The Administration of the Irinotecan with Oxaliplatin, Actinomycin and Methotrexate may not be Feasible for Relapsed Germ Cell Tumours with Poor Prognosis.

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ABSTRACT

A phase II single arm clinical trial was conducted in patients with relapsed germ cell tumours (GCT) using a combination of pegfilgrastim, actinomycin D, high dose methotrexate, irinotecan ,oxaliplatin [GAMIO]. The aims of this study were to establish response rates to GAMIO by investigating the safety and efficacy of combination of drugs. The planned sample size was 47. However, only five patients were recruited into the trial before recruitment was closed prematurely. There was a major drug interaction which caused severe diarrhoea and significant neutropenia and thrombocytopenia. Three patients out of the five died from serious adverse reactions (SAR) of the study treatment. One patient had a negative tumour marker response. Both the median overall survival and progression-free survival for this group of patients were 1.94 months. We concluded that the administration of the irinotecan with oxaliplatin, actinomycin and methotrexate may not be feasible.

Key words: GCT, *Irinotecan, Oxaliplatin, Actinomycin, Methotrexate.*

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INTRODUCTION

The treatment of germ cell tumours is considered to be one of the major successes in the arena of cytotoxic chemotherapy. Even in patients who relapse after first-line therapy, a durable remission rate of between 25% and 60% has been seen using further chemotherapy. In 1999, researchers at St Bartholomew's Hospital developed the GAMEC protocol (combination chemotherapy with GCSF, actinomycin-D, methotrexate, etoposide and cisplatin) which delivered dose intense cisplatin and etoposide with the addition of two other agents (actinomycin D & high dose methotrexate) which were known to be active in relapsed disease.

A recently conducted Phase II study of this regimen in relapsed germ cell tumours (GCT) showed that 80% of relapsed patients responded to this therapy and 50% of them had a durable remission.[1] Interestingly, when prognostic factors for survival were sought, only two were significant, namely raised Lactate Dehydrogenase (LDH) at relapse and age greater than 35. In the absence of these, the PFS was > 90%, however the presence of either made the progression-free survival fall to 25%.The

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impressive data with epirubicin led to the development of the GAMEC- A schedule with epirubicin substituted for etoposide.[2] Unfortunately in the first 15 patients given this regimen, who had either of the 2 poor prognosis factors identified, the PFS remained 25%.This study was therefore closed.

The realisation that oxaliplatin and irinotecan based therapy could salvage one third of GAMEC relapses and have considerable salvage potential in the 3rd line setting, as well as in patients with relapsed mediastinal germ cell tumours (a very difficult group of patients to treat successfully), lead to the design of this study, where 2 drugs in the original GAMEC schedule (etoposide and cisplatin) were replaced with oxaliplatin and irinotecan.[3] The cycles in this study were given every 14 days as with the previous GAMEC protocol, with an additional week off between cycles 2 and 3.

This substitution was expected to lead to benefits in terms of toxicity reduction (oxaliplatin does not cause renal dysfunction), a particular problem seen with GAMEC. The time in hospital on treatment was expected to be shortened, as cisplatin hydration was no longer required and methotrexate could be followed immediately by oxaliplatin rather than being deferred for 36 hours because of the risk of compounded renal toxicity. Irinotecan causes less mucositis than etoposide, thus reducing the severity of this dose-limiting toxicity. Irinotecan induced diarrhoea was expected to be a problem, although higher dose intensities of the drug have been delivered in other regimens without problems.[3] For this reason it was planned that the first 6 patients will have the dose divided into two weekly doses (100 mg/m2), therefore allowing omission of doses if diarrhoea proves problematic. Afterwards patients were to receive 200 mg/m^2 every cycle on day 1 of each cycle. If unacceptable toxicity were seen in the first 3 patients then the original schedule would be used.

FDG-PET scanning has a predictive role in several tumour types and has been used to demonstrate a rapid normalisation in metastatic germ cell tumours.[4] A rapid reduction in glucose avidity at 14 days (after 2 cycles) has been shown to predict long term progression-free survival. This would be a major advantage as early tumour marker responses are frequently favourable, even in those who subsequently progress.

Based on the above findings, it was proposed to give patients with either of the two adverse factors (raised LDH or age greater than 35), 4 cycles of GAMIO. In addition, patients who relapsed mediastinal GCT for whom current standard chemotherapy regimens (using etoposide and platinum-based agents) failed to show cure rates of >15%, would also be offered GAMIO.

The aims of this study were to establish response rates to GAMIO by investigating the safety and efficacy of substituting oxaliplatin and irinotecan for cisplatin and etoposide. We observed for any toxicities that may be associated with the study treatment, throughout the trial period. Progression-free survival and whether a repeat FDG PET-CT scan at 14 days (after 1 cycle of therapy but prior to cycle 2) may predict long-term, progression-free survival following GAMIO was also investigated.

PATIENTS AND METHODS

This was a phase II single arm clinical trial in patients with relapsed germ cell tumours (GCT) using a combination of Actinomycin D (1mg/m^2)- day 1, Methotrexate 8g/m^2 (dose was adjusted for glomerular filtration rate)-day 1 with folinic acid rescue 30 hours later, Irinotecan 100 mg/m^2 day 1 and day 8, Oxaliplatin 100mg/m^2day 2 and pegfilgrastim 6mg on day 3. Treatment was repeated every 14 days for 4 cycles. There was an additional 7 day gap between cycles 2 and 3. The study commenced on 16th July 2009 but recruitment closed prematurely on 1st September 2010 due to major toxicities. The planned sample size was 47, however, the actual number of patients recruited was five. Patients had to have a relapsing GCT following failure of platinum based chemotherapy and at least 1 of the following adverse criteria- > 35 years old, raised LDH or relapsed mediastinal non-seminomatous germ cell tumour. They had to have a glomerular filtration rate of > 40ml/min and a performance status of 0-3.

Patients received the four−drug combination chemotherapy in hospital over two nights. On the third day, the patient received an injection of pegfilgrastim. The treatment was repeated every two weeks. This constituted one cycle of treatment. We aimed to give the patient four cycles of treatment over a total of nine weeks (on week 5 no treatment would be given).

Before each cycle, the following was conducted – physical examination, full blood count, urea + electrolytes, liver function tests, LDH, aFP, ßHCG. Patients had a FDG PET−CT scan at baseline, prior to

cycle 2 (approximately 14 days after chemotherapy starts) and a final FDG PET−CT within 28 days of the last treatment. On each cycle, serum creatinine was measured 24 hours after the start of the methotrexate to exclude renal failure due to methotrexate.

The study was evaluated by monitoring toxicities and objective response rates. Toxicities based on NCI Common Toxicity Criteria version 3 were measured on day 1 of each cycle and at end of treatment. Objective response rate was based on tumour markers response. Progression-free survival (PFS) and overall survival were also observed, where PFS was measured from date of receiving first dose to the date of death or progression and overall survival was measured from date of receiving first dose to the date of death. In order to ascertain whether a repeat FDG PET-CT scan at 14 days (after 1 cycle of therapy but prior to cycle 2) may predict long-term, progression-free survival following GAMIO, FDG PET-CT scan of chest, abdomen and pelvis were performed at screening (up to 14 days prior to chemotherapy), prior to cycle 2 (approximately 14 days after chemotherapy starts) and within 28 days of the last treatment.

RESULTS

Five patients were enrolled into the study. Table 1 summarises patient characteristics at baseline. The median age of patients was 37 years. Two patients, GA-02 and GA-04, had two courses of chemotherapy prior to taking part in this trial. Only patient GA-03 had complete response to previous course of chemotherapy. This study treatment was completed by three of the five patients who took part. Table 2 shows the dose delivery – it can be seen that in patient 5 several doses of irinotecan were omitted and no irinotecan was given on course 4 – despite this diarrhea returned and worsened on course 4.

Patients GA-02 and GA-03 experienced several episodes of grade 3 diarrhoea, infection and platelets. They also experienced four counts of severe neutropenia each at grade 4 level while undergoing treatment. Patient GA-05 had 3 incidences of neutropenia and 2 episodes of platelets at grade 3 and above. Overall, grade 3 and 4 neutropenia and diarrhoea were the most frequent AEs, being present on 25% and 20% of the study visits. A further 16% and 14% toxicity were recorded in the form of platelets and infection among these patients. Three patients out of the five died from serious adverse events (SAE) related to the study treatment (Table 4). All three patients had severe GI toxicity with diarrhoea and small bowel dilatation. In patient GA-01, functional intestinal obstruction lasted 5 days, and an episode of vomiting led to aspiration followed by cardiac arrest. Patient GA-04 experienced a life threatening SAE- severe diarrhoea, gut dilatation and gastrointestinal haemorrhage; this started to resolve after a week with recovery of his blood count but was followed by massive pulmonary embolism which proved to be fatal. Patient GA-05 had severe diarrhoea and gut dilatation.

Table 1: Patient characteristics

	Patients				
	GA-01	GA-02	GA-03	GA-04	GA-05
Age	36	37	51	32	39
Histology	Non-seminoma	Non-seminoma	Other	Seminoma	Non-seminoma
Initial IGCCCG	Intermediate	Poor	Poor	Good	Poor
Orchidectomy	No	Yes	Yes	Yes	Yes
No. of previous therapies	1	2	1	2	1
Outcome to previous chemotherapy	Progressive disease	Partial response	Complete response	Partial response	Partial response
	-	Stable disease	-	Partial response	-
Performance status (WHO) at screening	1	0	1	1	0

Table 2: GAMIO chemotherapy schedule

	Cycle	Day	Patients				
			GA-01	GA-02	GA-03	GA-04	GA-05
Actinomycin	1	1	2.15 mg	1.60 mg	1.80 mg	2.40 mg	2.2 mg
	2	1	2.15 mg	2.15 mg	1.80 mg	-	2.2 mg
	3	1	-	2.15 mg	1.80 mg	-	2.2 mg
	4	1	-	2.20 mg	1.80 mg	-	2.2 mg
Irinotecan	1	1	210 mg	220 mg	170 mg	240 mg	130 mg
		8	210 mg	220 mg	170 mg	240 mg	Not given due to toxicity
	2	1	210 mg	220 mg	170 mg	-	Not given
		8	Dose ommitted due to acute sepsis and neutropenia	220 mg	170 mg	-	130 mg
	3	1	-	220 mg	170 mg	-	Not given
		8	-	Not given due to toxicity and neutropenia	170 mg	-	130 mg
	4	1	-	220 mg	170 mg	-	Not given as per new amendment
		8	-	220 mg	Not given due to toxicity	-	Not given due to toxicity
Methotrexate	1	1 (Bolus)	4280 mg	3240 mg	3460 mg	4700 mg	4380 mg
		1 (Infusion	8560 mg	4320 mg	6920 mg	14100 mg	8760 mg
	2	1 (Bolus)	4280 mg	3240 mg	3460 mg	-	4380 mg
		1 (Infusion	8560 mg	4320 mg	6920 mg	-	8760 mg
	3	1 (Bolus)	-	1620 mg	3460 mg	-	4380 mg
		1 (Infusion	-	2160 mg	6920 mg	-	8760 mg
	4	1 (Bolus)	-	1620 mg	3460 mg	-	4380 mg
		1 (Infusion	-	2160 mg	6900 mg	-	8760 mg
Oxaloplatin	1	2	210 mg	215 mg	175 mg	235 mg	220 mg
	2	2	215 mg	215 mg	175 mg	-	220 mg
	3	2	-	215 mg	170 mg	-	220 mg
	4	2	-	215 mg	175 mg	-	220 mg

He was noted to have had an adenoviral infection leading to diarrhoea and had Clostridium difficile. This was reported prior to him receiving any antibiotics. Patient GA-02 died in the follow-up period of progressive disease. No SUSARs were reported for this study.

Toxicity based on NCI Common Toxicity Criteria version 3 was measured on day 1 of each cycle and at the end of treatment. Table 3 summarises the grade 3 and 4 adverse events experienced by each of the patients while on the treatment. Prior to cycle 2, two patients showed metabolic complete response, one patient partial response, one patient non-metabolic response and one patient was not evaluable due to treatment related death (Table 5). Only patient GA-03 was evaluable for metabolic response at the end of treatment, showing a Partial Response. Patient GA-04 had negative tumour marker response i.e. objective response rate was 20%.

Table 6 provides a summary of progression-free survival and overall survival of the five patients. It was observed that four patients died before the end of the study period, and progression of disease was reported in two patients. Only patient GA-03 survived till the end of the study, but he did experience disease progression at about 5 months into the study. The median overall survival and progression-free survival for this group of patients were 1.94 months.

Table 3: Number of grade 3 and 4 toxicities

	Patients									
	GA-01		GA-02		GA-03		GA-04		GA-05	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Stomatitis	-	-	-	-	-	-	1	-	-	-
Diarrhoea	-	-	3	-	4	-	1	-	1	1
Anorexia	-	-	-	-	-	-	1	-	-	1
Infection	-	1	3	-	2	-	-	1	-	-
Weight loss	-	-	1	-	-	-	-	-	-	-
Fatigue	-	1	-	-	1	-	1	-	-	1
Neutropenia	-	1	-	4	-	4	-	1	-	3
Platelets	1	-	3	1	-	-	-	1	2	-
Haemoglobin	-	-	2	-	1	-	-	1	-	1

Table 4: Summary of serious adverse reactions (SAR)

	Patient			
	GA-01	GA-04	GA-04	GA-05
SAR/SUSAR	SAR	SAR	SAR	SAR
Description	Cardiac arrest, secondary to aspiration	Gastrointestinal Haemorrhage	Massive pulmonary embolism	Death
Type of event	Death	Life threatening, hospitalisation	Death	Death

Table 5: Response to GAMIO

	Patients				
	GA-01	GA-02	GA-03	GA-04	GA-05
Metabolic response prior to cycle 2	Complete Response	Progression	Partial Response	Non Evaluable	Complete Response
Metabolic response	Non Evaluable	Non Evaluable	Partial Response	Non Evaluable	Non Evaluable
Tumour markers response	Marker positive partial Response	Marker positive Stable Disease	Marker Positive Partial Response	Marker Negative partial response	Marker Positive Partial Response

Table 6: Progression free survival (PFS) and overall survival (OS)

	Patient				
	GA-01	GA-02	GA-03	GA-04	GA-05
Date chemo started	23/10/2009	2/12/2009	18/12/2009	22/03/2010	23/06/2010
Date of progression	N/A	7/4/2010	28/05/2010	N/A	N/A
Year of death	2009	2010	N/A	2010	2010
Last follow-up	29/11/2009	10/9/2010	18/10/2011	16/04/2010	21/08/2010
OS (Months)	1.22	9.26	21.98	0.82	1.94
PFS (Months)	1.22	4.14	5.29	0.82	1.94

DISCUSSION

The decision to close the study prematurely on the 1st September 2010 was made by the Trail Management Group due to significant problems with diarrhoea on this regimen. Two of the 3 deaths were clearly due to gastro-intestinal toxicity – in the third although the cause of death was pulmonary embolism it followed a prolonged period of immobility secondary to severe gut toxicity (small bowel dilatation with functional obstruction and neutropenia lasting 2 weeks). Even after introducing an amendment to the protocol to reduce the irinotecan dose from 100mg/m2 to 60mg/m2 on Day 1 & 8, the subsequent patient who received this dose still had severe diarrhoea on the 4th cycle despite the fact that the previous cycles had been tolerated well. Even at this reduced dose it seems that the administration of the irinotecan with oxaliplatin, actinomycin and methotrexate at these doses may not be feasible.

Combinations with irinotecan and oxaliplatin have been described by us (IPO) and others in germ cell tumours and diarrhoea was not dose limiting[5]. When combined with another drug – fluorouracil also capable of causing dose limiting diarrhoea an increase in severe diarrhoea was not reported. It is unlikely that a significant interaction with high dose methotrexate ocuured as the drug was cleared quickly by patients. This therefore suggests a possible interaction with actinomycin. It is unfortunate that pharmacokinetic studies were not performed as this could have helped elucidate this further.

Drug interactions are an important concern in the treatment of cancer.[6] We found that there was clearly a significant drug interaction which caused severe diarrhoea and significant neutropenia and thrombocytopenia. There are various drug interactions that may have lead to the adverse events. As there are other agents with documented activity in this setting and without the gastrointestinal side effects of irinotecan it would be best to close the current study rather than further dose reduce the irinotecan which would be the alternative strategy.

CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

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AUTHOR CONTRIBUTIONS

Jonathan Shamash was the chief investigator for this trial. He was responsible for trial conception and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept, design, supervision, critical revision of the manuscript for important intellectual content: J Shamash

Acquisition of data: Katherine Mutsvangwa

Analysis of data, interpretation of data and drafting of manuscript: S J Sarker and J Shamash

Statistical analysis: S J Sarker and K Chowdhury.

SPONSOR

Barts and The London NHS Trust acted as the sponsor for this study, taking on the legal responsilility for the initiation and management of the research, ensuring the study was carried out in compliance with all UK regulatory bodies.

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