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Vindesine in the Treatment of Breast Cancer

I. E. Smith and T. J. Powles

Royal Marsden Hospital, Sutton, Surrey, England

Summary. *A phase-II study of vindesine was carried out in 23 patients with histologically proven advanced breast carcinoma. Toxicity was assessed in a further 24 patients with several different tumour types. Treatment was given in a starting dose of 3 mg/m² weekly by IV bolus, increasing by 1 mg weekly as toxicity allowed. The response rate in 21 evaluable patients with breast carcinoma was 29%. In 47 patients evaluable for toxicity, leukopaenia occurred in 45% and was dose-related; thrombocytopaenia was rare (4%); neurotoxicity occurred in 40%; constipation in 17%, alopoecia in 46% and an influenza-like syndrome in 21%.*

It was concluded that vindesine was a clinically active agent in breast carcinoma, with a spectrum of toxicity lying between those of vincristine and vinblastine.

Introduction

Vindesine, a new semisynthetic vinca alkaloid, has been shown to have a wide range of anticancer activity in many experimental and human tumours [2–7].

However, little information is at present available on this acticity against breast cancer. We have therefore undertaken a phase-II study on 23 patients with breast carcinoma.

Patients and Methods

The study involved 23 patients with breast carcinoma. Ten of these patients, had minimal asymptomatic metastatic breast cancer involving soft tissue or pleura. Vindesine was given in initial weekly doses of 3 mg/m² in a single IV bolus injection. Dosage was then increased by 1 mg weekly as toxicity allowed. In five patients who responded to treatment the maintenance dosage was changed after 2 months to 4 mg/m² every 2 weeks. All patients were seen weekly and assessed for response and toxicity.

Investigations before and during treatment included weekly full blood count, plasma urea and electrolytes, serum calcium, uric acid, bilirubin, alanine transaminase, alkaline phosphatase, and total protein; chest X-ray and bone marrow examination were carried out initially and repeated subsequently as indicated; skeletal X-rays, bone scan, and liver scan and ultrasound were also done as appropriate.

Patients were assessed for response when they received treatment for at least 4 weeks or had shown clear evidence of disease progression after at least 2 weeks of treatment. Three categories of response were defined: (i) Complete remission (CR), where all measurable disease had disappeared for at least 1 month, as assessed both clinically and by appropriate investigations; (ii) Partial response (PR), defined as a reduction of over 50% in the sum of the products of the diameters of measurable lesions for at least 1 month, with no lesions appearing; (iii) Measurable response (MR) defined as a reduction of less than 50% in the product of the diameters of each lesion or a reduction of over 50% in some lesions but no change in other with no new lesions appearing. Response in bone was defined on the basis of radiological evidence of recalcification or the disappearance of hot spots on an isotopic bone scan. This was defined as a PR. All these responses were based on the UICC system for assessing response to treatment in this disease.

Results

Toxicity

We considered 47 patients assessable for toxicity in a larger study in which vindesine was used in several different tumour types including breast cancer. Leukopaenia occurred in 21 patients, and more commonly when the dose of vindesine was increased to 6 or 7 mg per patient. This usually occurred within 7 days of treatment, was moderate and transient, and was never associated with infection or septicaemia. Thrombocytopaenia was rare, occurring in only two patients, neither of whom had no marrow infiltration and both of whom had received previous extensive chemotherapy, and it was not associated with bleeding or purpura. On the other hand, 13 patients had a significant increase, greater than 100,000/mm³, in their platelet count during the first three courses of chemotherapy, although a count in excess of 350,00/mm³ was never seen.

Reprint requests should be addressed to: T. J. Powles

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Neurotoxicity

Peripheral neuropathy occurred in 40% of patients, particularly paraesthesiae of the fingers; symptoms developed after three or four courses, were usually mild, and progressed only slowly. Neurotoxicity was severe enough to stop treatment in four patients, one of whom developed ileus and abdominal pain after two courses of treatment. Constipation was not a major problem but occurred to a significant extent in eight patients.

Alopoecia

Alopoecia occurred in 23 patients, and in all but three of the patients who completed more than six courses of treatment.

Other Side Effects

Fatique, malaise, and an influenza-like illness lasting 3 or 4 days after injections occurred in ten patients, but myalgia occurred in only one. These symptoms could be relieved by 20 mg prednisone per day for 3 days after treatment. Three patients developed an itchy, erythematous maculo-papular rash over the trunk after the second course of treatment. This settled spontaneously in two patients with no interruption of the therapy, and in the third patient treatment was discontinued for other reasons. Nausea was usually mild and actual vomiting occurred in only three patients.

Response

Of the 23 patients with breast carcinoma, 21 were assessable for response. Two achieved CR and four achieved PR, giving an overall response rate of 29%. Five other patients achieved a measurable response, so that 11 patients in all had some objective improvement of metastatic disease. Six of these 11 patients had received no previous chemotherapy.

Assessment of the responses by site showed that five of the 14 patients with soft tissue disease, including local recurrence, achieved CR or PR, as did four of seven patients with lymph node involvement and four of eleven with lung involvement. Only one patient with bone metastases and none with liver or bone marrow involvement responded to the treatment.

Discussion

The 29% CR + PR rate for vindesine in the treatment of breast cancer was at least as good as that previously described with vincristine or vinblastine [1]. This agent must therefore be considered a clinically active agent against breast cancer, with a spectrum of toxicity that lies between those of vincristine and vinblastine. The possible advantages of its use in combination chemotherapy must now be considered seriously.

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