Original article

The efficacy of irinotecan, paclitaxel, and oxaliplatin (IPO) in relapsed germ cell tumors with high dose chemotherapy as consolidation- a non-cisplatin- based induction approach.

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bju.13004

ABSTRACT

Objectives: To determine the outcome of an expanded cohort of patients with relapsed germ cell tumors (GCT) treated with a salvage chemotherapy regimen consisting of irinotecan, paclitaxel and oxaliplatin (IPO) and assess the role of IPO as an alternative to standard cisplatin-based chemotherapy regimens in this setting.

Patients and methods: The results of 72 consecutive patients were reviewed retrospectively. IPO was used either as a second-line treatment (n=29), of which 20 patients subsequently received high-dose chemotherapy (HDCT), or third-line (n=43), of which 32 patients proceeded to HDCT.

Results: The 2-year PFS and 3-year OS rates for the whole cohort were 30.2% (95%CI 17.3-40.5%) and 33.4% (95%CI: 20.1-43.8 %) respectively. CR was achieved in 3%, m-ve PR in 41%, m+ve PR in 18%, SD in 17% and PD in 20%. In the second-line setting, the 2-year PFS rate was 43.5% (95%CI: 21.7-60.8%) and 3-year OS 49.1% (95%CI: 24.2-65.1%). In the third-line setting, the 2-year PFS rate was 21.0% (95%CI 9.5-35.4%) and the 3-year OS rate was 23.9% (95%CI 11.7-38.2).According to the current international prognostic factor study group criteria for first relapse for the high and very high risk group the 2 year PFS rates were 50% and 30% respectively. There were 2 treatment related deaths from IPO, and 4 from HDCT. Grade 3 or 4 toxicities included neutropenia (35%), thrombocytopenia (18%), infection (15%), diarrhea (11%) and lethargy (8%).

Conclusions: IPO offers an effective, well-tolerated, non-nephrotoxic alternative to cisplatin-based salvage regimens for patients with relapsed GCT. It appears particularly useful in high risk patients and for those in whom cisplatin is ineffective or contra-indicated.

Keywords: germ cell tumors, relapse, cisplatin resistance.

Introduction:

The most frequently used management approach for patients with relapsed germ cell tumors involves cisplatin-based induction regimens given with ifosfamide and a third drug (e.g. etoposide [1], vinblastine [2] or paclitaxel [3]), this may be followed by consolidation with high dose chemotherapy (HDCT) and peripheral blood stem cell (PBSC) rescue. An alternative has been to mobilize stem cells with conventional chemotherapy and proceed to sequential HDCT regimens usually containing intensified carboplatin and etoposide, although thiotepa or cyclophosphamide have been included in some series. Sequential high dose chemotherapy and may be less toxic and more effective [4], although the improvement in survival seems more to do with the reduction in treatment related toxicity rather than an improvement in tumour control when compared to a single cycle of carboplatin etoposide and cyclophosphamide. [4]

Both conventional-dose chemotherapy (CDCT) and HDCT are used in patients with metastatic germ cell tumors at first relapse, although it remains uncertain as to which is the most effective treatment strategy. A recent retrospective analysis of a large cohort of patients with metastatic GCTs at first relapse suggested a significant improvement in progression-free survival (PFS) and overall survival (OS) associated with intensified HDCT compared to CDCT in most prognostic groups [5]. These results are consistent with a large single-center analysis but challenge the results from the IT94 study, a prospective randomized trial that found no benefit from HDCT compared with CDCT in the first salvage setting [6, 7]. Currently there is no clear consensus on the optimal chemotherapy for patients with GCTs at second relapse, or those with mediastinal primaries at first relapse, who usually have very poor outcomes [8].

The efficacy of IPO (irinotecan, paclitaxel and oxaliplatin) in patients with relapsed GCTs was first described in a Phase II study of 28 patients in 2006 [9]. IPO offers a different side effect profile than cisplatin-based regimens and was used in patients with GCTs who relapsed despite two prior lines of cisplatin–based chemotherapy or in patients with primary mediastinal GCTs who relapsed after first-line cisplatin-based treatment.

Following this study, our network of hospitals adopted this protocol and has continued to administer it in this therapeutic setting. We have extended its use in the first salvage setting to include patients who are over the age of 35 and those who had raised levels of lactate dehydrogenase (LDH), a poor prognosis marker, at relapse [10]. The updated results presented here include all patients treated with this protocol at our institutions between 2001 and 2011.

Patients and methods:

Between March 2001 and September 2011, 72 patients were treated with IPO +/- HDCT using Thiotepa, carboplatin and topotecan. The intention was to proceed to high dose chemotherapy as consolidation of IPO unless either an insufficient number of stem cells were collected or the patient were deemed not fit enough to proceed due to poor performance status or rapidly progressive disease.Twenty-nine patients received IPO second-line, of whom 20 proceeded to consolidation with HDCT. Forty-three patients received IPO third-line, of whom 33 proceeded to HDCT. Patients who received IPO in the second-line setting had failed one platinum-based therapy and either had a mediastinal non-seminomatous GCT (NSGCT), or a raised LDH at relapse or were over the age of 35. Patients who received IPO in the third-line setting had failed two cisplatin-based chemotherapy regimens.

Treatment responses were measured using the same criteria described in our previous phase II study, which are in keeping with other published reports. Progressive disease (PD)

was defined as the development of new sites of disease with rising tumor markers if present. Stable Disease was defined as the lack of any new sites of disease and a <90% reduction in tumor markers, 28 days post-chemotherapy. Marker-positive partial response (M+ve PR) was defined as a >90% reduction in tumor markers (without normalisation) for >28 days, and no new sites of disease. Marker-negative partial response (M-ve PR) was defined as a normalisation of tumor markers and no new sites of disease for at least 28 days. For those patients who had normal tumor markers before chemotherapy, an M-ve PR required a 50% reduction in the bidimensional measurements of the residual masses to be maintained for at least 28 days. Complete remission (CR) was defined as a normalisation of tumor markers with a complete resolution of all sites of disease. Postsurgical outcome was defined as outcome following surgery performed to remove all sites of disease, and patients who achieved a radiological CR to chemotherapy alone or had a surgically induced CR were deemed to have no evidence of disease (NED). Platinum sensitivity prior to high-dose chemotherapy was defined according to the method described by Beyer [11] although it should be noted that in this study, treatment prior to high-dose therapy was oxaliplatin-based rather than cisplatin-based.

Regimen: (Supplementary Figure A)

IPO consisted of a 3-weekly regimen of irinotecan 200mg/m^2 and oxaliplatin 100mg/m^2 given on D1, and paclitaxel 80 mg/m^2 administered on D1, D8 and D15. Two cycles were given and patients who showed evidence of response were given two further cycles. Filgrastim 300mcg/day was given on alternate days from day 2 to day 14.

Mobilisation of autologous blood stem cells was achieved using Paclitaxel 300mg/m^2 over 24 hours, followed 48 hours after initiation, by filgrastim 5mcg/kg/day given daily until day 10 when a CD34 peripheral blood count was measured. Patients who had at least 8 CD34 cells/microlitre proceeded to cell collection whilst those who had less were given a further dose of filgrastim and assessed the following day. A minimum of 1x10^6 CD 34 cells /kg were

required to proceed to HDCT. Normally stem cell collection was attempted prior to starting IPO but in those where urgent therapy was required, it was deferred until treatment was completed. The median CD34 cells harvested was 5.08 $X10^6$ cells/kg (range 1.11-43.02 X 10^6 cells/kg) and the median interval between mobilization and harvesting was 10 days (range 3-21 days).

Patients with at least M+ve PR proceeded to high dose chemotherapy consisting of carboplatin AUC7 followed 12 hours later by topotecan 10 mg/m^2 on D1, D2 and D3. Thiotepa was given as a continuous infusion on D1-D4 at 125mg/m^2/day. Autologous blood stem cells were re-infused 2 days later. We selected this high dose to intensify topo-isomerase 1 targeting and increase penetration through the blood-brain barrier.

Statistical analysis:

Survival curves are shown using Kaplan-Meier method. ***

Results:

The median follow up was 48.3 months (range 7.7-150.7) , 2 patients were lost to follow up. Twenty-nine patients received IPO as the first salvage treatment of which 20 proceeded to HDCT with topotecan, carboplatin and thiotepa. Eleven patients went on to have surgery, and histological evaluation revealed necrosis in 5 patients, mature teratoma in 3 patients, and viable cancer in 3 patients. Nineteen patients (66%) had favourable responses, which included CR (N=6), NED following surgery (N=4) and M-ve PR (N=9) (Table 2). Of those patients with primary mediastinal GCTs, 8 (62%) had favorable responses (Table 2). According to the International Prognostic Factors Study Group criteria (IPFSG),the PFS rates at 2 years and the overall survival rates at 3 years for patients treated at their first relapse were 56.6% and 43.8% respectively for intermediate risk patients, 50% and 83.3% respectively for high risk patients, and 30% each for very high risk patients (Supplementary Table A).

Forty-three patients received IPO at their second relapse, of which 32 proceeded to HDCT and 6 subsequently received surgery. Twenty-one patients (49%) achieved a favorable response including CR (N=3), NED after surgery (N=3) and M-ve PR (N=15) as shown in Table 2. The 2-year PFS and 3-year overall survival were 21.0% and 23.9% respectively for this group of patients. Histological evaluation of surgically resected disease showed necrosis in 3 patient samples and viable cancer in the other 3, one of which demonstrated primitive neuroectodermal transformation.

Applying the Beyer's HDCT prognostic prediction, the 2-year PFS rates for patients in this study were 52%, 29% and 0% for the good, intermediate and poor risk groups respectively. The 3-year OS rates were 63%, 10% and 0% for the good, intermediate and poor risk groups respectively (Figure 2).

Toxicity

Toxicities from IPO and HDCT are shown in Supplementary Tables B & C respectively. There were two treatment related deaths associated with IPO, both due to neutropenic sepsis. Three treatment related deaths were associated with HDCT with topotecan, carboplatin and thiotepa which were due to staphylococcal sepsis in one patient, ARDS secondary to neutropenic sepsis in another, and fungal infection and liver failure in the third. Another treatment related death, secondary to mesenteric infarction, occurred in a patient who received a HDCT containing carboplatin/etoposide, having opted to receive this treatment at their local institution.

Discussion:

These results follow on from, and are consistent with, earlier data published in our original phase II study [9]. They strongly suggest that IPO can be used to achieve high response rates in patients with relapsed germ cell tumors, even in those with the most adverse risk factors for disease progression.

There is much debate as to which is the most effective CDCT regimen at first relapse, although TIP (cisplatin, ifosfomide, paclitaxel) has been adopted by many centers. Furthermore, whether HDCT should be routinely adopted as a first salvage modality, and if so, whether this should involve single or tandem transplantations remains uncertain. It is therefore unsurprising that there is no convention as to which regimen should be administered following further relapses. Issues surrounding specific toxicities and drug resistance related to the repeated use of cisplatin in such regimens have led to the search for other agents on which to base salvage therapies. This has involved exploring drugs of a similar class and those with different mechanisms of action that are relevant to GCT biology. Oxaliplatin is a third-generation diammine cyclohexane derivative with evidence of non-cross-resistance to cisplatin. Various agents have been combined with it in the treatment of GCTs, and doublets using paclitaxel and irinotecan have shown similar efficacy. In the initial monotherapy studies in heavily pre-treated patients, paclitaxel showed moderate activity [12] and irinotecan [13] showed none; although most patients were heavily pre-treated. Based on this apparent lack of activity as a single agent, the contribution of irinotecan in the IPO regimen may questionable. However, there is histochemical evidence supporting the validity of topo-isomerase-1 targeting in GCTs [14] and the increased response rates described following the addition irinotecan to oxaliplatin therapy supports its role in this therapeutic context [15]. The use of paclitaxel in the IPO regimen is supported by previous data demonstrating long-term progression-free survival rates of 29% in patients with relapsed GCTs who received TI/CE [16].

The management of patients with relapsed mediastinal NSGCTs has proved particularly difficult. Poor responses to induction therapy have led to the exclusion of this group of patients from subsequent high dose treatments and surgical approaches are usually adopted instead. None of the patients with relapsed mediastinal NSGCTs in our cohort were

amenable to surgical resection, either due to metastases or tumor size and location. Nevertheless, our data suggest that IPO is an effective regimen in this patient group.

There are inherent weaknesses in any retrospective study, particularly in a rare tumor type. In this study there was some heterogeneity of the patient groups and line of therapy, however the fact that follow up is complete and that our results mirror those reported in our original phase II study are re-assuring, The recent IPFSG criteria of prognostication at first relapse also add strength to the argument that salvage therapy for this patient group may be safely undertaken using non cisplatin-based approaches [17].

Salvage therapy in germ cell tumors has been dominated by phase II studies and attempts to conduct phase III randomized trials have, to-date, been undermined by poor recruitment and under powering. We suggest that IPO can overcome problems associated with cisplatin resistance and toxicity by utilizing drugs that target cellular mechanisms shown to be important in GCT biology. IPO therefore appears to be an appropriate salvage therapy for routine use in patients with relapsed GCTs and high IPFSG scores including those with mediastinal NSGCTs.

Conflicts of interest: None declared

We would like to thank the Orchid Cancer Appeal for their financial support of nursing staff involved in treating these patients.

Tables and figures:

Figures

Figure 1: progression-free and overall survival after 1st and 2nd relapse.

Figure 2: outcome based on pre-high dose chemotherapy prognostic factors (Beyer HD prognostic categories).

Supplementary Figure A: summary of regimen and stem cell collection procedure.

Supplementary Figure B: outcome of patients with mediastinal disease.

Tables

Table 1: characteristic of patients receiving IPO chemotherapy at first and relapse.

Table 2: outcome of patients receiving IPO at first and second relapse.

Supplementary Table A: Progression free and overall survival by IPFSG criteria at first relapse.

Supplementary Table B: Toxicity on IPO.

Supplementary Table C: Toxicity on High Dose Topotecan, Carboplatin and Thiotepa.

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Table 1: Characteristics of patients receiving IPO at first and second relapse

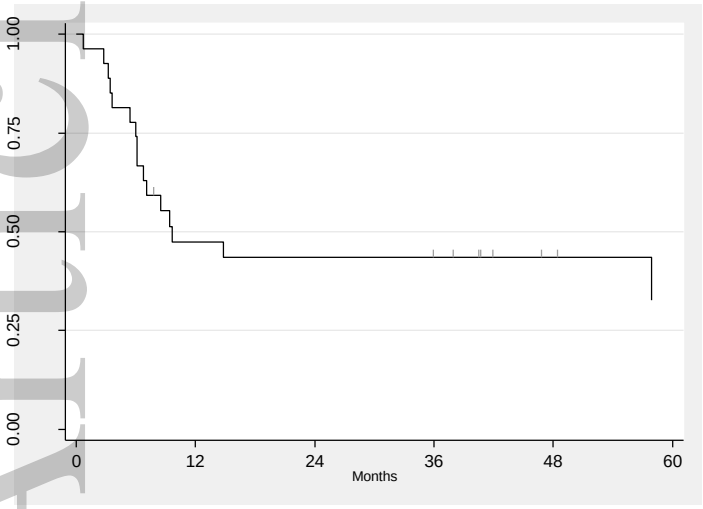
	First Relapse (N=29)	Second Relapse (N=43)
Median age (range)	**33 (17-74)**	**37 (18-65)**
IPFSG at diagnosis		
• **Good**	**6**	**15**
• **Intermediate**	**5**	**13**
• **Poor**	**18**	**7**
• **Unknown**	**N/A**	**8**
Histology		
• **NSGCT**	**26**	**37**
• **Seminoma**	**3**	**6**
Primary site		
• **Testis**	**13**	**39**
• **Mediastinum**	**13**	**N/A**
• **Retroperitoneal**	**2**	**1**
• **Extragonadal**	**N/A**	**3**
• **Unknown**	**1**	**N/A**
Platinum sensitivity		
• **Sensitive**	**26**	**35**
• **Refractory**	**1**	**4**
• **Absolutely refractory**	**1**	**4**
• **Not applicable**	**1**	**N/A**
IPFSG at relapse		
• **Low risk**	**5**	
• **Intermediate risk**	**8**	
• **High risk**	**6**	
• **Very high risk**	**10**	

Table 2: Outcome of patients at first and second relapse (mGCT: mediastinal GCT).

	IPO		IPO+HD		Final		
	First Relapse *N*=29 (%)	Second Relapse *N*=43 (%)	First Relapse *N*=20 (%)	Second Relapse *N*=32 (%)	First Relapse *N*=29 (%)		Second Relapse *N*=43 (%)
					All *N*=29	mGCT *N*=13	
Response							
CR	1 (3.4)	1 (2.3)	5 (25)	3 (9.4)	6 (20.7)	2 (15.4)	3 (7)
NED (after surgery)	1 (3.4)	0	3 (15)	3 (9.4)	4 (13.8)	1 (7.7)	3 (7)
M-ve PR	9 (31.1)	19 (44.2)	8 (40)	10 (31.2)	9 (31)	5 (38.5)	15 (34.8)
M+ve PR	9 (31.1)	6 (14)	0	4 (12.5)	2 (6.9)	1 (7.7)	4 (9.3)
SD	4 (13.8)	6 (14)	1 (5)	7 (21.9)	1 (3.4)	1 (7.7)	7 (16.3)
PD	5 (17.2)	9 (20.9)	1 (5)	3 (9.4)	5 (17.3)	3 (23)	7 (16.3)
TRD	0	2 (4.6)	2 (10)	2 (6.2)	2 (6.9)	0	4 (9.3)
Favorable response rate (CR+NED+M-VE PR)					19 (66)	8 (62)	21 (49)

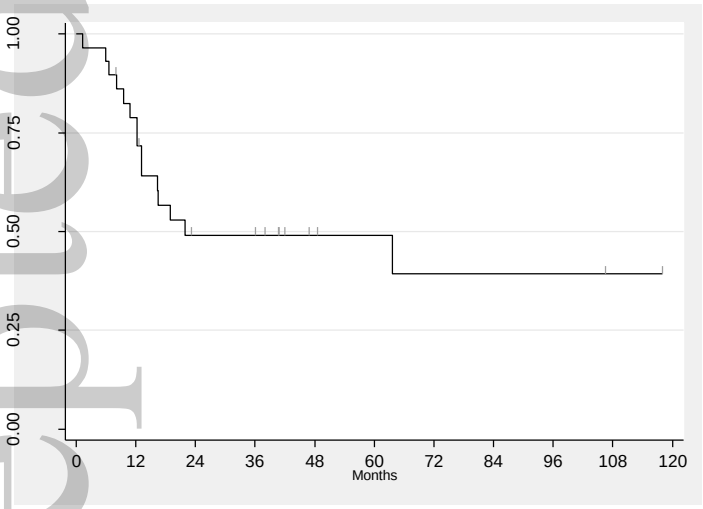
FIGURE 1

First relapse – Progression free survival



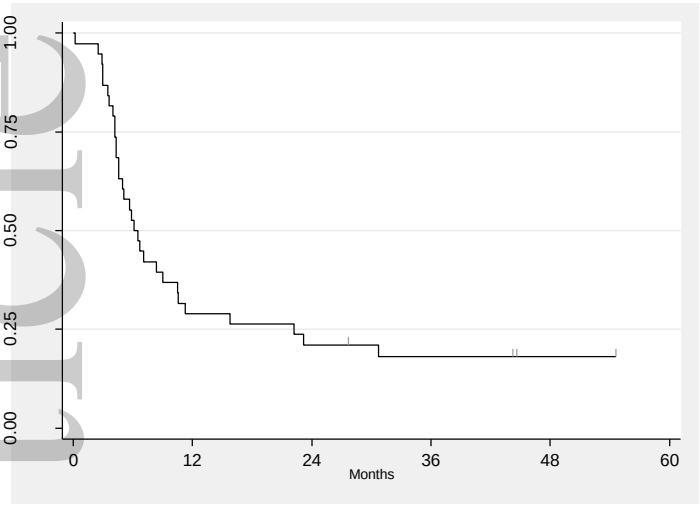
Time (months)		0	12	24	36	48	60
At risk	27	12	11	10	5	3	

First relapse – Overall survival



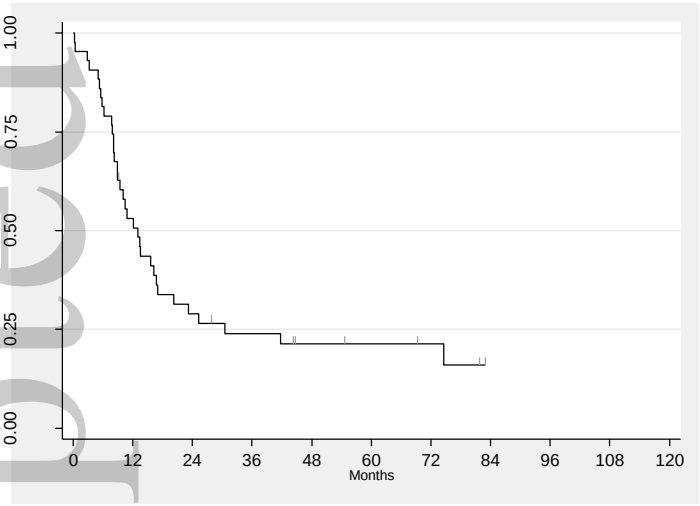
0	12	24	36	48	60	72	84	96	108	120
29	22	12	11	6	5	4	4	4	3	2

Second relapse – Progression free survival



Time (months)		0	12	24	36	48	60
At risk	38	11	8	6	4	3	

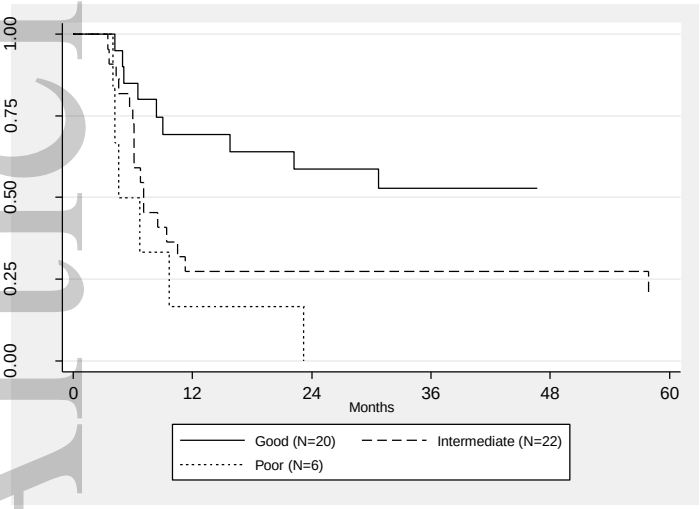
Second relapse – Overall survival



0	12	24	36	48	60	72	84	96	108	120
43	22	12	9	6	5	4	1	1	1	1

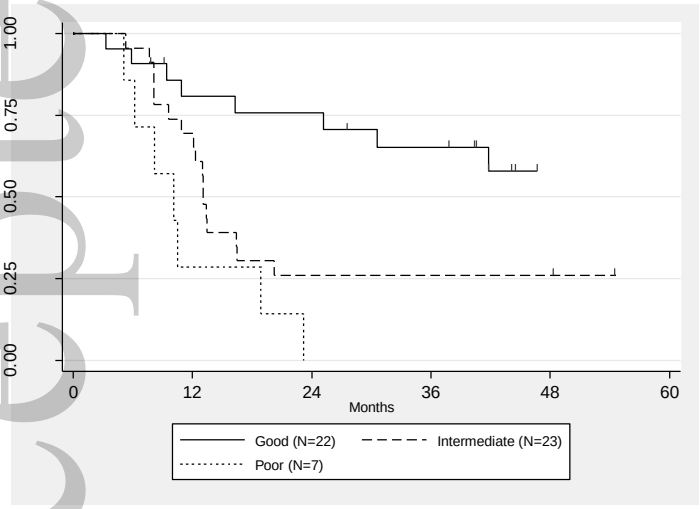
FIGURE 2

Progression free survival



Time (months)		0	12	24	36	48	60
Good at risk	20	13	11	9	2	2	
Intermediate at risk	22	6	6	6	6	3	
Poor at risk	6	1	0	0	0	0	

Overall survival



Time (months)		0	12	24	36	48	60
Good at risk	22	16	15	12	4	4	
Intermediate at risk	23	16	6	6	6	4	
Poor at risk	7	2	0	0	0	0	