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Gemcitabine-Based Treatment in Poor-Prognosis Patients with Relapsed and Refractory Hodgkin Lymphoma and Non-Hodgkin Lymphoma – a Multicenter Polish Experience

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Abstract

Background. The treatment of patients with relapsed or refractory Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) remains challenging. Gemcitabine is a cytidine analog with a wide spectrum of antitumor activity. Gemcitabine treatment is widely used to treat patients with certain solid tumors and relapsed/refractory hematological malignancies. There are several reports indicating that this compound is active in lymphoid malignancies. In patients with relapsed or refractory HL and NHL, gemcitabine has demonstrated efficacy as a single agent and in combination with other cytostatics.

Objectives. The aim of the study was to analyze the efficacy and toxicity of gemcitabine-based chemotherapy in patients with relapsed or refractory lymphomas.

Material and Methods. The study evaluated 68 heavily pretreated patients with relapsed/refractory HL and NHL. The median age of the patients was 36 years. All the patients received gemcitabine-based chemotherapy (gemcitabine monotherapy or gemcitabine in combination with other cytostatics).

Results. The overall response rate was 46%. Complete response was achieved by 21% of the patients and partial response by 25%. Out of those who responded to gemcitabine treatment, 26 patients proceeded to autologous stem cell transplant. Toxicities connected with gemcitabine therapy occurred in 44% of the patients and included grade 3/4 neutropenia, thrombocytopenia and anemia.

Conclusions. The results suggest that gemcitabine-based salvage chemotherapy is effective and well tolerated in patients with relapsed/refractory HL and NHL (*Adv Clin Exp Med* 2015, 24, 5, 783–789).

Key words: Hodgkin lymphoma, gemcitabine, non-Hodgkin lymphoma, refractory disease, autologous stem cell transplant.

The treatment of patients with relapsed or refractory Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) remains challenging. In general, the standard care is high-dose chemotherapy followed by autologous stem cell transplant (ASCT) for patients who are sensitive to salvage chemotherapy. There are no standard options of treatment for

patients who show no response to second-line regimens, nor for patients who are not eligible for transplants [1, 2]. For those patients it is therefore very important to establish the satisfactory salvage therapy with optimal response and a low toxicity rate.

Gemcitabine is a cytidine analog with a wide spectrum of antitumor activity. Gemcitabine needs

to be phosphorylated to gemcitabine monophosphate (dFdCMP) by deoxycytidine kinase (dCK), which is then converted to gemcitabine di- and triphosphate (dFdCDP and dFdCTP – the active drug metabolites) [3, 4]. Gemcitabine is widely used in the treatment of patients with metastatic pancreatic cancer, non-small cell lung cancer, bladder cancer, breast cancer and ovarian cancer [5–8].

In patients with relapsed or refractory HL and NHL, gemcitabine has demonstrated efficacy as a single agent and in combination with other cytostatics such as cisplatin, vinorelbine and liposomal doxorubicin [9, 10]. Bartlett et al. reported an overall response rate (ORR) of 70% in patients with relapsed HL treated with a combination of gemcitabine, vinorelbine and liposomal doxorubicin (GVD regimen) [11]. In patients with resistant non-Hodgkin lymphoma, the ORR after gemcitabine in combination with cisplatin and dexamethasone was 32% [12]. Gemcitabine is active in lymphoid malignancies but the optimal schedule and combination remain to be established.

The aim of the present study was to assess the efficacy and toxicity of gemcitabine regimens in patients with relapsed or refractory lymphomas.

Material and Methods

The study included 68 patients (42 males and 26 females) with HL and NHL. It was a multicenter study, enrolling patients at 5 institutions in Poland between May 2009 and January 2014. The participants included 42 patients with a histologic diagnosis of HL and 26 with NHL. The median age of the patients was 36 years (range: 21–71 years). Relapsed or refractory disease was confirmed in all the patients. In 18 patients (26%) a relapse of HL/NHL had occurred after autologous stem cell transplantation (ASCT); 20 patients (29%) with HL/NHL had an early relapse of disease (less than 12 months after the last treatment). All the patients had previously been treated with at least two chemotherapy regimens and presented resistance or relapse after second-line chemotherapy (the median count of previous regimens was 4). The response after gemcitabine therapy was assessed every three or six cycles using the International Workshop Response Criteria for NHL [13]. All patients were evaluated by physical examination, computed tomography (CT) or positron emission tomography/computed tomography (PET/CT).

The overall response rate (ORR), overall survival (OS), progression-free survival (PFS) and toxicity after gemcitabine treatment were analyzed. The ORR included complete response (CR) and partial response (PR). OS and PFS were determined using

Table 1. Clinical characteristics of 68 patients

Gender	42 M/26 F
Median age	36 (range: 21–71)
Diagnosis	HL: 42 NHL: 26 DLBCL: 15 PTCL: 4 MCL: 2 T-NHL: 2 anaplastic: 1 FL: 1 mycosis fungoides: 1
Stage according to Ann Arbor staging	I: 1 II: 12 III: 18 IV: 37
Bulky disease	10
LDH	normal: 15 elevated: 53
Refractory disease	32
Relapsed disease	36
Median of treatment regimens	4 (2–6)

HL – Hodgkin lymphoma, PTCL – peripheral T cell lymphoma, DLBCL – diffuse large B-cell lymphoma, MCL – mantle cell lymphoma, FL – follicular lymphoma.

the Kaplan-Meier method. The log-rank test was used to compare the curves. A p value of < 0.05 was considered significant. All statistical analyses were performed using STATISTICA 8.0 software (StatSoft, USA). The toxicity grade was evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) [14].

The clinical characteristics of the patients are summarized in Table 1.

Results

Treatment and Response

The study included 45 patients (66%) who were treated with gemcitabine in combination with other cytostatics. Gemcitabine-based chemotherapy included gemcitabine, vinorelbine and dexamethasone/prednisone (GVD/GVP) in 28 patients; gemcitabine, ifosfamide and vinorelbine (IGEV) in 16 patients; and gemcitabine, methylprednisolone and cisplatin (GEM-P) in 1 patient. The other

23 patients (34%) received gemcitabine monotherapy. Gemcitabine monotherapy was used in elderly patients and in patients with relapsed/refractory after high-dose therapy with ASCT (HDT-ASCT) who were not eligible for further intensive chemotherapy. The median count of gemcitabine based cycles was 4 (range: 3–12).

The ORR in the whole group of patients was 46% (31 patients); it was higher in patients with HL than in patients with NHL (31% vs. 15%). CR was achieved in 14 patients (21%): in 5 patients with NHL and in 9 patients with HL. PR was achieved in 17 patients (25%): in six patients with NHL and in 11 patients with HL. Among the patients with PR, five were treated with gemcitabine monotherapy. Among the patients with CR and PR, 26 (38%) were treated with high-dose therapy followed by autologous stem cell transplant (HDT-ASCT). Among them there were 17 patients with HL and nine patients with NHL. After HDT-ASCT 3 patients underwent allogeneic stem cell transplant.

The remaining patients comprised 32 (47%) who had progressive disease (PD) and 5 (7%) with stable disease (SD) after gemcitabine regimens.

Toxicity

In 23 patients treated with gemcitabine regimens (34%), mild hematological toxicity (neutropenia and thrombocytopenia grade 1/2) was observed. Grade 3/4 neutropenia occurred in 12 patients (18%), thrombocytopenia in 11 patients (16%) and anemia in seven patients (10%). Ten patients with grade 3/4 neutropenia had neutropenic fever. Three patients (4%) presented an allergic rash. One patient developed renal failure and in one patient ileus occurred. There were no treatment-related deaths.

Survival

The median PFS in all the patients was 10 months (range: 2–52 months; Fig. 1). The median PFS in the patients who responded to gemcitabine therapy was 13 months (range: 3–53 months; Fig. 2). The median OS after gemcitabine therapy in all the patients was 17 months (range: 6–53 months; Fig. 3). The median OS in the patients who responded to gemcitabine therapy was 21 months (range: 3–51 months; Fig. 4). The median OS in the patients treated with HDT-ASCT after gemcitabine therapy was 26 months (range: 6–54 months).

PFS and OS after gemcitabine-based chemotherapy was longer in the patients with HL than in those with NHL (PFS 10 months vs. 6 months respectively, and OS 15 months vs. 9 months). It was only a tendency; the difference was not statistically significant.

OS was significantly longer in the patients treated with gemcitabine in combination with other cytostatics than in those treated with gemcitabine monotherapy ($p = 0.01$).

Discussion

The treatment of patients with relapsed or refractory HL and NHL is challenging. High-dose chemotherapy followed by autologous stem cell transplant remains the standard approach for chemosensitive patients [1]. However, there are no guidelines for patients with relapsed/refractory disease after second- or third-line treatment. There are limited options in this group of patients.

Barlett et al. reported 91 patients with relapsed HL treated with gemcitabine, vinorelbine and pegylated liposomal doxorubicin. The ORR in that

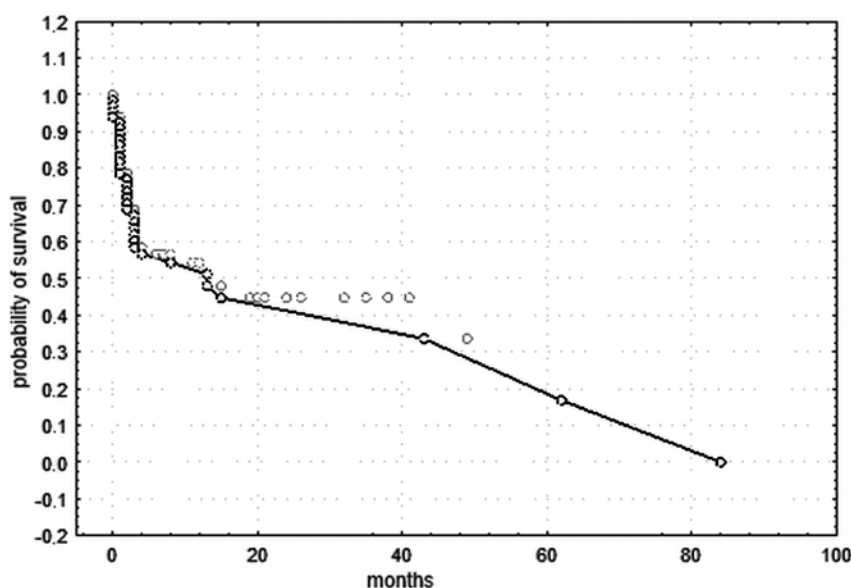


Fig. 1. The Kaplan-Meier estimate of PFS in all the patients

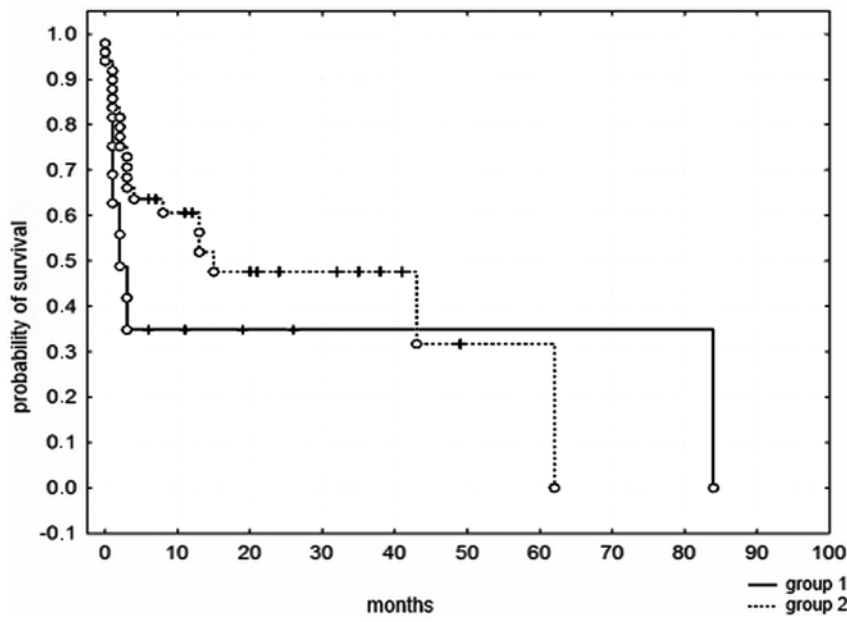


Fig. 2. The Kaplan-Meier estimate of PFS in all the patients stratified by response to gemcitabine therapy. Group 1 – patients who had no response; Group 2 – patients who responded (CR and PR)

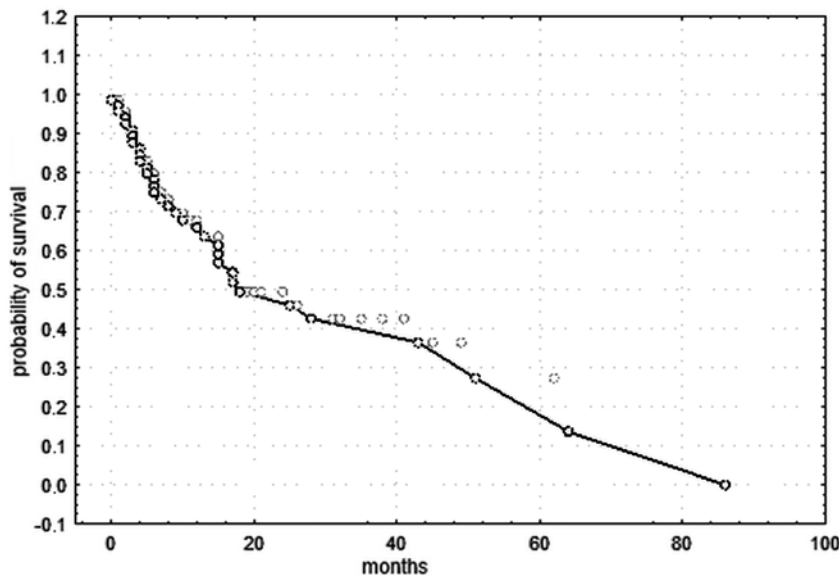


Fig. 3. The Kaplan-Meier estimate of OS in all the patients

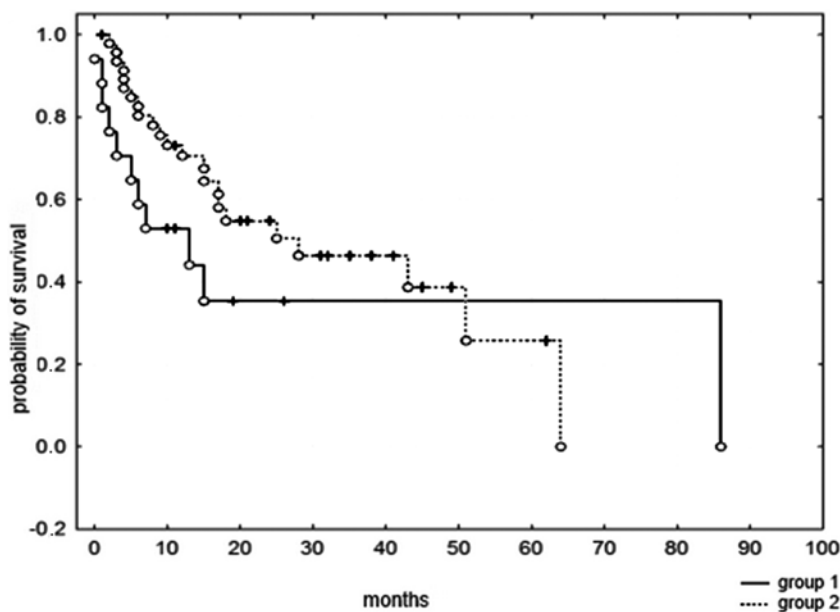


Fig. 4. The Kaplan-Meier estimate of OS in all the patients stratified by response to gemcitabine therapy. Group 1 – patients who had no response; Group 2 – patients who responded (CR and PR)

study group was 70%, with 19% CR. Toxicities included mucositis in 23% of the patients and febrile neutropenia in 9% [11]. Hawkes et al. analyzed a population of 41 patients with relapsed/refractory HL who received the GEM-P regimen; the ORR to GEM-P was 80%, with 37% CR [15]. A study by Bai et al. included patients with relapsed and refractory aggressive NHL and HL. All the patients had been treated previously; the median count of courses of treatment was three. The patients received the GVD regimen. The ORR in the whole group of patients was 48%, with 31% CR and 17% PR. The median PFS was 13 months for the patients who responded to GVD, and the median OS was 36 months. Among the patients with CR and PR, 16 were treated by HDT ASCT. In 34% of the patients neutropenia grade 3/4 occurred; in 9% anemia occurred; and in 7% thrombocytopenia occurred [10].

The present study involved 68 heavily pretreated patients with relapsed or refractory HL and NHL. The median count of previous courses of therapy in this group was four. All the patients were treated with gemcitabine monotherapy or gemcitabine in combination with other cytostatics. The ORR in this population was 46%; the ORR was higher (but not significantly) in the patients with HL in comparison with the patients with NHL (31% and 15%, respectively). These results are similar to the outcomes reported by Bai et al. with a similar population of patients [10].

In the present study the median PFS in patients who responded to gemcitabine treatment was 13 months, which was again comparable with the results of the study by Bai et al. [10]. In the present study the median OS among the patients who responded to gemcitabine therapy was 21 months. This OS was shorter than in other reports, but in the group of patients who had HDT ASCT, the OS was longer: 26 months. A tendency was also observed that OS and PFS were longer in the patients with HL than in those with NHL.

Gemcitabine may be used both in patients eligible for more intensive treatment and in elderly or frail patients. The combination of gemcitabine with other cytostatics is a good therapeutic strategy and results in a reasonable response rate. In elderly patients or in patients with comorbidities, gemcitabine monotherapy allows the course of the disease to be controlled. In the present study 7% of the patients who had gemcitabine monotherapy achieved PR, while 7% of the whole study group achieved stable disease.

Relapsed/refractory NHL patients, especially those with aggressive lymphomas, have a poorer prognosis than HL patients. OS without stem cell transplantation in this population is less than

1–2 years [16, 17]. In the present study, 24 patients (92%) with NHL had aggressive lymphomas, including diffuse large B-cell lymphoma (DLBCL) in 15 cases. It seems that gemcitabine-based therapy could be a good option in patients with aggressive lymphomas who have been heavily pretreated. A favorable option for patients with aggressive lymphomas is gemcitabine in combination with other chemotherapy agents [18]. In a phase I/II trial Evens et al. analyzed the efficacy of gemcitabine combined with bortezomib for relapsed/refractory DLBCL and peripheral T-cell lymphomas (PTCL). The study included 32 patients with DLBCL and PTCL, and the median number of prior therapies was three. The ORR in this population was 24%, with 19% CR. The ORR in DLBCL patients was 10% and in PTCL patients it was 36% [19]. In a study by Mounier et al., 49 patients with refractory/relapsed DLBCL were treated with gemcitabine in combination with rituximab and oxaliplatin. After four cycles, 44% of the patients achieved CR and 17% achieved PR. The ORR for the whole group of patients was 61% [20]. Gemcitabine in combination with immunotherapy or some immunomodulatory agents could be a key to improving outcomes in aggressive relapsed/refractory NHL.

The efficacy of gemcitabine therapy in patients with relapsed/refractory lymphomas is comparable with effect of lenalidomide or bendamustine. Ivanov et al. reported on 17 patients with relapsed/refractory DLBCL who were treated with a combination of lenalidomide and rituximab. The ORR was 41%, with 35% CR [21]. In another study lenalidomide was used as a single agent in relapsed/refractory mantle cell lymphoma (MCL) with an ORR of 35% [22]. Patients with HL relapsed after autologous or autologous/allogeneic stem cell transplantation were given salvage therapy with bendamustine. The ORR in this population was 57%, with 25% CR and 31% PR [23]. Investigational therapies including gemcitabine in combination with agents like lenalidomide or bendamustine could be a promising option for patients with poor-prognosis HL and NHL.

In retrospective study, Czyz et al. analyzed patients with relapsed HL after autologous stem cell transplant. There were 37 patients treated with gemcitabine-based regimens. The ORR in this population was 68%, with 22% CR and 46% PR. The patients with CR and PR had significantly longer OS and PFS; 15 patients who responded to gemcitabine therapy proceeded to allogeneic stem cell transplant and 5 patients to autologous stem cell transplant [24]. In another report, 40 patients with relapsed HL after HDT ASCT were treated with the GVD regimen and the ORR was 75% [11].

In the present retrospective analysis, 26 patients who responded to gemcitabine treatment proceeded to HDT-ASCT. In this group there were 12 patients (46%) who relapsed after HDT-ASCT. Mobilization of CD34 (+) stem cells was effective in most of the patients. In three patients mobilization of stem cells after gemcitabine salvage therapy was unsuccessful (two patients with NHL and one patient with HL).

In the current study significant toxicity after gemcitabine treatment occurred in 30 patients (44%) and included grade 3/4 neutropenia, thrombocytopenia and anemia. Bai et al. described grade 3/4 toxicities in 49% of the patients [10]. Czyz et al. reported neutropenia, thrombocytopenia and anemia as the most common adverse events in patients treated with gemcitabine-based therapy [15].

The authors have concluded that salvage therapy with gemcitabine is good as a bridging-cytore-

duction strategy to an autologous or allogeneic stem cell transplantation. Mobilization of stem cells after gemcitabine regimens is successful in most heavily pretreated patients. The results of this study suggest that gemcitabine-based chemotherapy is a good treatment option for heavily pretreated patients with relapsed/refractory HL or NHL. Gemcitabine in combination or as monotherapy resulted in good disease control with an ORR of 46%, and it allows the mobilization and collection of CD34+ stem cells. Gemcitabine in combination with other cytostatics or new immunomodulatory agents is more effective than gemcitabine monotherapy, while gemcitabine as single agent could be a solution for elderly patients or for patients with comorbidities.

The toxicity profile of gemcitabine regimens is acceptable with manageable hematological toxicity. Therefore the results of this study should be validated in prospective trials.

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