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Intermediate dose gemcitabine–cisplatin combination chemotherapy without treatment delay for cytopenia followed by autografting—a new standard of care in relapsed or refractory Hodgkin lymphoma?

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Abstract Ten percent to 20% of patients with Hodgkin Lymphoma (HL) are refractory to first-line therapy or relapse. Existing salvage regimens have response rates of 60–85%, considerable toxicity and frequent treatment delay or dose reduction. We report a gemcitabine, cisplatin, and dexamethasone regimen (GemCis) with intensive growth factor and platelet support and no treatment delay. Seventeen patients with relapsed or refractory biopsy proven HL were treated. Toxicity, transfusion requirement, stem cell harvesting and engraftment data were collected. Response assessment was by computed tomography and positron emission tomography. Overall and complete response rates were high (94% and 65%, respectively). There were no episodes of febrile neutropenia, treatment delays or hospital admissions. All 15 patients intended for autograft were successfully harvested. All engrafted successfully with a median time for the entire group to neutrophil engraftment of 14 days. With a median follow-up of 22 months, the median survival has not yet been reached, and the estimated 2-year survival is 88%. GemCis is a well-tolerated outpatient regimen for relapsed/ refractory Hodgkin lymphoma which does not inhibit stem cell

mobilisation, gives excellent response rates and compares favourably with previously published salvage regimens using these or other chemotherapy agents.

Keywords Hodgkin's lymphoma · Salvage chemotherapy · Transplant

Introduction

Most patients with Hodgkin Lymphoma (HL) are cured by primary chemotherapy, typically adriamycin, bleomycin, vincristine, dacarbazine (ABVD) with or without involved field radiotherapy [1]. However, 10–20% of patients, especially those with advanced stage or bulky disease, will be refractory to first-line therapy or will relapse [2]. The best treatment for most of these patients is salvage chemotherapy followed by autologous stem cell transplant. Many salvage regimens are used, usually platinum-based, with the most commonly used regimen in the UK being etoposide, methylprednisolone, high dose cytarabine and cisplatin (ESHAP) [3, 4]. These regimens have response rates of 60–85% [5], considerable toxicity and may require hospitalisation either for administration or to manage complications. Effective alternative regimens with high response rates and low toxicity which permit subsequent autologous transplantation are, therefore, required. We report the use of a modified gemcitabine and cisplatin combination in 17 patients with refractory or relapsed HD. The rationale for the combination is based on the following: gemcitabine is a cell cycle phase specific pyrimidine analogue structurally similar to

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cytarabine which inhibits DNA synthesis and induces apoptosis through incorporation of its triphosphate metabolite into DNA whereas cisplatin binds to DNA preventing DNA and RNA synthesis and is phase non-specific. Gemcitabine has shown single agent activity in HD [6] and has been used in combination with non-platinum drugs, for example, the IGEV regimen [7] which consists of 4 cycles (each of ifosfamide with MESNA rescue, vinorelbine, prednisolone and gemcitabine at 800 mg/m² for two doses) followed by single or tandem autologous or non-myeloablative allogeneic stem cell transplants if at least a partial response is achieved. Although, despite this aggressive approach, over 3 years freedom from progression is only 53% and 30% of patients die. Gemcitabine and cisplatin in combination have shown effectiveness in solid tumours, non-Hodgkin's lymphoma (NHL) and, in two small patient series, in relapsed or refractory Hodgkin lymphoma [8–11].

In the first of these gemcitabine, 1,000 mg/m² intravenous (IV) was administered on days 1 and 8, dexamethasone 40 mg orally on days 1–4 and cisplatin 75 mg/m² IV on day 1 only (GDP) [8]. This outpatient regimen was repeated every 21 days for 2 cycles followed by autologous stem cell transplant or, in patients unsuitable for transplant, up to 6 cycles. Primary prophylaxis with colony-stimulating factor was not permitted but treatment delay or dose omission was permitted for cytopenia. Treatment delay or dose reduction occurred in 14(30%) of the 47 cycles administered with a complete response (CR) rate of only 17%. Remission status was determined by computed tomography (CT) scanning and no follow-up data were provided.

The second series [9–11] used gemcitabine 1,000 mg/m² IV on days 1, 8 and 15, methylprednisolone 1,000 mg orally or IV days 1–5 and cisplatin 100 mg/m² IV on day 15 (GEM-P). This outpatient regimen was repeated every 28 days for 1 to 6 cycles. Seventeen Hodgkin lymphoma patients were treated, but their data was not separated from the 24 patients with NHL. There were high rates of grade 3/4 haematological toxicity (61% patients) though only eight patients received colony stimulating factor. Treatment delay or discontinuation occurred in 32 (78%) of 41 patients, usually (59%) due to myelosuppression, with a complete response rate of only 12% (two patients) in the Hodgkin lymphoma group. Only eight of 42 patients underwent subsequent autologous stem cell transplant. The most common reason for not proceeding to autograft was treatment failure. Remission status was determined by CT scanning. Median follow-up was not specified for the Hodgkin lymphoma patients.

Drawing on these two studies, we modified the published regimens to maximise response with minimal treatment delay, acceptable toxicity and minimal inter-

ference with stem-cell harvesting and engraftment. Because response to chemotherapy is a key determinant of response to autografting in Hodgkin lymphoma [12] and response is dependent on dose and intensity, we used three doses of gemcitabine 1,000 mg/m² IV per cycle (on days 1, 8 and 15) with a cycle length of 28 days. We used cisplatin at 75 mg/m² on day 1 because of high toxicity reported in the GEM-P regimen and, since we were concerned about the toxicity/benefit profile of a cumulative dose of 5 g of methylprednisolone per cycle, we used dexamethasone 20 mg once daily on days 1–5 (cumulative dose per cycle equivalent to 937.5 mg methylprednisolone) as in the GDP regimen. Since neutropaenia exposes patients to the risk of sepsis and as treatment delay or dose reduction are associated with lower response rates, we incorporated routine colony-stimulating factor support and a policy of no dose alteration or delay for cytopenias, with transfusion support as necessary to achieve this. Patients received a maximum of 3 cycles with response assessment after two.

Methods

The records of all patients treated with GemCis and their stem-cell harvesting data between October 2005 and June 2007 at our institution (Table 1) were obtained from an electronic database. Details of clinical course were obtained from laboratory databases and review of individual case notes. Pathology was reviewed prior to initiation of treatment. All patients gave informed written consent. Kaplan–Meier survival curves were created with SPSS 15.0 software (SPSS Inc, Chicago, IL, USA)

Treatment for all patients was with gemcitabine (1,000 mg/m² IV on days 1, 8 and 15), cisplatin (75 mg/m² IV on day 1) with dexamethasone 20 mg once daily on days 1–4 in a 28-day cycle. Pegylated granulocyte colony stimulating factor was routinely administered on day 9 of each cycle. Therapy was administered as an outpatient. To reduce the risk of cisplatin-related nephrotoxicity, patients received pre-hydration with 250 ml 5% dextrose in saline given i.v. over 30 min, and then 250 ml 20% mannitol in normal saline i.v. over 1 h given concurrently with the cisplatin. Cisplatin was mixed in 500 ml saline and administered over 1 h followed by an additional 500 ml saline. Ondansetron 8 mg twice daily and domperidone 20 mg four times daily for 2 days were given with each dose of cisplatin. The only dose alteration permitted was division of cisplatin into two consecutive daily doses if the creatinine clearance was 45–59 ml/min or omission of cisplatin if it was <45 ml/min. Response assessment was according to the Revised International Workshop Re-

Table 1 Characteristics of patients receiving GemCis

stage	Primary refractory (P) or relapse (R)	Time to relapse (months)	Previous treatment	No of cycles of GemCis	Response	Current status A = alive D = dead	Auto graft Y/N
3a	R	28	Chlvpp +auto	2	PR (PET)	A	Y
2b	R	23	6 ABVD	2	CR(PET)	A	Y
2a	R	34	3 Chlvpp+IFRT	3	CR (PET)	A	N
2e	R	9	8 ABVD	3	CR(PET)	A	Y
2	R	7	6 ABVD + Chlvpp IFRT	3	CR(PET)	A	Y
4b	R	12	8ABVD	3	PR (CT)	A	N
2b	R	5	6 ABVD/Chlvip	3	PET + ve	D	Y
1a	R	13	IFRT/8ABVD	3	CR(PET)	A	Y
4a	R	36	LOPP, auto CHP	3	PR (CT)	D	Y
2	R	84	Mantle RT	2	CR (CT)	A	Y
2B	P	NA	6 ABVD	2	CR (PET)	A	Y
2B	P	NA	8ABVD +IFRT	2	CR(PET)	A	Y
2A	P	NA	6ABVD	3	CR(PET)	A	Y
2B	P	NA	6ABVD	2	CR(PET)	A	Y
2	P	NA	6ABVD +Chlvpp	2	PR(CT)	A	N
2B	P	NA	8ABVD	2	CR(PET)	A	Y
2E	P	NA	8ABVD	2	PET +Ve	A	Y

response Criteria [13] with all patients undergoing CT scanning within 2–4 weeks of completing treatment and most undergoing PET scanning 4–6 weeks after treatment. Toxicity was assessed weekly using standard NCI common toxicity criteria.

Results

Patients

Seventeen patients were treated between October 2005 and June 2007. Their median age was 27 years (range 15–46) with seven males and ten females. All patients had classical Hodgkin lymphoma. Ten (59%) patients had previously achieved CR but three had a response duration of less than 12 months. Seven (41%) had primary refractory disease as defined as failure to achieve a CR with standard first line therapy. The characteristics of these two groups are given in Table 2. Of the ten patients treated with GemCis for relapsed disease, five were treated on first relapse and five were treated on second or higher relapse.

Treatment received

All 17 patients received 2 cycles of GemCis and eight received 3 cycles depending on response to cycle 2. Fifteen of the 17 patients proceeded to stem-cell harvest and the other two had relapsed after previous autologous SCT, and

further autografting was not considered appropriate. Harvest was successful in 15 cases (median CD34+ cell count $4.6 \times 10^6/\text{kg}$ donor body weight, no final cell yield of $<2.1 \times 10^6/\text{kg}$) although four patients required two harvest attempts to yield adequate numbers of cells. Of these four, three had received only 2 cycles of GemCis. All patients successfully engrafted with a median time to engraftment (neutrophils $>0.5 \times 10^9/\text{l}$ for two consecutive days) of 14 days (range 12–23 days).

Treatment response

Sixteen (94%) patients showed response to GemCis with 11 (65%) patients achieving CR, five achieving PR and one having stable disease. Twelve patients had post-GemCis PET scanning resulting in two patients with stable disease and four with CRu on CT scanning being upgraded to CR. Three patients were PET positive post treatment, of whom one had progressive disease and died while the other two proceeded to autograft and now have stable PET-positive disease at 12 and 20 months from initial treatment. Two patients with PR and three with unequivocal CR on CT scanning did not undergo PET scanning. With 22 months median follow-up, 15 (94%) of patients are still alive with 12 in complete remission, two with stable disease and one with progressive disease. Of the two patients who died, one had received three lines of therapy including prior autologous stem-cell transplant, and the other had received suboptimal therapy with ABVD-Chlvpp prior to being

Table 2 Comparison of published salvage regimens for Hodgkin lymphoma and GemCis

Regimen	No. patients	CR rate (%)	PR rate (%)	OR rate (%)	Grade 3/4 Neutropenia (%)	Grade 3/4 platelet (%)	Grade 3/4 Vomiting (%)	Toxic deaths (no.)	EFS/TTP where stated
Dexa-BEAM [14]	55	31	29	60	90	87	10	4	
Mini-BEAM [15]	55	49	33	82	86	60	Not stated	2	36% at 7 years
ASHAP [16]	56	34	36	70	100	Not stated	Not stated	0	45% at 2 years
VIP [17]	42	38	29	67	87	26	Not stated	0	Not stated
ICE [18]	65	26	59	85	Not stated	Not stated	Not stated	0	58% at 3 yrs
DHAP [19]	102	21	68	89	68	69	26	0	30-65% at 18 months
ESHAP [3]	22	41	32	73	59% (with GCSF primary prophylaxis)	64		1	27% at 3 yrs
IGEV [7]	91	54	28	81	28 (with GCSF primary prophylaxis)	20	3	0	53% at 3 years
GDP [8]	23	17	52	70	9	13	13	0	Not stated
GEM-P [9–11]	17	12	71	82	61	54	2	0	Not stated
GemCis	17	65	29	94	47	35	0	0	88% at 22 months

treated with GemCis and autograft. Survival curves are shown in Fig. 1.

Toxicity

Toxicity data were available on all patients. Non-haematological toxicity was mild. Six patients had grade 2 nausea and one had grade 1. All patients had \geq grade 1 alopecia. No patient had neuropathy. One patient developed ototoxicity during their second and final cycle. Five patients had grade 4 and four had grade 3 haematological toxicity. Transfusion requirement data were available on all patients. Five required red-cell transfusion with one or more courses, three required both platelets and packed red cells. No renal toxicity, episodes of febrile neutropenia or deaths occurred and no patient required hospital admission. There were no dose alterations or treatment delays.

Cost analysis

The cost of GemCis and ESHAP are compared based on a recent study of ESHAP in relapsed or refractory Hodgkin lymphoma [3] (Table 3). The source for each cost is identified in the table. In the ESHAP study, six of 22 patients developed neutropenic fever over 4 cycles, assuming a minimum 3-day stay for intravenous antibiotics. This equates to a minimum of 0.2 inpatient days per patient per cycle. In the same study, 14 patients required blood and/or

platelets during the study period and, assuming a transfusion episode consists of 1 unit of irradiated random donor platelets and 2 units of irradiated packed red cells, this equates to 0.16 platelet units and 0.32 red cell units per patient per cycle. The requirements for GemCis are 0.76 red cell units and 0.47 platelet units per patient per cycle. Although the per cycle chemotherapy and transfusion support costs for GemCis are higher than those for ESHAP (£1878.82 vs. £1234.11) this difference is outweighed by the greater costs of a 5 day inpatient stay for ESHAP against 3 short day case attendances for GemCis resulting in GemCis being less costly overall by £865.29.

Discussion

Although autologous stem-cell transplantation is the treatment of choice for patients with relapsed or refractory Hodgkin lymphoma, the optimal pre-transplant salvage regimen has not yet been defined [5]. Many regimens have been reported, often containing a platinum-based agent, but no single regimen has emerged as the accepted standard. Table 2 provides a summary of commonly used salvage regimens [3, 13–18]. All of these have inferior or comparable response rates to those reported here and where data is given the haematological toxicity is generally comparable or higher. Several of the other regimens also reported deaths due to therapy, but none of the studies of

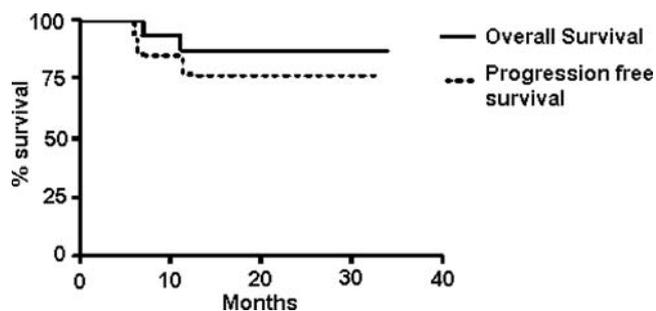


Fig. 1 OS and PFS in patients treated with GemCis ($n=17$)

gemcitabine-and cisplatin-based therapies for relapsed/refractory Hodgkin lymphoma (in aggregate, 56 patients) have had fatalities.

Administering three doses of gemcitabine together with one dose of cisplatin per cycle produced a complete response rate of 65% (11/17) compared to 17% (4/23) reported with only two gemcitabine doses per cycle. Although the rate of haematological toxicity of grade ≥ 3

is higher with the more dose intense regime, it is well tolerated when adequate blood product and colony stimulating factor support is given (no deaths, admissions or treatment delays). The regimen is designed for patients intended to proceed to autografting and the long-term efficacy and toxicity of giving a higher number of cycles without autograft, an approach reported with other gemcitabine/cisplatin combination regimens has not been evaluated. In comparison to the most commonly used UK salvage regimen (ESHAP), GemCis has a superior response rate (overall response 94% in our series vs. 60%), comparable toxicity (53% grade III/IV haematological toxicity in our series vs. 59% grade III/IV) [3] and lower cost.

Given the importance of autografting in the management of relapsed/refractory Hodgkin disease, non-interference with stem-cell harvesting and subsequent engraftment is a vital feature of effective salvage regimens. All patients treated with the GemCis regimen and intended for autograft were successfully harvested with no patient having a

Table 3 Cost comparison of GemCis and ESHAP

		Quantity	Cost per cycle	Total cost per cycle
ESHAP				
Drug costs	Etoposide		48. ^a	
	MethylPred	500 mg x 5	48 ^a	
	Cisplatin	25 mg/m ² x 4	101.48 ^a	
	Cytarabine	2000 mg/m ² x 1	136.5 ^a	
	Filgrastim	300 µg x 12	820	
Administration	Routine in patient days	5	1780 ^c	
Supportive care	Days of emergency admission with neutropaenic fever	0.2	90 ^c	
	Units of platelets	0.16	34.45 ^b	
	Units of packed red cells	0.32	45.08 ^b	
				3104.11
GemCis				
Drug costs	Gemcitabine	1000 mg/m ² x3	878.88 ^a	
	Cisplatin	70 mg/m ² x1	67.77 ^a	
	Dexamethasone	40 mg x 4	9.56	
	Pegfilgrastim	6 mg x 1	714.24	
Administration	Routine day case—days	3	460 ^c	
Supportive care	Days of emergency admission with neutropaenic fever	0	0 ^c	
	Platelets	0.47	101.32 ^b	
	Packed red cells	0.76	107.05 ^b	
				2238.82

^a Based on vial usage and a body surface area of 1.75 m² where appropriate, all costs from the latest edition of the British National Formulary [21]

^b Based on a cost per unit for irradiated red cells of £140.85 and for irradiated platelets of £215.30, costs taken from the UK National Blood Service tariffs for 2007/8

^c The costs of hospital attendance are based on data from local hospitals and include staff, consumables, overheads, capital charges and diagnostic tests

harvest below the $2 \times 10^6/\text{kg}$ threshold. The regimen also had no adverse impact on time to engraftment with all patients engrafting successfully and a median time to neutrophil engraftment of only 14 days. This is also the only study reporting response rates to a salvage chemotherapy regimen using PET scanning in relapsed/refractory Hodgkin lymphoma. PET increased the overall response rate slightly from 81% to 94% but increased the CR rate from 24% to 65%. By CT criteria, eight patients would have been designated CR/CRu (47%); GemCis, therefore, compares favourably to regimens reported in the pre-PET era. The only regimen with a comparable non-PET determined CR rate was mini-BEAM, but this has a fatality rate of 3.6% in 55 patients and is associated with poor peripheral blood stem-cell yields in Hodgkin lymphoma [20], thus, limiting its utility in patients intended for autografting. The PFS for all patients treated with GemCis is 88% at 22 months, and no patient who was PET negative pre-autograft has yet relapsed.

In summary, we report that this combination of gemcitabine and cisplatin is well tolerated, has high response rates, no impairment of stem cell mobilisation or engraftment, acceptable cost profile and excellent subsequent post-PBSCT progression-free and overall survival. The number of patients treated is modest, but the results are sufficiently encouraging that we believe this regimen should be compared to others in larger randomised trials and further evaluated in both Hodgkin lymphoma and non-Hodgkin lymphoma.

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