A multicenter study of gemcitabine-containing regimen in relapsed or refractory Hodgkin's lymphoma patients

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The aim of this study was to assess the efficacy of a gemcitabine-containing regimen in pretreated Hodgkin's lymphoma (HL) patients. Relapsed or refractory HL patients treated with gemcitabine, used alone or in combination with other cytotoxic agents, were retrospectively reviewed. Fifty-five patients were included in the study. Initial characteristics before gemcitabine administration were: Ann Arbor stage III–IV: 84%; International Prognostic Score less than 3 in 18/39 cases (46%); 31 primary refractory patients at the end of first-line therapy (56%); median number of previous chemotherapy regimens of 3. Twenty-nine patients received gemcitabine alone with a median maximal dose of 900 mg/m^2 per injection (range: 300–1500 mg/m^2). Gemcitabine was administered at a maximal dose of 1000 mg/m^2 per injection (range: 650–1250) in combination with vinorelbine in 10 patients, oxaliplatin in 13 patients, and other drugs in three patients, with a median of six injections (range: 1–18). Reported toxicity was mainly hematologic. Overall response rate was 20% with 11% of complete remission. On univariate analysis, two adverse factors at progression were significant for response to gemcitabine-based regimen: stage III–IV disease and hemoglobin level was less than 10.5 g/dl. This study demonstrated the limited efficacy of gemcitabine-containing regimen in heavily pretreated HL patients. *Anti-Cancer Drugs* 19:309–315

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Introduction

The treatment of Hodgkin's lymphoma (HL) constitutes one of the great successes of oncology in the last 40 years. This is because most patients with HL are cured by conventional treatment methods, such as chemotherapy and radiotherapy [1,2]. In particular, ABVD (doxorubicin, bleomycin, vincristine, dacarbazine) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) regimens induce complete remission rates of 80 and 90%, respectively [3,4]. Patients with refractory or relapsed lymphoma, however, have a much poorer prognosis [5]. Salvage treatment of these patients including high-dose therapy with autologous stem cell transplantation (ASCT) resulted in improved survival rates compared with those achieved after conventional-dose chemotherapies and a 25–50% probability of disease-free survival [6–8]. Few other innovative therapeutic approaches have been proposed in these poor prognosis HL patients, such as ^{131}I-labelled anti-CD30 monoclonal antibody (Ab) [9] or ^{90}Y-labelled antiferritin polyclonal Ab radioimmunotherapy [10,11], immunotherapy with monoclonal anti-CD30 Ab [12,13], but neither of these treatments could be at the present time considered as standard therapies. Monochemotherapy with vinblastine [14] or vinorelbine [15] could therefore be used as standard therapies.

Gemcitabine (difluorodeoxycytidine) is a pyrimidine antimetabolite that has a self-potentiating mechanism of action, resulting in enhanced accumulation and prolonged retention within malignant cells [16]. Gemcitabine has a favorable toxicity profile and is now commonly used to treat patients with solid tumors such as pancreas, bladder, and lung tumors [17–19]. In this particular setting of refractory or relapsed disease, gemcitabine-based regimens have been used as salvage therapy for HL [20–27]. As few studies have yet been reported, the total number of treated patients remains low and the long-term outcome of HL patients receiving gemcitabine has not been clearly defined. In particular,

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prognostic factors that may influence response to gemcitabine-based chemotherapy have not been studied in a large representative cohort of patients. Therefore, we retrospectively reviewed all patients with refractory or relapsed HL treated in nine clinical hematology departments by gemcitabine used as single-agent or in combination with other cytotoxic agents. The aims of this study were to define (i) the overall response rate (ORR) to gemcitabine-based regimens, (ii) the duration of response, (iii) the safety, particularly the hematologic toxicity, (iv) the prognostic factors influencing the therapeutic response, and (v) the long-term outcome in this cohort of poor prognosis HL patients.

Patients and methods

Patient selection

All HL patients treated in nine institutions between January 1999 and August 2006 by a gemcitabine-based regimen were retrospectively reviewed. Patients were included in the study when they presented: (i) histopathologic evidence for the diagnosis of HL according to the WHO classification [28]; (ii) sufficient clinical data to determine extension of the disease at initial diagnosis and at the time of gemcitabine treatment; (iii) sufficient clinical data to determine previously administered treatment(s) and corresponding response(s); and (iv) evaluable disease for response to gemcitabine-based chemotherapy. When all four criteria were satisfied, patients were then included in the study. Patients were not selected according to clinical or therapeutic criteria; in particular, patients who had been treated by autologous or allogeneic stem cell transplantation were not excluded from the study.

Staging

Staging work-up at the initial diagnosis of HL and before gemcitabine administration included physical examination with determination of performance status according to the Eastern Cooperative Oncology Group classification [29] and a search for B symptoms and nodal or extranodal peripheral sites. Staging of the disease was completed by blood count, erythrocyte sedimentation rate, liver and renal function tests, serum protein electrophoresis, serum lactate dehydrogenase determination, computed tomography scans, and bone marrow biopsy. Staging was performed according to the Ann Arbor classification [30]. When data were available, the International Prognostic Score (IPS) for advanced HL was defined for each patient included in the study [31]. A mediastinal bulky mass, as measured by a mediastinal–thoracic ratio of 0.35, was also determined [32]. For each patient included in the study, the response to previous treatments was assessed to define refractory or relapsed patients. Refractory patients were defined as patients whose disease progressed during treatment or in the 3 months after completion of treatment. Relapsed patients were defined as patients whose disease progressed at least 3 months after completion of treatment; among these patients, early relapsed patients (within the first year after completion of treatment) were distinguished from late relapsed patients (more than 1 year after completion of treatment).

Treatment

Gemcitabine was used on a compassionate basis as single-agent therapy or in combination with vinorelbine, oxaliplatin, doxorubicin, vinblastine, rituximab, and/or corticosteroids. According to the treatment regimen and the patient's blood count, gemcitabine was administered on day 1 ± days 8 and 15, every 21 or 28 days, until disease progression or unacceptable hematologic toxicity. Antiemetic prophylaxis was performed according to each center's usual practice.

The efficacy of gemcitabine-based chemotherapy was assessed according to the international workshop to standardize response criteria for non-HLs [33] and the best response observed for each patient after gemcitabine-containing regimen was selected for the ORR determination. The toxicity of gemcitabine-based chemotherapy was assessed according to the WHO Common Toxicity Criteria, as data could be collected in this retrospective analysis.

Statistical analysis

Univariate analysis was performed to identify poor prognostic factors for response to gemcitabine-based regimen (χ^2 test). Overall survival was defined from the start date of treatment with gemcitabine to the date of death (or last news from the patient). Survival curves were estimated using the Kaplan–Meier method [34].

Results

Patient characteristics

Among the 65 screened patients, 55 cases were included in the study on the basis of our selection criteria. All patients were diagnosed as having HL, including 46 cases of nodular sclerosis HL (84%), one case of lymphocyte-rich classical HL, five cases of mixed cellularity HL (9%), and three cases of lymphocyte depletion HL (5%). No case of nodular lymphocyte-predominant HL was included.

Patient characteristics at the time of initial diagnosis were median age: 27 years (range: 14–84); B symptoms: 72%; bulky disease in 34%; Ann Arbor stage III–IV 73%; and extranodal involvement in 19 patients (34%). When data were available (44 patients), the IPS was lower than 3 in 25 cases (57%) and ≥ 3 in 19 cases (43%). Patient characteristics before gemcitabine administration are presented in Table 1 [21–27]: median age: 29 years (range: 15–85 years); stage III and IV in 15 and 69%, respectively; and extranodal involvement in 38 patients

Table 1 Patient characteristics at the time of gemcitabine administration

Parameters	*N*	%
Total number	55	–
Sex ratio male/female	1.1	–
Median age (years)	29	–
B symptoms	21	46
Bulky disease	1	2
Stage III–IV	46	84
Lung involvement	26	47
Bone involvement	12	22
Soft tissues and skin involvement	8	15
Liver involvement	5	9
Bone marrow involvement (28 cases)	1	4
WBC count $\geq 15.10^9$/l (46 cases)	2	4
Hemoglobin level <10.5 g/dl (47 cases)	20	42
Lymphocyte count $<0.6.10^9$/l (46 cases)	17	37
Albumin <40 g/l (34 cases)	20	59
IPS (39 cases)		
0–2	18	46
≥ 3	21	54

IPS, International Prognostic Score; WBC, white blood cell.

(69%). Among the 39 patients for whom all data were available, the IPS was less than 3 in 18 cases (46%) and ≥ 3 in 21 cases (54%).

Previous therapies before gemcitabine administration

The first-line chemotherapy regimens were ABVD, EBVP/VBVP (epirubicin, bleomycin, vinblastine, prednisone/etoposide, bleomycin, vinblastine, prednisone), MOPP (mechlorethamine, vincristine, procarbazine, prednisone)/ABVD, COP/OPPA (vincristine, procarbazine, prednisone, doxorubicin), or BEACOPP (escalated and/or standard) regimens in 26, 11, 6, 6, and 2 patients, respectively. Involved-field radiotherapy was performed in 19 patients after completion of chemotherapy. At the end of first-line therapy (chemotherapy ± radiotherapy), 20 patients (36%) were in complete response (CR) and 14 of them relapsed within 1 year, four were in partial response (PR), and 31 patients were primary refractory (56%). Salvage chemotherapy protocols were MINE (mitoguazone, ifosfamide, vinorelbine, etoposide), IVA (ifosfamide, etoposide, doxorubicin), DHAP (dexamethasone, cisplatin, cytarabine arabinoside), ESHAP (etoposide, cisplatin, cytosine arabinoside, methylprednisolone), and VIP (etoposide, ifosfamide, cisplatin) regimens in 31, 14, 12, 10, and 5 patients, respectively. Overall, the number of previous lines of chemotherapy was one in four patients (7%), two in 16 patients (29%), three in 23 patients (42%), and more than three in 12 patients (22%).

Among the 55 patients, 35 (64%) had received radiotherapy at some time during their previous treatments, as part of first-line treatment in 19 cases (35%), and during salvage treatment in 21 cases (38%), in the form of total body irradiation (TBI) in five cases, and after intensive regimen and autologous and/or allogeneic stem cell transplantation in eight cases. One patient received irradiation as part of both first-line and salvage therapies. Twenty-one patients (38%) had received one ASCT and 13 cases (24%) had received two ASCTs after BEAM (carmustine, etoposide, cytosine arabinoside, melphalan) (24 cases), CBV-Novantrone (cyclophosphamide, carmustine, etoposide, mitoxantrone) (10 cases), BAM (busulfan, cytosine arabinoside, melphalan) (five cases), TAM6 (TBI-cytosine arabinoside, melphalan) (three cases), high-dose cyclophosphamide (one case), and other (four cases) intensified regimens. Four patients had received TBI-cyclophosphamide (two cases) or fludarabine, alkeran (two cases) regimens followed by allogeneic transplantation after first ASCT.

Gemcitabine-based regimen administration

Gemcitabine was administered alone or in combination in 29 (53%) and 26 (47%) patients, respectively. Gemcitabine was administered intravenously on days 1 and 15 every 4 weeks in 26 patients, on days 1 and 8 every 3–4 weeks in 16 patients, and on days 1, 8, and 15 every 4 weeks in 10 patients. Three patients received only one gemcitabine administration. When gemcitabine was administered alone, the median maximal dose was 900 mg/m^2 per injection (range: 300–1500 mg/m^2) with a median number of six injections (range: 2–27). Gemcitabine was administered at a maximal dose of 1000 mg/m^2 per injection (range: 650–1250) in combination with vinorelbine in 10 patients, oxaliplatin in 13 patients in addition to rituximab in four patients, and with other drugs in three patients, with a median number of six injections (range: 1–18).

Toxicity assessment

Reported toxicity was mainly hematologic. Among the 55 evaluable patients, 41 (75%) developed bi-pancytopenia or pancytopenia. Grade 3–4 anemia, neutropenia, and thrombocytopenia were observed in 12 patients (22%), five patients (9%), and 17 patients (31%) (nine patients with grade 4 thrombopenia), respectively. Nineteen patients (35%) required white blood cell and/or platelet transfusion support. Seven patients (13%) developed infectious complications, namely two lung infections, one case of bronchitis, one central catheter infection, one urinary tract infection, one case of peritonitis, and one case of *Candida albicans* septicemia. Two patients developed skin rash leading to discontinuation of chemotherapy, and one patient experienced neurologic disorders such as dystonia that were not directly related to gemcitabine administration. No toxic death was reported in this series.

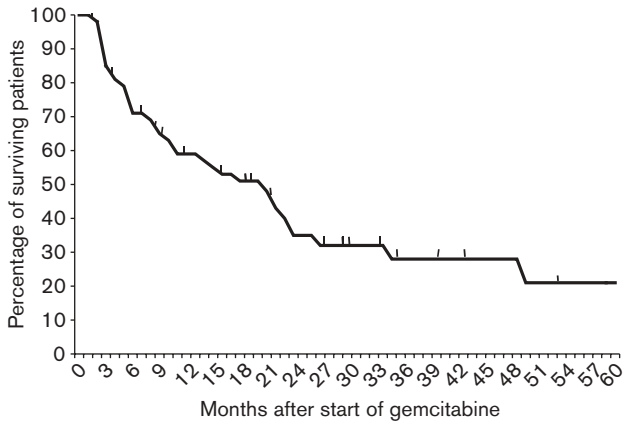
Response assessment

All patients were evaluable for response. Six achieved CR (11%) and five achieved PR with an ORR of 20%. The ORR was 25 and 18% for patients treated with a maximal dose of gemcitabine per injection ≤ 750 and > 750 mg/m^2, respectively. The duration of response to gemcitabine-based chemotherapy was not evaluable, as

five of the six patients with CR subsequently received ASCT or allogeneic stem cell transplantation and two patients received radiotherapy, with two cases of persistent CR at 16 and 44 months. With a median follow-up of 14 months (range: 2–69 months), seven responding patients (13%) were still alive with prolonged CR in two cases. The 1- and 2-year overall survival rate, defined from the start date of treatment with gemcitabine to the date of death, were 59 and 35%, respectively (Fig. 1). Among the 11 responding patients, two patients were alive in persistent complete remission (16 and 44 months after start of gemcitabine), five patients were alive with progressive HL, and four patients were dead (three of tumor evolution and one of infectious complication after ASCT performed after gemcitabine administration).

Finally, the ORR was correlated with clinical and therapeutic features of the selected patients. As shown in Table 2 and Fig. 2, two factors were prognostic for lower ORR to gemcitabine-based chemotherapy: stage III–IV disease and hemoglobin level less than 10.5 g/dl. Neither the number of treatment lines, IPS greater than 2, achievement of first complete remission, previous radiotherapy or autologous/allogeneic stem cell transplantation, or gemcitabine combination (gemcitabine alone vs. gemcitabine combined with other cytotoxic drugs) were predictive for ORR. Surprisingly, an age less than 45 years was almost significantly associated with a poorer response to gemcitabine ($P = 0.06$). To analyze patients' characteristics according to their outcome, we have detailed in Table 3 all features at the time of gemcitabine administration of the patients who are still alive or patients who are dead at the delay of 18 months after the start of gemcitabine (seven patients were excluded of this analysis because of a too small follow-up). No characteristics at the start of gemcitabine administration has been shown to influence the 18-month survival probability.

Fig. 1



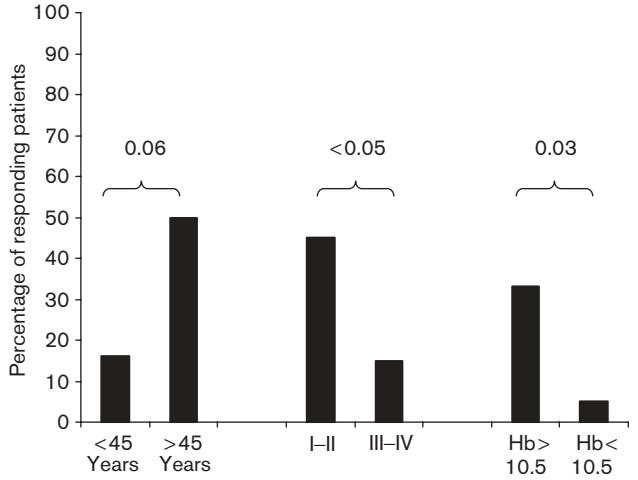
Overall survival of the 55 selected patients since the start of gemcitabine-based chemotherapy.

Table 2 Correlation between patient characteristics[a] and overall response rates

Characteristics	*N*	No. of responding patients (%)	No. of nonresponding patients (%)	*P*
Sex				
Male	28	5 (18)	23 (82)	NS
Female	27	6 (22)	21 (78)	
Age				
<45 years	49	8 (16)	41 (84)	**0.06**
≥ 45 years	6	3 (50)	3 (50)	
Bulky disease				
Yes	1	0 (0)	1 (100)	NE
No	54	11 (20)	43 (80)	
Stage				
I–II	9	4 (45)	5 (55)	**<0.05**
III–IV	46	7 (15)	39 (85)	
Lung involvement				
Yes	26	3 (12)	23 (88)	NS
No	29	8 (28)	21 (72)	
Bone involvement				
Yes	12	1 (8)	11 (92)	NS
No	43	10 (23)	33 (77)	
Soft tissues and skin involvement				
Yes	8	2 (25)	6 (75)	NS
No	47	9 (19)	38 (81)	
Liver involvement				
Yes	5	1 (20)	4 (80)	NS
No	50	10 (20)	40 (80)	
WBC (10^9/l)				
<15	44	9 (20)	35 (80)	NE
≥ 15	2	1 (50)	1 (50)	
Lymphocytes (10^9/l)				
≥ 0.6	29	7 (24)	22 (76)	NS
<0.6	17	3 (18)	14 (82)	
Hemoglobin (g/dl)				
≥ 10.5	27	9 (33)	18 (67)	**0.03**
<10.5	20	1 (5)	19 (95)	
Albumin (g/l)				
≥ 40	14	5 (36)	9 (64)	NS
<40	20	2 (10)	18 (90)	
IPS				
0–2	18	6 (33)	12 (67)	NS
≥ 3	21	3 (14)	18 (86)	
CR after first line				
Yes	20	6 (30)	14 (70)	NS
No	35	5 (14)	30 (86)	
Refractory after first line				
Yes	31	4 (13)	27 (87)	NS
No	24	7 (29)	17 (71)	
No. of treatment lines				
1	4	3 (75)	1 (25)	NS
2	16	3 (19)	13 (81)	
3	23	3 (13)	20 (87)	
4	6	2 (33)	4 (67)	
5 and more	6	0 (0)	6 (100)	
No. of treatment lines				
1–2	20	6 (30)	14 (70)	NS
≥ 3	35	5 (14)	30 (86)	
Radiotherapy				
Yes	35	9 (27)	26 (73)	NS
No	20	2 (10)	18 (90)	
Autologous/allogeneic SCT				
Yes	34	6 (18)	28 (82)	NS
No	21	5 (24)	16 (76)	
Gemcitabine				
Alone	29	4 (14)	25 (86)	NS
Combined	26	7 (27)	19 (73)	

CR, complete response; IPS, International Prognostic Score; NE, not evaluable; NS, not significant; SCT, stem cell transplantation; WBC, white blood cell.
[a]At the time of gemcitabine administration.

Fig. 2



Prognostic factors for response to gemcitabine-based chemotherapy.

Table 3 Patient characteristics according to their survival 18 months after start of gemcitabine administration

Parameters	Alive patients		Dead patients		*P*
	N	%	*N*	%	
Total number (seven excluded patients)	22	–	26	–	–
Sex ratio male/female	1.2	–	0.86	–	–
Median age (years)	29	–	31	–	–
B symptoms	6	32	12	57	NS
Stage III–IV	15	68	24	92	NS
Lung involvement	7	32	16	62	NS
Bone involvement	5	23	7	27	NS
Soft tissues and skin involvement	4	18	3	12	NS
Liver involvement	1	5	2	8	NS
Bone marrow involvement (28 cases)	0	0	1	9	NS
Hemoglobin level <10.5 g/dl (47 cases)	8	42	11	50	NS
Lymphocyte count $<0.6.10^9$/l (46 cases)	5	26	11	52	NS
Albumin <40 g/l (34 cases)	8	50	10	71	NS
IPS (39 cases) ≥ 3	8	44	14	64	NS

IPS, International Prognostic Score.

Discussion

The optimal management of heavily pretreated HL patients remains unresolved. A gemcitabine-based regimen is one of the more valid treatment options for these patients with a very poor prognosis. This multicenter study therefore retrospectively reviewed 55 HL patients treated with gemcitabine alone or in combination and observed an ORR of 20% with 11% of complete remissions. The efficacy of treatment in this series was not influenced by the treatment protocol with 29 and 26% of ORR in patients receiving gemcitabine alone or in combination with other cytotoxic drugs, respectively. Despite the fact that the heterogeneity of treatment regimens used significantly reduces the strength of the conclusions, a few points can be discussed. As shown in Table 4, the results of the exclusive gemcitabine regimen were not different from those reported in the literature, except for the paper published by Aurer *et al.* [20–23]. In this treatment setting, the ORR was 38% with 13% of complete remissions among the 79 reported patients. The discordant data between those reported by Aurer *et al.* and all other authors and our data cannot be explained by patient characteristics, particularly in terms of median age, proportion of advanced stage disease, and median number of lines of treatment before gemcitabine administration, or by the doses or duration of infusion used, and therefore remain controversial. In contrast, the results of the various series of HL patients treated by gemcitabine-combined regimens, mainly with cisplatin or derivatives, vinorelbine, ifosfamide, doxorubicin, and prednisone, are very different due to different patient characteristics. In heavily pretreated cases, as in our study, the ORR was 26%; inversely, in patients who had received only one or two lines of chemotherapy, as in other reports [24–27], the ORR varied between 64 and 82% with 9–54% of complete remissions. This discordance can probably be explained by the prognostic impact of previous treatment lines in the response to gemcitabine, as suggested by our results showing that three of the four patients who had received only one line of chemotherapy responded to gemcitabine, and by the study reported by Bartlett *et al.* [26] in which event-free and overall survivals were significantly influenced by previous ASCT. This observation underlines the fact that our selected patients were of particularly worse prognosis and that gemcitabine should possibly be used earlier in the treatment of HL, namely at the time of first relapse or after first-line treatment in primary refractory HL patients, as shown by the large series of Santoro *et al.* [27]. Concomitant administration of gemcitabine and bleomycin, as in the modified BEACOPP regimen must, however, be avoided because of severe pulmonary toxicity [35], and the use of gemcitabine in first-line treatment with ABVD-modified or BEACOPP-modified regimens should therefore be excluded.

We then evaluated the prognostic factors for response to gemcitabine in our series of refractory or relapsed HL patients receiving gemcitabine-based chemotherapy, and found that two factors were prognostic for a lower ORR to gemcitabine-based regimen, namely stage III–IV disease and a hemoglobin level less than 10.5 g/dl. It is noteworthy that these two factors are part of the IPS of HL [31], suggesting that response to gemcitabine is mainly influenced by the specific prognostic factors of lymphoma. Very few reported series have studied the prognostic factors for response to gemcitabine [20,21,27] and shown that a time to HL relapse less than 12 months [21], an incomplete or PR after last chemotherapy [27],

Table 4 Gemcitabine-based chemotherapy in relapsed or refractory Hodgkin's lymphoma patients

References	*N*	Protocol	Median age (years)	Advanced stage (%)	Refractory patients[a] (%)	Median treatment lines	A/ASCT (%)	RT (%)	ORR (CR) (%)	Prognostic factors[b]
Santoro *et al.* [27]	22	G	35	–	–	2	0	100	39 (9)	None
Zinzani *et al.* [21]	14	G	35	79	29	–	14	0	43 (14)	Time to relapse
Venkatesh *et al.* [22]	29	G	43	–	–	>2	62		22 (0)	–
Aurer *et al.* [23]	14	G	29	93	–	4	64	64	64 (43)	–
Ng *et al.* [25]	17	GEM-P	–	–	–	2	–	–	82 (12)	–
Kuruvilla *et al.* [24]	34	GDP	43	56	56	1	0	15	62 (9)	–
Bartlett *et al.* [26]	91	GVD	33	–	–	–	44	–	70 (19)	–
Santoro *et al.* [27]	91	IGEV	30	–	40	1	0	60	81 (54)	Response to last CT, ≥ 3 sites
Validire *et al.*	55	Various	29	84	56	3	62	64	20 (11)	Stage, Hb, (age)

A/ASCT, autologous/allogeneic stem cell transplantation; CR, complete remission; CT, chemotherapy; GDP, gemcitabine, dexamethasone, cisplatin; GEM-P, gemcitabine, cisplatin, methylprednisolone; GVD, gemcitabine, vinorelbine, pegylated liposomal doxorubicin; IGEV, ifosfamide, gemcitabine, vinorelbine, prednisolone; ORR, overall response rate; RT, radiotherapy.
[a]Refractory patients after first-line treatment.
[b]Prognostic factors for response to gemcitabine-based chemotherapy.

and more than three tumor sites [27] had a negative impact on response to gemcitabine. Nevertheless, all these reported series together with the present series constitute a cohort of HL patients that is still too small to define statistically significant prognostic factors for response to gemcitabine-based regimen.

Finally, a surprising result of this study was that, despite a very low ORR to gemcitabine administration in these heavily pretreated HL patients, the 5-year survival rate was 20%, suggesting that a proportion of patients who relapsed or who were refractory to standard chemotherapy, high-dose regimens with autologous/allogeneic stem cell transplantation, and/or radiotherapy, were able to achieve long-term survival. This observation confirms the data of Little *et al.* [14] showing a median overall survival of 38.8 months in 17 relapsed HL patients treated by vinblastine after autologous bone marrow transplantation. The correlation between gene expression profile performed in microdissected classical Reed–Sternberg cells and in stromal and immunologic tumor environments and response to chemotherapy and/or radiotherapy will probably be able to explain this outcome of HL.

In conclusion, we showed a limited efficacy of gemcitabine-based regimens in a cohort of heavily pretreated HL patients, which constitutes one of the largest published series. Data from the literature and the results of the present series, however, suggest that gemcitabine could be added earlier to salvage combinations of cytotoxic drugs, namely at the time of first relapse or in refractory HL patients.

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References

1 Rosenberg S, Kaplan H. The evolution and summary results of the Stanford randomized clinical trials of the management of Hodgkin's disease. *Int J Radiat Oncol Biol Phys* 1985; **11**:5–22.
2 Urba W, Long D. Hodgkin's disease. *N Engl J Med* 1992; **326**: 678–687.
3 Canellos GP, Anderson JR, Propert KJ, Nissen N, Cooper MR, Henderson ES, *et al.* Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med* 1992; **327**:1478–1484.
4 Diehl V, Franklin J, Hasenclever D, Tesch H, Pfreunschuh M, Latha B, *et al.* BEACOPP, a new dose-escalated and accelerated regimen, is at least as effective as COPP/ABVD in patients with advanced-stage Hodgkin's disease lymphoma: interim report from a trial of the German Hodgkin's lymphoma Study Group. *J Clin Oncol* 1998; **16**:3810–3821.
5 Longo D, Duffey P, Young R, Hubbard SM, Ihde DC, Glatstein E, *et al.* Conventional-dose salvage combination chemotherapy in patients relapsing with Hodgkin's disease after combination chemotherapy: the low probability for cure. *J Clin Oncol* 1992; **10**:210–218.
6 Linch D, Winfield D, Goldstone A, Moir D, Hancock B, McMillan A, *et al.* Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet* 1993; **341**:1051.
7 Bolwell BJ, Kalaycio M, Goormastic M, Dannley R, Andresen SW, Lichtin A, *et al.* Progressive disease after ABMT for Hodgkin's disease. *Bone Marrow Transplant* 1997; **20**:761–765.
8 Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, *et al.* Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haematopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet* 2002; **359**:2065–2070.
9 Schnell R, Dietlein M, Staak JO, Borchmann P, Schomaecker K, Fischer T, *et al.* Treatment of refractory Hodgkin's lymphoma patients with an iodine-131-labeled murine anti-CD30 monoclonal antibody. *J Clin Oncol* 2005; **23**:4669–4678.
10 Vriesendorp HM, Morton JD, Quadri SM. Review of five consecutive studies of radiolabeled immunoglobulin therapy in Hodgkin's disease. *Cancer Res* 1995; **55**:5888S–5892S.
11 Decaudin D, Levy R, Lokiec F, Morschhauser F, Djeridane M, Kadouche J, *et al.* Radioimmunotherapy of refractory or relapsed Hodgkin's lymphoma with ^{90}yttrium-labelled antiferritin antibody. *Anticancer Drugs* 2006; **17**:685–695.
12 Hu XF, Xing PX. MDX-060. Medarex. *Curr Opin Invest Drugs* 2005; **6**:1266–1271.
13 Schnell R, Borchmann P. SGN-30 (Seattle genetics). *Curr Opin Mol Ther* 2006; **8**:164–172.
14 Little R, Wittes RE, Longo DL, Wilson WH. Vinblastine for recurrent Hodgkin's disease following autologous bone marrow transplant. *J Clin Oncol* 1998; **16**:584–588.
15 Devizzi L, Santoro A, Bonfante V, Viviani S, Balzarini L, Valagussa P, *et al.* Vinorelbine: an active drug for the management of patients with heavily pretreated Hodgkin's disease. *Ann Oncol* 1994; **5**:817–820.
16 Plunkett W, Huang P, Searcy CE, Gandhi V. Gemcitabine: preclinical pharmacology and mechanisms of action. *Semin Oncol* 1996; **23**:3–15.

17 Van Zandwijk N, Smit EF, Kramer GW, Schramel F, Gans S, Festen J, *et al*. Gemcitabine and cisplatin as induction regimen for patients with biopsy-proven stage IIIA N2 non-small-cell lung cancer: a phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative group (EORTC 08955). *J Clin Oncol* 2000; **18**:2658–2664.
18 Von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, *et al*. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer. *J Clin Oncol* 2000; **18**:3068–3077.
19 Colucci G, Giuliani F, Gebbia V, Biglietto M, Rabitti P, Uomo G, *et al*. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. *Cancer* 2002; **94**:902–910.
20 Santoro A, Bredenfeld H, Devizzi L, Tesch H, Bonfante V, Viviani S, *et al*. Gemcitabine in the treatment of refractory Hodgkin's disease: results of a multicenter phase II study. *J Clin Oncol* 2000; **18**:2615–2619.
21 Zinzani PL, Bendandi M, Stefoni V, Albertini P, Gherlinzoni F, Tani M, *et al*. Value of gemcitabine treatment in heavily pretreated Hodgkin's disease patients. *Haematologica* 2000; **85**:926–929.
22 Venkatesh H, Di Bella N, Flynn TP, Vellek MJ, Boehm KA, Asmar L. Results of a phase II multicenter trial of single-agent gemcitabine in patients with relapsed or chemotherapy-refractory Hodgkin's lymphoma. *Clin Lymphoma* 2004; **5**:110–115.
23 Aurer I, Radman I, Nemet D, Zupancić-Salek S, Bogdanić V, Mrsić M, *et al*. Gemcitabine in the treatment of relapsed and refractory Hodgkin's disease. *Onkologie* 2005; **28**:567–571.
24 Kuruvilla J, Nagy T, Pintilie M, Tsang R, Keating A, Crump M. Similar response rates and superior early progression-free survival with gemcitabine, dexamethasone, and cisplatin salvage therapy compared with carmustine, etoposide, cytarabine, and melphalan salvage therapy prior to autologous stem cell transplantation for recurrent or refractory Hodgkin lymphoma. *Cancer* 2005; **106**:353–360.
25 Ng M, Waters J, Cunningham D, Chau I, Horwich A, Hill M, *et al*. Gemcitabine, cisplatin and methylprednisolone (GEM-P) is an effective salvage regimen in patients with relapsed and refractory lymphoma. *Br J Cancer* 2005; **92**:1352–1357.
26 Bartlett NL, Niedzwiecki D, Johnson JL, Friedberg JW, Johnson KB, van Besien K, *et al*. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. *Ann Oncol* 2007; **18**:1071–1079.
27 Santoro A, Magagnoli M, Spina M, Pinotti G, Siracusano L, Michieli M, *et al*. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. *Haematologica* 2007; **92**: 35–41.
28 Harris NL, Jaffe ES, Diébold J, Flandrin G, Muller-Hermelink HK, Vardiman J, *et al*. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the clinical advisory committee meeting – Airlie House, Virginia, November 1997. *J Clin Oncol* 1999; **17**:3849–3855.
29 Oken MM, Creech RH, Tormay DC, Horton J, Davis TE, McFadden ET, *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**:649–655.
30 Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, *et al*. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 1989; **7**:1630–1636.
31 Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. *N Engl J Med* 1998; **339**:1506–1514.
32 Lee CK, Bloomfield CD, Goldman AI, Levitt SH. Prognostic significance of mediastinal involvement in Hodgkin's disease treated with curative radiotherapy. *Cancer* 1980; **46**:2403–2409.
33 Cheson BD, Horning JS, Coiffier B, Shipp MA, Fisher RI, Connors JM, *et al*. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. *J Clin Oncol* 1992; **17**:1244–1253.
34 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**:457–481.
35 Bredenfeld H, Franklin J, Nogova L, Josting A, Fries S, Mailänder V, *et al*. Severe pulmonary toxicity in patients with advanced-stage Hodgkin's disease treated with a modified bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, and gemcitabine (BEACOPP) regimen is probably related to the combination of gemcitabine and bleomycin: a report of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2004; **22**:2424–2429.