoma the combination was better tolerated when gemcitabine at 1000 mg/m^2 was given on Day 1 and oxaliplatin at 100 mg/m^2 on Day 2 of a 14-d cycle compared to both drugs at 1500 mg/m^2 and 85 mg/m^2, respectively, given on Day 1.[22]

The MTD of gemcitabine as single agent in children with relapsed solid tumours was 1200 mg/m^2 when given as a 30-min infusion on Days 1, 8, and 15 of a 28-d cycle with haematological dose-limiting toxicity (DLT), whilst all doses up to 1500 mg/m^2 were tolerated when given on Days 1 and 8 of a 21-d cycle.[2] Oxaliplatin has been evaluated in phase I trials in children with relapsed or refractory solid tumours given on D1 of a 21-d cycle[25] or on Days 1, 8, and 15 of a 28-d cycle.[5] In the 21 d cycle MTD was 130 mg/m^2 but no DLT was observed when oxaliplatin was given every 14 d at the same dose intensity (85 mg/m^2 q2 weeks). In the 28-d cycle MTD was 90 mg/m^2/week. In both studies DLTs were neurological.

Gemcitabine and oxaliplatin pharmacokinetics do not differ significantly in children compared to adults.[2,5,6,25–28] Moreover, no significant interactions between oxaliplatin and gemcitabine and its main metabolite 2′,2′-difluorodeoxyuridine were noted during clinical dosing.[23,29,30] Therefore GEMOX doses and scheduling evaluated in adults can be safely taken forward into paediatric phase II trials without further dose-finding combination trials.

No clinical data are yet reported on the GEMOX combination in children. We explored its efficacy in a multicentre, non-comparative, phase II study. The trial included five disease strata, to capture a large series of relapsing or refractory paediatric solid tumours. Both drugs were given as outpatient therapy on Day 1 of a 14-d cycle, minimising hospitalisation for children with relapsed disease.

2. Patients and methods

2.1. Eligibility

Eligibility criteria included: age 6 months to 21 years; histological or cytological diagnosis of solid malignancy (except diffuse infiltrative pontine glioma); refractory/relapsed tumour in which correct standard approaches to treatment have failed; measurable disease: i.e. at least one bi-dimensionally measurable lesion; for neuroblastoma, bi-dimensional lesions or mIBG positive metastatic disease as defined by the modified International Neuroblastoma Staging System[31]; for osteosarcoma, lung metastases and osseous lesions with soft-tissue tumour, excluding completely calcified or necrosed lesions; not more than 1 salvage therapy for relapse; life expectancy >3 months; no concomitant anticancer or investigational drug; Eastern Cooperative Oncology Group (ECOG) performance status $\leqslant 1$ or Lansky play score $\geqslant 70\%$; completion of anticancer therapy $\geqslant 3$ weeks prior to study entry, 6 weeks in case of nitrosourea, 4 weeks in case of irradiation; no clinical evidence of peripheral sensory or motor neuropathies; adequate bone marrow function (neutrophil count $\geqslant 1.0 \times 10^9$/l, platelet count $\geqslant 100 \times 10^9$/l; or $\geqslant 75 \times 10^9$/l in patients with bone marrow involvement); AST/ALT $\leqslant 2.5$ times the upper limit of normal (ULN); bilirubin $\leqslant 1.5$ times the ULN; creatinine $\leqslant 1.5$ times the ULN for age; no organ toxicity grade $\geqslant 2$; and informed consent signed. The protocol (NCT00407433), informed consent as well as child adopted assent forms, and amendments were approved by independent ethics committees, and complied with local laws and regulations, and the Declaration of Helsinki.

2.2. Treatment

Gemcitabine was provided as lyophilised powder in 200 mg or 1 g vials by Lilly Oncology. Oxaliplatin was provided as 10 or 20 ml solution at 5 mg/ml concentration by sanofi-aventis. Gemcitabine was administered intravenously at 1000 mg/m^2 over 100 min followed by oxaliplatin at 100 mg/m^2 over 2 h on Day 1 of a 14-d cycle. Anti-emetic treatments, including anti-5-HT$_3$ and corticosteroids, were allowed. Calcium and magnesium infusions were allowed before and after oxaliplatin administration if peripheral neuropathy occurred. Treatment was continued until disease progression, unacceptable toxicity, patient's or parental refusal, or treatment delay of >3 weeks.

2.3. Study design

The study included five strata: refractory/relapsed (1) neuroblastoma, (2) osteosarcoma, (3) medulloblastoma, (4) other central nervous system (CNS) tumours and (5) miscellaneous non-CNS solid tumours. A two-stage Simon design was used for each of the strata 1–4 with different hypotheses and decision rules according to the strata (see Table 1) and a descriptive design for miscellaneous non-CNS tumours.

2.4. Toxicity

Adverse events and laboratory variables were assessed using NCI-CTCAE version 3.0 (see http://ctep.info.nih.gov). Neurotoxicity was graded based on an oxaliplatin neurotoxicity scale: grade 1, paresthesias/dysesthesias possibly cold-induced, not interfering with function; grade 2, paresthesias/dysesthesias interfering with function but not with activities of daily living (ADL); grade 3, paresthesias/dysesthesias with pain or functional impairment and also interfering with ADL; and grade 4, paresthesias/dysesthesias that are disabling or life-threatening.

The next cycle began on Day 15 provided that there was recovery to $\leqslant$grade 2 for neutropenia and thrombocytopenia or $\leqslant$grade 1 for non-haematological toxicity. Paresthesiae/dysesthesiae were required to be $\leqslant$grade 2 prior to the next cycle. In the event of pharyngo-laryngeal dysesthesia, the infusion duration was increased from 2 to 6 h. In case of grade 4 neutropenia with documented infection or lasting more than 7 d, thrombocytopenia grade 3/4 lasting more than 7 d or requiring platelet substitutions during more than 7 d, grade 3 or 4 treatment-related non-haematological toxicity, or $\geqslant 14$ d delay in starting the new cycle, subsequent doses were adjusted to gemcitabine 800 mg/m^2 over 80 min and oxaliplatin 85 mg/m^2 over 120 min. If necessary, a second dose reduction was allowed to gemcitabine 600 mg/m^2 and oxaliplatin 65 mg/m^2. No re-escalation was allowed for doses that had been reduced for toxicity.

2.5. Tumour response

Tumour response was assessed by magnetic resonance imaging (MRI) or computed tomography (CT scan) according to the

Table 1 – Two-stage Simon design used for strata 1–4.

Cohort	p0 (%)	p1 (%)	α (%)	β (%)	First stage $\geqslant$ response/patients	Patients second stage	Total patients
Neuroblastoma	5	20	5	20	$\geqslant 1/10$	19	29
Osteosarcoma	15	35	5	25	$\geqslant 2/9$	20	29
Medulloblastoma	20	40	5	25	$\geqslant 3/12$	17	29
CNS tumours	5	20	5	20	$\geqslant 1/10$	19	29

World Health Organization (WHO) criteria[32] for every 4 cycles. For neuroblastoma, the INSS was used for response evaluation and mIBG scintigraphy was scored by extent and intensity. Objective responses were confirmed at 4–6 weeks. Imaging was reviewed by two independent radiologists or by a radiologist and a nuclear medicine physician. Efficacy parameters included: complete response (CR) or partial response (PR) after 4 cycles; best response over the whole duration of treatment; duration of response (time from CR or PR to disease progression); progression-free survival (PFS, time from first treatment to disease progression, death, or death whatever the cause) and overall survival.

3. Results

3.1. Patient characteristics

Between February 2007 and July 2008, 95 patients were enrolled in 25 centres in five countries. Ninety-three patients were treated: 12 neuroblastoma; 12 osteosarcoma; 14 medulloblastoma; 13 other CNS tumours and 42 miscellaneous non-CNS tumours (Table 2). Median age at inclusion was 11.7 years; 52 patients were male. Most patients had ECOG performance status 0–1; 78% had metastatic disease at study entry, and 70% had relapsed after prior therapy (median, two previous lines of systemic treatment), including platinum compounds in 66 patients: 38 patients (41%) had received prior cisplatin and 46 (49%) carboplatin.

3.2. Study treatment and safety

Overall, 60 out of 93 patients received at least four gemcitabine–oxaliplatin cycles (median, 4 cycles per patient; range 1–24); a total of 481 cycles were administered. The median gemcitabine and oxaliplatin doses per cycle were 1000 mg/m^2 (range 0–1111 mg/m^2) and 99 mg/m^2 (range 0–500 mg/m^2), respectively. On the whole treatment duration, 30 patients received a cumulative oxaliplatin dose above 500 mg/m^2, including 12 with a dose above 1000 mg/m^2 (max 2389 mg/m^2). The dose of gemcitabine was reduced in 43 cycles and omitted in 9, and the dose of oxaliplatin was reduced in 60 cycles and omitted in 2, leading to a total of 66 modified cycles (13%) in 15 patients (16%) mainly due to haematological toxicity; four of these patients had prior high-dose regimens and six had prior craniospinal irradiation. Excluding the first cycle, 152 out of the 388 cycles (in 50 patients) were delayed for more than 3 d (39%), due to haematological toxicity in 111 cases.

All grade 3 and 4 adverse events are summarised in Table 3. The most common toxicities reported were leukopenia (116 cycles, 25%, in 50 patients, 54%), neutropenia (183 cycles, 39%, in 68 patients, 73%), and thrombocytopenia (164 cycles, 35%, in 49 patients, 53%). Furthermore, 19 patients (20%) experienced 25 episodes of grade 3 or 4 pain. Grade 3 or 4 peripheral sensory neuropathy was noted in 8 cycles (2%) in 7 patients (8%); 24% of all treatment cycles had been accompanied by calcium and magnesium infusions.

The commonest reason for treatment discontinuation in all study cohorts was disease progression (69 patients, 74%), including three early deaths (4%). Ten patients (11%) discontinued treatment due to adverse events: haematological tox-

Table 2 – Patients' characteristics.

	Total N = 93
Age (years)	
Median (range)	11.7 (1.3–20.8)
Gender	
Male	52 (56%)
Female	41 (44%)
Lansky play scale/ECOG performance status	
100–90%/0	58 (63%)
80–70%/1	31 (33%)
60–50%/2	3 (3%)
Not done	1 (1%)
Tumour diagnosis	
Medulloblastoma	14
Other CNS tumours	13
Ependymoma	5
Oligodendroglioma	3
Brainstem glioma	2
Cerebral PNET other than medulloblastoma	2
Papillary tumour of the pineal region	1
Neuroblastoma	12
Osteosarcoma	12
Other non-CNS solid tumours	42
Rhabdomyosarcoma	12
Other soft-tissue sarcoma	4
Ewing and other PNET	6
Nephroblastoma	5
Desmoplastic small round cell tumour (DSRCT)	5
Malignant peripheral nerve sheath tumour (MPNST)	3
Adrenal carcinoma	2
Extracranial rhabdoid tumour	2
Malignant germ cell tumour	1
Hepatocellular carcinoma	1
Pancreatic tumour	1
Time between initial diagnosis and start of study treatment (months)	
Median (range)	18.7 (1.5–129.5)
Time between last anticancer treatment and study treatment (months)	
Median (range)	1.8 (0.1–116.2)
Tumour staging at study entry	
Metastatic	73 (78%)
Non metastatic	20 (22%)
Disease status at study entry	
Relapsing	65 (70%)
Refractory	28 (30%)
Number of relapses(including the one for which patients were included in the study)	
1	47 (72%)
2	15 (23%)
$\geqslant 3$	3 (5%)
Prior lines of systemic treatment	
1	39 (43%)
2	52 (57%)
Prior anticancer therapies	
Conventional chemotherapy	91 (98%)
High-dose chemotherapy with stem cell rescue	19 (20%)
Radiotherapy	62 (67%)
Surgical resection	89 (96%)
Other	9 (10%)

Table 3 – All grade 3 and 4 adverse events (according to NCI-CTCv3.0 criteria) reported in patients per treatment cycle.

	By cycle							Nb event	Patients experiencing AE[a] N = 93
	No. 1 (%)	No. 2 (%)	No. 3 (%)	No. 4 (%)	Nos. 5–8 (%)	Nos. 9–12 (%)	⩾12 (%)		
Haematological toxicitygrade 3–4	47	66	63	59	63	60	37	277/473	82
Anemia[b]	11	1	10	2	7	6	0	29/473	21
Leucopenia[b]	25	29	27	25	27	15	5	116/473	50
Neutropenia[b]	34	43	47	38	38	39	16	183/473	68
Thrombocytopenia[b]	15	39	42	39	45	31	26	164/473	49[c]
Extra-haematological toxicitygrade 3–4	37	23	19	15	14	5.6	16	96/479	58
Allergic reaction	0	0	1	0	0	0	5	2/478	2[c]
Vomiting	4	1	3	0	1	0	0	8/478	7
Diarrhoea	1	1	0	0	0	0	0	2/478	2
Febrile neutropenia	3	1	0	0	1	0	0	5/478	5
Infection with normal ANC	10	2	3	0	1	0	0	14/478	13
Peripheral sensory neuropathy	1	5	3	0	0	0	5	8/478	7[c]
Pain	11	7	3	7	2	0	5	25/477	19[c]
Pulmonary toxicity	4	1	1	0	0	0	0	6/477	6
Hepatic toxicity	8	8	9	8	11	4	0	35/430	16
Fatigue	5	2	1	2	0	0	5	10/479	7

[a] Number of patients that experienced at least one grade 3–4 toxicity during complete treatment duration.
[b] Haematological data for 8 cycles were missing.
[c] One patient had accidental exposure to 500 mg/m^2 oxaliplatin which led to haematological toxicity, pain, neurotoxicity and allergic reaction.

Table 4 – Tumour response to gemcitabine–oxaliplatin combination at 4 cycles.

Disease strata	Number of evaluable patients	PR	SD	PD
Total	93	4	26	63
Medulloblastoma	14	1[a]	6[b]	7
Other CNS	13	0	7	6
Ependymoma	5		2	3
Brain stem glioma	2		1	1
Oligodendroglioma	3		2	1
PNET	2		1	1
Papillary tumour of the pineal region	1		1[c]	
Neuroblastoma	12	0	5[d]	7
Osteosarcoma	12	1	4	7
Other non-CNS	42	2	4	36
Rhabdomyosarcoma	12	1		11
Other soft-tissue sarcoma	4	1		3
Ewing or other PNET	6			6
Nephroblastoma	5			5
DSRCT	5			5
MPNST	3		2	1
Adrenal carcinoma	2			2
Extracranial rhabdoid tumour	2			2
Malignant germ cell tumour	1			1
Hepatocellular carcinoma	1		1[e]	
Pancreatic tumour	1		1	

PR: partial response, SD: stable disease, and PD: progressive disease.
[a] Patient experienced PR at 4 cycles, CR at 7 cycles and relapsed 12 months later.
[b] One patient with SD at 4 cycles experienced PR at cycle 8; he progressed 18 months later.
[c] Patient presented SD at 4 cycles and PR at 8 cycles; he was reported with PD 7 months later.
[d] Including one patient classified as SD who presented a PR on MRI and a SD on MIBG.
[e] Patient presented with SD during 8 cycles and PR at 10 cycles, confirmed at cycle 12; the patient was reported with PD 8 months later.

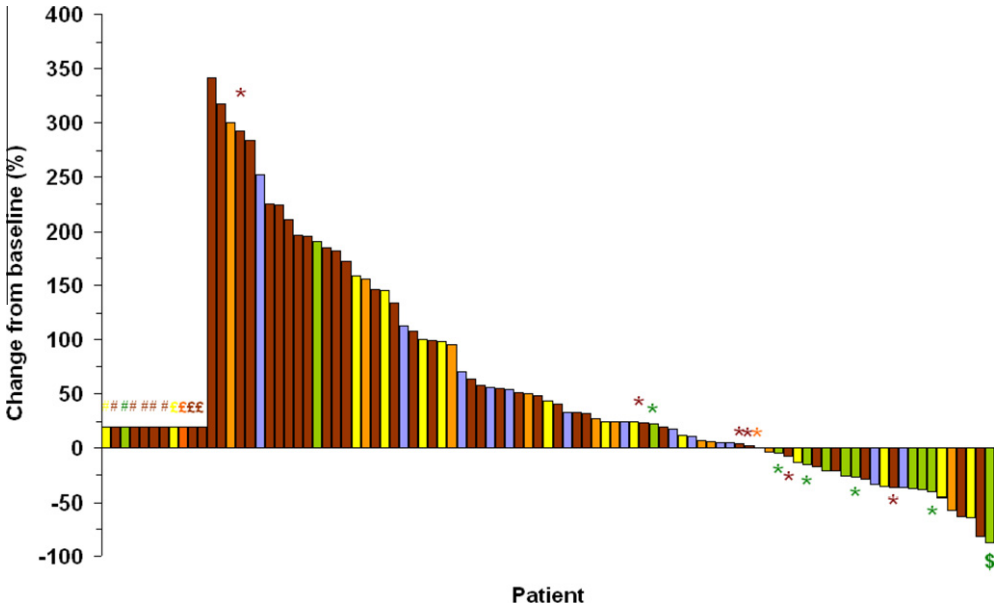

Fig. 1 – Waterfall plot of tumour response in 93 patients treated with GEMOX. Graph shows best response after 4 cycles, as percentage decrease in tumour size by WHO criteria of the bi-dimensional lesions in 82 patients; 11 patients with early progression and without adequate imaging at study end are included in lower bars. Yellow bars are patients with medulloblastoma; blue bars, patients with CNS tumour other than medulloblastoma; green bars, patients with neuroblastoma, orange bars, patients with osteosarcoma; and brown bars, patients with miscellaneous solid tumours. *Patients with change from baseline between −50% and +25% but classified as progressive disease due to apparition of new lesion on imaging (n = 6), progression on MIBG (n = 4) or increase of one lesion of more than 25% (n = 1). $Patient with neuroblastoma: −87% decrease in tumour size on MRI but stable disease of metastatic sites on MIBG. £Early progressive disease in X-ray without bi-dimensional tumour measurements at study end in 4 patients. #Bi-dimensional tumour measurements at study end were not performed in 7 patients with clinically early progressive disease. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

icity (6), hepatic toxicity (1), peripheral neuropathy following accidental overdose of 500 mg/m^2 in 60 min at cycle 3 (1), allergy and dyskinesia (1) and increasing tumour pain (1).

3.3. *Efficacy*

Ninety-three patients were evaluable for tumour response (Table 4; Fig. 1). Tumour control (CR + PR + SD) at 4 cycles was obtained in 30 patients (32.3%; 95% confidence interval (CI), 22.9–42.7%), including 4 PR (response rate = 4.3%, 95% CI, 1.2–10.6%) and 26 SD. A PR was observed after 4 cycles in 1/12 patients with osteosarcoma (8.0%, 95% CI, 0.21–38.5%), in 1 out of 14 patients with medulloblastoma (7.0%, 95% CI, 0.18–33.9%), in 1 out of 12 rhabdomyosarcoma and in 1 out of 4 other sarcomas (Fig. 2). The first two responding patients had received prior cisplatin, and the latter had carboplatin treatment. Five of 12 patients with neuroblastoma experienced stable disease during 4–34 months but no objective tumour response was observed (one patient experienced partial tumour regression of the primary tumour on MRI but had stable mIBG metabolic activity and was thus considered as stable). Additionally, in the miscellaneous non-CNS cohort, one hepatocellular carcinoma was stable during 8 cycles with subsequent PR at 10 cycles. In the CNS tumour cohort other than medulloblastoma, 7 patients experienced stable disease, 2 ependymomas during 4 and 22 months, respectively. At cut-off date the median follow-up was 30.8 months (range [19–33.8 months]). The median PFS was 1.91 months (95% CI, 1.77–2.20 months).

4. Discussion

The gemcitabine–oxaliplatin combination at 1000 mg/m^2 and 100 mg/m^2 every 2 weeks was well tolerated in children and adolescents with advanced solid malignancies. Objective tumour responses and prolonged tumour stabilisation were observed in this large study evaluating different paediatric tumour types. Nevertheless the overall objective response rates at four treatment cycles were limited to 8% in osteosarcoma, 7% in medulloblastoma and 8% in extra-osseous sarcoma. Interestingly in some patients a further improved tumour control was observed with prolonged treatment. One patient with medulloblastoma experienced partial response at the first 4 cycles of treatment and then prolonged complete response during 12 months. One case of a papillary tumour of the pineal region with stable disease after 4 cycles of treatment showed partial response after 8 cycles, and one patient with hepatocellular carcinoma experienced stable disease during 8 cycles and partial response at 10 cycles as reported by the local investigator.

As for other non-randomised combination studies, this phase II does not allow us to dissect synergistic antitumour

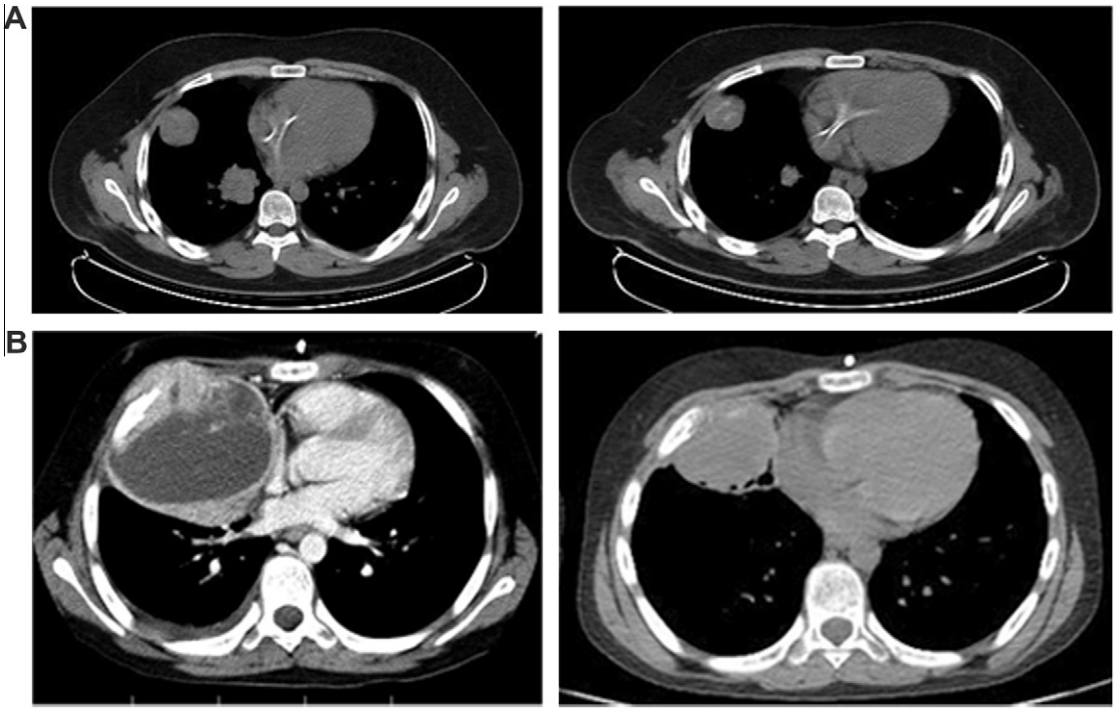

Fig. 2 – Computed tomography (CT) scans in a 19-year-old patient with relapsed osteosarcoma showing confirmed partial response of pulmonary metastases after four gemcitabine–oxaliplatin treatment cycles (right panel) compared to baseline evaluation (left panel) (A). Computed tomography (CT) scans in a 13-year-old patient with relapsed sarcoma showing confirmed partial response of pulmonary metastasis after four gemcitabine–oxaliplatin treatment cycles (right panel) compared to baseline evaluation (left panel). Although not relevant to the size determination of the metastasis here, it is noteworthy that the initial CT study was done after intravenous contrast-enhancement whilst the follow-up examination is a non-contrast study (B).

effects of the combination compared to those of single agents. However, even considering the best response rates, there is no clear improvement compared to the previously documented activity of oxaliplatin as single agent at least in osteosarcoma, neuroblastoma and medulloblastoma.[5,6] A retrospective study of gemcitabine at a dose of 675 mg/m^2 on Days 1 and 8 in combination with docetaxel at 75–100 mg/m^2 on Day 8 in 22 children and adolescents with recurrent or refractory bone or soft-tissue sarcomas reported an objective response rate of 29%.[33] Results of a prospective phase II study of gemcitabine plus docetaxel in children with recurrent osteosarcoma, Ewing's sarcoma, or chondrosarcoma (NCT00073983) are awaited. A phase I study of oxaliplatin in combination with etoposide (NCT00101205) has reported interesting preliminary responses,[34] but not when combined with irinotecan (NCT00101270).[35] Results of a phase II combining oxaliplatin and 5-fluorouracil (NCT00281944; POETIC) are awaited.

The present study further highlights the particularity in evaluating paediatric tumour types which are either rare in incidence or have high cure rates. Due to the existing adult data, the GEMOX combination appeared of particular interest to young patients with hepatocellular carcinoma, pancreatic carcinoma, germ cell tumours or lymphomas. As to be expected, only few patients entered with these tumour types during an inclusion period of 18 months, and indeed, the patient with a hepatocellular carcinoma profited from study treatment. A clinical phase II study with a 'miscellaneous' cohort allows enrollment of these kinds of patients but without any ability to determine clear objective response rates.

However this large combination study with five disease strata allowed both the formal testing by a classical two-stage design in tumour types where responses were expected based on the single agent data (i.e. neuroblastoma, osteosarcoma and medulloblastoma), and the ability to search for further hints of activity in other diseases in the 'basket' cohorts of the study. In order to limit the number of children with brain tumours if the combination has little activity, we also chose a two-stage design for the non-medulloblastoma cohort taking into account the difference in response rates in medulloblastoma compared to other brain tumours. This strategy enabled exploration of investigational drugs also in patients with rare diseases that under other conditions would have not access to a new treatment, and where no data would otherwise be available on activity of new agents in these diseases. If promising results are observed in a descriptive cohort it may lead to further focused studies in a specific disease type.

Based on the assumption of identical pharmacokinetics parameters in children and adults and lack of drug interactions between both agents, we have taken forward the doses used for the recent phase III trials in pancreatic and hepatocellular cancer in adult patients with 1000 mg/m^2 gemcitabine and 100 mg/m^2 oxaliplatin every 2 weeks without a prior dose-finding study of the combination in children. As

to be expected, toxicity profile was largely predictable and manageable with haematological toxicity and peripheral sensory neuropathy being the main observed toxicities. Increased haematological toxicity necessitating dose reductions was particularly found in patients with prior craniospinal irradiation or insufficient haematological recovery following stem cell rescue and high-dose regimens. Importantly, 12 patients had prolonged GEMOX treatment with cumulative oxaliplatin doses above 1000 mg/m^2 and up to 2389 mg/m^2 during this study. Only one of these patients experienced grade 3 sensory neuropathy at cycle 13, and no cumulative neurological toxicity was observed with prolonged treatment. One may argue that doses could have been increased further, i.e. oxaliplatin to 110 or even 130 mg/m^2, doses at which objective responses have been observed in the paediatric phase I trials.[5,6] Nevertheless, a dose intensity of 50 mg/m^2/week was achieved in the present combination study which compares favourably to the 67.5, 42.5 and 43.3 mg/m^2/week for the weekly, bi- or three-weekly schedules, respectively, used for single agent oxaliplatin.[5,6,25] Although phase I studies in adults with solid tumours determined MTD as high as gemcitabine at 1800 mg/m^2 on Days 1 and 8 and oxaliplatin 130 mg/m^2 administered on Day 8 of a 21-d cycle,[22,24] a further challenge of the chosen gemcitabine dose (1000 mg/m^2) is questionable given the high incidence of grade 3 and 4 thrombocytopenia and neutropenia as well as myelosuppression being the main reason for treatment delays in this study.

In conclusion, the gemcitabine–oxaliplatin combination given as a 14 d cycle has acceptable safety in children and adolescents, but only moderate activity in sarcoma, medulloblastoma or neuroblastoma suggesting its potential use for advanced stage disease rather than its integration in current upfront treatment protocols.

Conflict of interest statement

None declared.

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