Short report

Activity of single agent vinorelbine in pretreated non-Hodgkin's lymphoma

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Summary

Background: To assess the activity of single agent vinorelbine in pretreated non Hodgkin's lymphoma.

Patients and methods: Twenty-three pretreated patients with non-Hodgkin's lymphoma (14 intermediate-high grade, nine low-grade) were treated with vinorelbine 30 mg/m²/week for six months or up to four doses after achieving CR.

Results: Among 13 evaluable patients with intermediate-high grade lymphoma, three obtained CR and three PR, for an overall response rate of 46% (95% CI: 19%-75%). Median duration of response was six months. Otherwise, vinorelbine did not show any significant activity in chemotherapy-refractory low-grade non-Hodgkin's lymphoma. Toxicity was acceptable, and the drug was well-tolerated even in elderly patients.

Conclusions: The good activity and tolerability of vinorelbine in relapsed intermediate-high grade lymphoma suggest its inclusion in first-line regimens, especially in elderly patients.

Key words: non-Hodgkin's lymphoma, salvage therapy, vinorelbine

Introduction

Approximately 50% of all patients with aggressive non-Hodgkin's lymphoma (NHL) relapse after first line treatment or fail to achieve complete response (CR). Despite response rate of 40% to 60% with standard dose salvage chemotherapy, the duration of response is usually short and more than 80% of relapsed patients eventually die from lymphoma [1-3]. High-dose chemotherapy with autologous bone marrow or peripheral stem-cell rescue, which has increased the event-free survival to 40%-50%, can be applied to a selected group of patients, i.e., younger than 60 years and with proven sensitive relapse [4]. Therefore, as the majority of patients can be offered very poor therapeutic options for their relapsed or refractory disease, the identification of active new drugs remains a priority in lymphoma research.

Low grade lymphomas are incurable diseases, characterized by several relapses. Thus, their management requires the availability of the largest numbers of active drugs.

Vinorelbine, a widely accepted drug in the treatment of a number of solid tumors [5-7], has shown good activity both as single agent and in combination chemotherapy in malignant lymphoma and Hodgkin's disease [8, 9]. Eghbali et al. [9] showed a response rate of 39% in patients with non-Hodgkin's lymphoma pretreated with vinca alkaloids. The postulated non-cross resistance with other vinca alkaloids, along with its good tolerability even in elderly patients, make vinorelbine a promising agent in the management of malignant lymphoma. In the present report, we describe the results of a phase II study employing single agent vinorelbine as salvage treatment in non-Hodgkin's lymphoma.

Patients and methods

From September 1992 to November 1994, 23 consecutive patients with pretreated non-Hodgkin's lymphoma were enrolled in this phase II study. Eligible patients had to meet conventional criteria for a phase II study (e.g., WHO performance status <2 and adequate bone marrow, liver and renal function unless impaired for organ infiltration by lymphoma). There was no limitation related to patient age. Informed consent was required.

Treatment plan consisted in weekly administration of vinorelbine at a dose of 30 mg/m² as an intravenous bolus. In case of peripheral vein injection pain, insertion of a central vein line was recommended. No antiemetic profilaxis was given, unless vomiting occurred or under patient specific request. Vinorelbine was continued up to four doses after achieving complete remission (CR) or for a maximum of six treatment months in the case of stable disease. Treatment delay was necessary if neutrophils were <1500/ml and/or platelets were <100,000/ml on the day of scheduled treatment administration. Toxicity was evaluated according to NCI Common Toxicity Criteria.

Results

Pretreatment characteristics and treatment outcome

Twenty-three consecutive patients, 15 males and 8 females, were enrolled in the study. According to Working Formulation, 9 patients had low-grade and 14 intermediate/high grade lymphoma. Median age was 63 years, ranging between 22 and 75.

Seven out of nine patients with low-grade lymphoma had refractory disease at the time of vinorelbine ad-
ministration and had previously received a median of four chemotherapeutic regimens (range 2–6), always including chlorambucil and CVP (cyclophosphamide, vincristine, prednisone). A single patient showed a partial remission (PR) lasting no more than two months, while the remaining patients developed progressive disease within the third dose of vinorelbine.

Among the 14 patients with intermediate-high grade lymphoma, five had refractory and nine relapsed disease. Median number of previously received treatments was two (range 1–6). Prior first line chemotherapy consisted in CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like regimen as first-line treatment in nine patients, ProMACE/Cytarabine (cyclophosphamide, doxorubicin, etoposide, prednisone alternated to cytarabine, bleomycin, vincristine, and methotrexate) in three and MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, bleomycin, and prednisone) in two. An etoposide-containing regimen such as MINE (mitoxantrone, ifosfamide/mesna, and etoposide) represented the second-line treatment in most patients (9/14). One patient received only chlorambucil for relapsed T-cell lymphoma of AILD type, and one high-dose chemotherapy followed by autologous bone marrow rescue. In three cases, vinorelbine constituted the second-line regimen because of bad performance status not allowing more aggressive polychemotherapeutic options.

Of the 14 patients with intermediate-high grade lymphoma, three achieved CR and three PR, for an overall response rate of 46% (95% CI: 19%–75%). Median duration of response was six months (range: two–eight months). No patient with refractory disease responded to single agent vinorelbine. Of interest, however, in a patient retreatment with vinorelbine for further relapse after eight months of CR determined a second, although short-lasting, CR. Response rate according to patient characteristics is shown in Table 1.

Toxicity

A total of 150 vinorelbine courses were delivered to the whole patient population. On the basis of hematological tolerability, vinorelbine was delayed of several days (range 3 to 15 days) in 67% of courses (101 out of 150). Grade 4 leucopenia occurred in 1% of cases, and grade 2–3 in 13% and 11%, respectively. The incidence of thrombocytopenia was low, with one grade 3, two grade 2 and four grade 1 episodes. Anemia was negligible. Grade 1–2 infections were observed in a total of six courses. Stomatitis as well as alopecia were never seen. Neurotoxicity was acceptable, with only seven grade 1 and two grade 2 paresthesias. Adynamic ileum was never observed. No vomiting and only sporadic episodes of nausea were observed.

Discussion

In our case series, response rate was 46% in patients with aggressive non-Hodgkin’s lymphoma. With the exception of three cases, all patients with aggressive lymphoma had been previously treated with at least two chemotherapeutic regimens. Furthermore, they all had received at least one vinca-alkaloid containing regimen, thus confirming the non cross-resistance of vinorelbine with other drug of the same group [8]. Toxicity was acceptable, with myelosuppression representing the main side-effect and 67% of courses delayed one week or more on the basis of hematological tolerability. As thrombocytopenia was negligible, myelosuppression can be overcome whenever necessary by the use of hematopoietic colony-stimulating factors. Neurotoxicity was mild and acceptable. Tolerability in patients above 65 years of age was comparable to that of younger patients.

Otherwise, vinorelbine as single agent at conventional doses did not show any significant activity in patients with refractory disease both in low grade and intermediate/high grade group. We believe that refractory disease more than the number of previous regimens can be the most important predictive factor for poor response to vinorelbine treatment. The use of higher dose intensity of vinorelbine with growth-factors support might be investigated in this subset of patients to evaluate the possibility of improving the therapeutic results.

In conclusion, vinorelbine shows good activity and good tolerability in pretreated aggressive non-Hodgkin’s lymphoma. Furthermore, considering the excellent tolerability in elderly patient, and in particular a lower neurotoxicity compared to other vinca alkaloids, vinorelbine should be considered in first-line regimens for these patients.

Table 1. Aggressive lymphoma: Response to vinorelbine according to patient characteristics.

<table>
<thead>
<tr>
<th>No. pts</th>
<th>CR</th>
<th>PR</th>
<th>OR (%)</th>
</tr>
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<tr>
<td>&lt;65 yrs</td>
<td>7</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>&gt;65 yrs</td>
<td>6</td>
<td>2</td>
<td>1</td>
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</tbody>
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References


2. Velasquez WS, McLaughlin P, Tucker S et al. ESHAP an effective chemotherapy regimen in refractory and relapsing lymphoma: A


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