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Malignant Lymphomas

Value of gemcitabine treatment in heavily pretreated Hodgkin's disease patients

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ABSTRACT

Background and Objectives. **To assess the efficacy and the toxic profile of gemcitabine, a novel pyrimidine antimetabolite active against several solid tumors, we carried out a study in heavily pretreated Hodgkin's disease (HD) patients.**

Design and Methods. **From May 1997 to January 1999, 14 pretreated patients (10 relapsed and 4 refractory to previous treatments) were enrolled in a phase II trial and treated with gemcitabine. The drug was given on days 1, 8 and 15 of a 28-day schedule at a dose of 1,200 mg/m^2 intravenously for a total of 6 cycles.**

Results. **Two (14%) patients achieved complete remission (CR) and 4 (29%) had partial responses (PR), giving an overall response rate of 43%. In the relapsed subset there was an overall response rate of 50% with 2 CR and 3 PR. Among the refractory patients there was only 1 PR (25%). Both patients who had relapsed after autologous bone marrow transplant achieved a response (1 CR and 1 PR). No major toxic effects were recorded.**

Interpretation and Conclusions. **These data suggest that gemcitabine is an effective drug with a low toxicity profile in patients with heavily pretreated HD. Further trials using gemcitabine in combination with other conventional drugs are needed.**

Key words: Hodgkin's disease, gemcitabine, pretreated patients

In recent decades very effective polychemotherapy regimens have been developed for the treatment of Hodgkin's disease (HD). As a result, more than 70% of HD patients can now be cured with chemotherapy administered either alone or in combination with radiotherapy.[1] However, for those patients who relapse after initial treatment, salvage therapy remains a difficult challenge. The choice of therapy must be individualized to fit the clinical circumstances of the relapse. In recent years several attempts have been made to develop salvage regimens to treat HD patients who are refractory to first-line treatment or who have relapsed after two or more different lines of treatment.[2-7] Moreover, the recent introduction of autologous bone marrow transplantation (ABMT) or peripheral blood stem cell reinfusion to support the intensification of chemotherapy has expanded the repertoire of options available for patients who have relapses.[8-10] Under these circumstances, new chemotherapeutic agents are required to enhance standard HD treatments. Some drugs currently under investigation in the management of HD include: the new vinca alkaloid, vinorelbine;[11,12] the anthracycline, idarubicin;[13] the nitrogen mustard, bendamustine;[14] and the recently developed nucleoside analog, gemcitabine.[15,16]

Gemcitabine is a new pyrimidine antimetabolite with metabolic and mechanistic properties that are unique among the nucleoside analogs.[17] A special feature of gemcitabine is its self-potentiating mechanism of action, resulting in enhanced accumulation and prolonged retention within malignant cells. Gemcitabine has been shown to have remarkable activity against solid tumors[18-20] and appears active against leukemia and lymphoma cell lines and cultures *in vitro*.[21,22] In this study, we report our experience with gemcitabine in terms of efficacy and toxicity in 14 heavily pretreated HD patients.

Design and Methods

From May 1997 to January 1999, 14 previously treated HD patients (10 relapsed and 4 refractory to previous chemotherapy regimens) completed therapy with gemcitabine. Criteria for entry into the study included: histologic diagnosis of HD; stage II-IV as outlined by the Costwolds Meeting;[23] disease resistant to primary and secondary treatment or relapsed after second or third complete remission (CR). At the time of recurrent or progressive disease before gemcitabine, all patients were restaged by chest X-ray, hematologic and chemical profiles, bone marrow biopsy, measurement of all tumor masses, computerized tomography of the chest and abdomen, and biopsy of tumor masses when possible. Other studies included lymphography and liver biopsy when appropriate. Informed consent was obtained from all patients in accordance with the ethics policy of the institute, and the study was performed in line with the Helsinki declaration.

The patients' characteristics are summarized in

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Table 1. The median age was 35 years (range, 22 to 58 years); 10 patients were male and 4 female. The bulk of palpable lymph nodes was defined by the largest dimension (cm) of the single largest lymph node or conglomerate node mass in each region of involvement. A node or nodal mass had to be 10 cm or greater to be recorded as bulky. Four patients had bulky disease. Nine patients had nodal disease presentation only. Five patients had extranodal disease associated with nodal presentation.

Ten of the 14 patients had relapsed. Of these, 8 patients had initially been treated with alternating or sequential MOPP-ABVD and then with the CEP regimen and 2 patients were treated first with one combination, the second being utilized as first salvage treatment (ABVD⇒MOPP) and then the IEV[7] regimen and ABMT. The remaining 4 patients were resistant to prior ABVD, MOPP and ABMT. Among the 10 relapsed patients, 6 had experienced a complete remission (CR) lasting more than 1 year with prior chemotherapy, and the other 4 patients had failed within 1 year of the initial chemotherapy.

Treatment protocol

Gemcitabine hydrochloride (Gemzar, Eli-Lilly, Italy) was supplied as a freeze-dried powder. The drug was diluted in normal saline and administered intravenously over 30 minutes. Gemcitabine was given on days 1, 8 and 15 of a 28-day schedule at a dose of 1,200 mg/m^2 for a total of six cycles. All cycles were delivered in an outpatient setting.

No antiemetic prophylaxis was given, but nausea and vomiting could be treated routinely if necessary.

Evaluation of response

CR was defined as the complete disappearance of signs and symptoms due to lymphoma for at least 6 weeks; partial response (PR) was defined as a reduction of at least 50% in the product of the largest perpendicular diameters of all measurable lesions for a duration of at least 6 weeks. Disease progression was considered to be present when there was clear evidence of advancing disease, despite continuation of the treatment. Patients were evaluated by weekly history and physical examination, complete blood counts, and chemistry profiles. All signs, symptoms or laboratory abnormalities were assessed using ECOG criteria[24] for toxicities. One month after completion of the last course of therapy, clinical and pathologic evaluation was undertaken by repeating radiographic investigations, and bone marrow and/or liver biopsies which had been positive before treatment.

Results

Response

The therapeutic results are shown in Table 2. Major responses (CR + PR) were seen in 6 (43%) patients with 2 (14%) CR and 4 (29%) PR. In the subset of 10 patients who relapsed following third- or fourth-line therapy, there were 2 (20%) CR and 3 (30%) PR. Subdividing these patients into those who had relapsed at ≤12 months or >12 months, there were 1/4 (1 PR, 25%) and 4/6 (2 CR + 2 PR = 67%) responses, respectively. The response rate was not affected either by type of relapse presentation (nodal versus nodal plus extranodal) or by the presence of bulky disease. Both of the patients who had had ABMT obtained a response (1 CR and 1 PR). Among the patients who obtained PR, 1 was given involved-field radiation and 2 received ABMT with the aim of achieving CR. The patient who received the additional radiotherapy had disease progression after 6 months. In contrast, the 2 patients who received ABMT after salvage chemotherapy obtained a CR: both these patients are currently in CR 10 and 12 months after ABMT. The remaining patient who obtained PR progressed and died 12 months later. Of the 4 patients with refractory disease, only one (25%) achieved a PR; this patient died 8 months later because of disease progression. At the time of writing, both of the patients who achieved CR are still in remission after 12 and 15 months. As far as regards the 8 patients who did not respond to gemcitabine, two died of HD and the remaining 6 are still alive with the disease.

Table 1. Characteristics of the 14 HD patients.

Age (years)	
Median	35
Range	22-58
Sex (male/female)	10/4
Symptoms (no/yes)	5/9
Stage	
II	3
III	8
IV	3
Disease presentation:	
Nodal	9
Nodal + extranodal	5
Bulky disease	
Present	4
Absent	10
Response to prior chemotherapy	
Responsive	10
Refractory	4

Table 2. Response of 14 HD patients to gemcitabine.

	CR		*CR+PR*	
	N.	*%*	*N.*	*%*
All patients	2	14	6	43
Response to prior chemotherapy				
Responsive (10)	2	20	5	50
Refractory (4)	/	/	1	25
Timing of relapse				
≤ 12 months (4)	/	/	1	25
> 12 months (6)	2	33	4	67

Side effects

Gemcitabine treatment was generally well tolerated, and all the patients who responded completed

the drug therapy. With regard to hematologic toxicity, grade 3-4 neutropenia was recorded following only 5 (6%) of a total of 85 courses, and grade 3-4 thrombocytopenia occurred in 2/85 (3%) cycles. Fifteen (18%) courses were temporarily postponed for one week because of neutropenia and/or thrombocytopenia. Non-hematologic toxicity was minimal. Hair loss was mild to moderate, and no patient experienced complete alopecia. No nausea/vomiting was recorded. There were no instances of renal, hepatic or cardiac toxicity. No patient died of complications related to gemcitabine.

Discussion

The therapeutic approaches developed for HD patients who have failed first-line regimens or relapsed after a first or second CR include the use of conventional salvage chemotherapy regimens and, in recent years, high-dose chemotherapy with ABMT. It is apparent from the literature that an important variable affecting outcome is the ability of conventional-dose programs to reduce tumor volume before transplantation: thus, most of the long-term survivors in ABMT programs are patients who relapsed after chemotherapy but responded to subsequent chemotherapy. At the same time, although 90% of adults with advanced HD can achieve a CR with new polychemotherapy regimens such as BEACOPP,[25] it is too early to assess how many of them can ultimately be cured. With the previous generation of combination treatments, remission rates of 80% have been reported, but 30-50% of these patients still relapse and less than 25% of those in first relapse can be cured.[26,27] What is more, these regimens are associated with severe side effects including infertility, cardiac sequelae or secondary malignancies. Thus, alternative strategies or new drugs are being investigated to improve the life expectancy of patients with HD. Among the new cytostatic drugs, gemcitabine is the only one currently under investigation that presents a novel cytostatic mechanism of action. The drug is well tolerated: although myelosuppression is the dose-limiting form of toxicity, there is no other severe organ toxicity or hair loss.

In this study, mostly involving heavily pretreated relapsed patients, we obtained 2 (14%) CR with an overall response rate of 43%. Furthermore, 2 patients who initially obtained a PR went on to achieve a CR after ABMT. In addition, both patients who had had prior ABMT showed a response (1 PR and 1 CR). The patients who had been resistant to first-line treatment had the worst outcome, with only 1 obtaining a brief PR. In terms of side effects, we observed moderate myelosuppression but no organ toxicity. Standard antiemetics were not called for, and no cumulative toxicity patterns were observed.

While confirming the preliminary data reported by other authors on the activity and modest toxicity profile of gemcitabine,[28,29] the present study shows that the drug can also be useful for heavily pretreated patients, including ones who have already undergone ABMT. One interesting therapeutic option is first to reduce the tumor burden by administration of gemcitabine prior to ABMT, with the aim of an eventual cure. Our data from the use of gemcitabine alone in heavily pretreated HD patients are very promising and, together with those reported by others,[15,16] may open up new polychemotherapeutic approaches in this particular subset of HD patients, considering that this drug is very well tolerated as regards both hematologic and non-hematologic toxic effects.

These findings, even with the limitation of a relatively short follow-up and the small size of the patient cohort, lead us to conclude that gemcitabine seems to be the most active of the new conventional drugs for HD. It has a substantial activity and, at the same time, an acceptable toxicity, as has already been evidenced in patients with other lymphomas such as pretreated aggressive and peripheral T-cell lymphomas.[28-31] Larger randomized trials might be necessary to explore the therapeutic potential of gemcitabine further as front-line treatment for patients with HD in place of some old drugs that cause major side effects during treatment and long-term sequelae.

Contributions and Acknowledgments

PLZ was the principal investigator involved in the conception of the study, its design, and the writing of the paper. MB and FG helped the principal investigator (PLZ) with data analysis and interpretation. PA, MT, VS, and PPP collected the study data. ST critically revised the paper and gave final approval for its submission.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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Potential implications for clinical practice

- On the basis of our data gemcitabine might be considered an interesting therapeutic option for relapsed/refractory HD patients.

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