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VINORELBINE IN THE TREATMENT OF LYMPHOMA

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SUMMARY

Seventeen patients with previously treated Hodgkin's disease or non-Hodgkin's lymphoma (NHL) were treated with single-agent vinorelbine (Navelbine® Pierre-Fabre Medicament) in an open study to assess the activity of this new-generation vinca alkaloid. Responses were obtained in four out of eight patients with Hodgkin's disease and four out of nine patients with NHL, including four patients who had been previously treated with high-dose therapies. Toxicity was very mild. The study demonstrates worthwhile activity and justifies the inclusion of vinorelbine in combination therapies for lymphoma.

KEY WORDS vinorelbine; Hodgkin's disease; non-Hodgkin's lymphoma

INTRODUCTION

The chance observation that extracts of the leaves of the white-flowered periwinkle, *Vinca rosea*, were inactive in controlling the elevated blood sugar of diabetic animals but would produce significant suppression of their bone marrow resulted in the synthesis and screening of the alkaloids extracted from this plant as cytotoxic agents.[1] Vinblastine (Velbe® Lilly) was shown to have activity against both Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) even in patients previously treated with alkylating agents[2], and by the early 1960s the activity of vincristine (Oncovin® Lilly) had also been established.[3] The structure of these compounds consists of a catharanthine moiety linked to a vindoline ring, and manipulation of the vindoline group resulted in the production of vindesine (Eldesine® Lilly). However, initial optimism of improved efficacy by this modification was not sustained by subsequent clinical experience.[4]

Vinorelbine is a semi-synthetic vinca alkaloid resulting from modification of the catharanthine ring, and was first synthesized in the mid-1970s. In common with vincristine, vinblastine and vindesine, it interferes with the polymerization of tubulin, thereby hampering cell division by its effect on the mitotic spindle, but its low affinity for neuronal microtubules suggests that it might not be associated with significant neurotoxicity.[5] Early pre-clinical evaluation of the drug demonstrated broad anti-tumour activity both *in vitro* and *in vivo* in animal models.[6] Phase II studies with vinorelbine demonstrated that the dose-limiting toxicity was neutropenia with some peripheral neuropathy and constipation documented at higher doses; the recommended dose selected for further clinical evaluation was 30 mg/m^2/wk.[7] Most studies have been conducted in patients with non-small-cell lung cancer (NSCLC) producing overall responses of 29–33 per cent, and advanced breast cancer giving response rates of about 40 per cent at the weekly schedule, although lowered dose-intensity in some trials reflected difficulty in maintaining

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Table 1. Patient characteristics and response to vinorelbine

Patient no.	Age/sex	Histology/stage	Prior therapies/PSCT	Primary refractory	No. courses	Response/length of response
1	38/M	HD IIA	2/Y	Y	3	PR/9
2	65/M	HD IIA	2/N	N	2	NR/-
3	47/M	NHL IIIB	3/Y	N	3	PR/8
4	24/M	NHL IVB	2/Y	N	4	CR/26
5	50/M	NHL IVB	3/Y	N	6	PR/16
6	51/M	NHL IIB	2/Y	Y	1	NR/-
7	26/F	HD IVB	3/Y	Y	2	NR/-
8	36/M	HD IIIA	3/Y	N	9	SD/-
9	78/F	NHL IVB	1/N	N	2	NR/-
10	59/M	HD IVB	2/N	N	4	PR/12
11	60/F	NHL IIIA	1/N	N	2	NR/-
12	46/M	NHL IVB	5/N	N	2	PR/4
13	38/M	HD IVA	8/Y	N	3	NR/-
14	64/M	NHL IVB	3/N	N	6	NR/-
15	74/M	NHL IVA	2/N	Y	3	NR/-
16	65/M	HD IIB	5/N	N	6	PR/8
17	53/F	HD IIIB	3/N	N	8	PR/15

treatment in the face of transient neutropenia.[8,9] Response rates have been further improved as vinorelbine has been incorporated into combination chemotherapy regimens. Vinorelbine has also demonstrated efficacy against ovarian, oesophageal, cervical carcinoma and squamous cell carcinoma of the head and neck.

Vinorelbine has shown good activity both as a single agent and also in combination therapy in the treatment of non-Hodgkin's lymphoma and Hodgkin's disease. Responses in up to 50 per cent of patients with both relapsed refractory NHL and heavily pre-treated HD occur when vinorelbine is employed as a single agent, with some complete responses seen in both groups.[10,11] Since the majority of patients with relapsed HD and NHL will ultimately die of their disease and many are not eligible for high-dose treatments, new agents are required. We report the results of a phase II study employing single agent vinorelbine as a salvage treatment in patients with NHL and HD, half of whom had received prior high-dose therapy.

PATIENTS AND METHODS

Seventeen patients with pre-treated NHL or HD were enrolled into this phase II study. The characteristics of these patients are shown in Table 1. The median age was 51 years (range 24–78) and enrolment required normal hepatic and renal function unless secondary to disease involvement. All patients gave informed consent. Nine patients had high/intermediate grade NHL as defined by the working formulation; one patient had multiply relapsed follicular lymphoma. Eight patients had Hodgkin's disease. All patients had advanced disease at the time of treatment with vinorelbine, and four had primary refractory disease. The median number of prior treatment regimens was 2 (range 1–8) and in eight of the patients this included a high-dose procedure (seven autograft, one allograft).

Vinorelbine was given at 25 mg/m^{2}IV on days 1 and 8, each cycle repeated every 21 days. The drug was administered peripherally by IV bolus over five minutes into a running saline infusion

followed by a 500 ml saline flush. Whenever required, the dose of vinorelbine was reduced to 20 mg/m^2 for one week to permit recovery from drug-induced myelosuppression (granulocytes $\leq 1{\cdot}5 \times 10^9$/l and/or platelets $\leq 100 \times 10^9$/l). If granulocytes were $<1 \times 10^9$/l and/or platelets $<75 \times 10^9$/l on the day of administration, the drug was delayed for one week. Toxicity was assessed according to the common toxicity criteria established by the World Health Organization (WHO).[12] Response was defined by WHO criteria.[13] If patients achieved a response with vinorelbine, treatment was continued for two cycles beyond a maximum response unless there was significant toxicity.

RESULTS

Seventeen patients received a total of 66 cycles (132 injections) of treatment, with a median number of cycles of 3 (range 1 to 9). The overall response was 47 per cent which included 1 Complete Response (CR), 7 Partial Responses (PR), and there was one patient with stable disease; the median length of response was 12 weeks (range 4 to 26). A response was more likely in patients with HD, with 50 per cent (4 out of 8) of patients having an objective response compared with NHL with 44 per cent (4 out of 9). One patient with primary refractory HD had a response to therapy. Four out of the eight patients who had relapsed following a high-dose procedure had a response, including one patient with marrow involvement who achieved a CR lasting six months.

Toxicity

The dose of vinorelbine was temporarily reduced in four patients due to neutropenia (two cases), severe constipation (grade III) and abnormal liver function tests (grade III) in one case each. Treatment was delayed in four patients following infectious complications, febrile neutropenia (2 cases), herpes zoster and pneumonia. The only other side-effect seen was phlebitis in three patients, severe in one who required insertion of a central line for subsequent treatment; two other patients required central lines because of problems related to poor peripheral venous access. There was little nausea or vomiting and no alopecia seen. All side-effects were reversible on discontinuation of the drug, with the exception of the abnormal liver function which was at least in part attributable to lymphoma infiltration of the liver.

DISCUSSION

Our study has shown an overall response rate of 47 per cent in patients with heavily pre-treated HD and NHL. In the patients with HD a response rate of 50 per cent was seen, compared with 44 per cent in NHL: results that are broadly in line with previous phase II single agent studies.[10,11,14] We used a less intense schedule of vinorelbine than had been used previously, and less than 5 per cent of scheduled drug administration was delayed (6 out of 132 injections) compared with the 67–80 per cent with a schedule of 30 mg/m^2 per week. The therapy was generally well-tolerated. There were no problems with nausea, vomiting or alopecia, and with the exception of one case of severe constipation, neurotoxicity was not a problem. Tolerance was also sufficiently good in patients who had been previously treated with high-dose therapy and who might have been expected to have reduced hematological reserve. The use of single agent vinblastine in patients with HD relapsing post-Bone Marrow Transplant (BMT) bears comparison. In a recent study,[15] a 59 per cent response rate was observed in this setting, with a

median event-free survival of 8·3 months, with the majority of patients receiving 6 mg/m^2 vinblastine every two weeks. The authors continued treatment indefinitely until evidence of disease progression, saw no cumulative toxicity, and described some very prolonged remissions. Our response rates are similar, and perhaps by continuing therapy the length of the observed remissions could have been increased.

Vinorelbine would appear to have efficacy in both Hodgkin's disease and in non-Hodgkin's lymphoma, but in common with solid tumour experience, better responses are seen when the drug is incorporated into combination regimens. Response rates of up to 88 per cent are seen when vinorelbine is used in combination as part of the initial therapy of high/intermediate NHL,[16] and in relapsed Hodgkin's/non-Hodgkin's lymphoma responses of 75 per cent[17] and 60 per cent[18] respectively are seen. The good response rates seen together with the excellent toxicity profile, especially the low incidence of neurotoxicity, should lead to a greater use of this drug in combination regimes, particularly in the elderly, where vinca alkaloids can be problematic and high-dose therapy is not an option.

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