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Short report

Primary therapy of multiple myeloma with paclitaxel (Taxol)

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Summary

Background: The treatment of multiple myeloma remains unsatisfactory and new active agents are needed. Paclitaxel is effective against a variety of solid tumors and we assessed the utility against multiple myeloma.

Patients and methods: From March 1993 to May 1994, we treated 33 patients with newly diagnosed multiple myeloma with paclitaxel given intravenously at a dose of 125 mg/m^2 over 24 hours (13 patients) or at a dose of 135 mg/m^2 over 3 hours (20 patients).

Results: Five of 33 patients responded (15%; 95% CI: 5 to 32%) with an unmaintained remission of 3–11+ months. Severe but reversible neutropenia was the major dose limiting toxicity, but myalgias and alopecia were also common.

Conclusion: Paclitaxel was slightly active against multiple myeloma. Whether higher doses or new analogues of this agent can produce superior results requires further study.

Key words: multiple myeloma, paclitaxel

Introduction

The standard treatment of multiple myeloma consists of a combination of melphalan with prednisone which induces responses in about one-half of the patients and results in a median survival of about three years. Despite extensive trials, combinations of multiple alkylating agents with or without doxorubicin, vincristine or a nitrosourea, have not improved on the outcome. High dose therapy with autologous bone marrow or blood stem cell transplantation has increased the response rate, but the impact on survival is unclear [1]. New therapies are needed for myeloma, especially those with different mechanisms of action that may lead to more effective combination or sequential treatments. Because paclitaxel has been effective against several solid tumors [2], we administered this agent to 33 patients with previously untreated multiple myeloma in order to assess the potential utility.

Patients and methods

Patient characteristics

Between March 1993 and May 1994, 33 previously untreated patients with multiple myeloma were treated with paclitaxel (Taxol, provided by the National Cancer Institute) after written informed consent was obtained according to institutional guidelines. All were at low risk for complications of multiple myeloma, without bone pain, severe anemia, or abnormal renal function (Table 1). All had measurable myeloma protein in blood or urine. The tumor mass grade was low in 79% of patients based on a hemoglobin >10.5 g/dl and serum myeloma protein of <4.5 g/dl.

Table 1. Patient characteristics.

No. patients	33
Median age (range)	57 (44–68)
Male (%)	73
Hemoglobin <10.5 (%)	27
Tumor mass (%)	
Low	79
Intermediate	21
Myeloma protein type (%)	
IgG	73
IgA	18
Light chain only	9
Lytic bone lesions (%)	38

Dose regimen

All patients received at least two courses of paclitaxel and only those with a 25% or greater reduction of myeloma protein synthesis received further treatment until a maximum reduction of myeloma protein. Other patients were followed without further treatment or, if symptomatic, received standard chemotherapy.

The initial 13 patients received paclitaxel at a dose of 125 mg/m^2 given as a 24 hour continuous infusion via central venous catheter every 3 weeks. Pre-medication consisted of dexamethasone 20 mg orally 12 hours and 6 hours before treatment; cimetidine 300 mg with diphenhydramine 25 mg were given intravenously 30 minutes before treatment. Because of marked neutropenia in all patients, the subsequent 20 patients received 135 mg/m^2 by a 3 hour infusion.

Toxicity and response

Toxicity was graded using the National Cancer Institute common toxicity criteria. The dose was reduced by 25% in patients who experienced grade 4 neutropenia (absolute neutrophils <500 cells/ul) or febrile neutropenia that required hospitalization and antibiotics.

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Response of the myeloma required a 50% reduction of serum myeloma protein synthesis and marrow plasmacytosis.

Results

Toxicity

Neutropenia was the most common dose-limiting toxicity (Table 2). Twelve of 13 patients who received the 24 hour infusion and 5 of 20 patients who received the 3 hour infusion developed grade 4 neutropenia. The granulocyte nadir occurred between days 7 and 14 but recovery was complete by day 21 in all patients. Neutropenic fever occurred in 2 patients who required hospitalization and intravenous antibiotics. In 13 of 20 patients receiving the 3 hour infusion, diffuse myalgias for which a narcotic was required occurred during the first week; these symptoms did not occur with the 24 hour infusion. There was a similar frequency and severity of other extramedullary toxicities among patients who received either schedule (Table 2).

Table 2. Toxicity.

	Grade				
	0	1	2	3	4
Granulocytopenia					
125 mg/m² (24 hour infusion)	0	0	0	1	12
135 mg/m² (3 hour infusion)	4	1	2	8	5
Thrombocytopenia	32	0	0	0	1*
Alopecia	6	20	7	0	0
Stomatitis	30	3	0	0	0
Nausea/vomiting	28	4	1	0	0
Myalgias	20	10	2	1	0
Neuropathy	31	1	1	0	0

* With neuropenic fever.

Response

Five of 33 patients responded (15%; 95% CI: 5 to 32%) with a median halving time of myeloma protein of 2.0 months (range 0.6 to 3.0 months). Responding patients received a median of 6 courses (range 4 to 9) before follow up on no treatment. Unmaintained remissions have been sustained for 2+, 3, 4, 7+, and 11+ months.

Fourteen of 26 unresponsive patients remain asymptomatic for 2 to 14 months; 5 of 12 patients have responded to subsequent chemotherapy. No patient has died after a median follow up of 8 months.

The degree of microtubule bundling in bone marrow plasma cells was assessed in 8 patients after completion of the 24 hour infusion [3]. Significant microtubule bundling was observed in a median 12% of plasma cells (range 0%–35%), with the highest percentage observed in the only responder studied.

Discussion

The treatment of multiple myeloma remains unsatisfactory since the median survival of approximately 3 years has remained constant for the past 25 years [1]. Attempts to improve on the outcome have been made with myeloablative therapy and stem cell rescue. Such treatment with allogeneic bone marrow transplantation may have a curative potential in some patients, but this procedure is associated with substantial treatment-related mortality. Autologous marrow or blood stem cell transplantation is safer, has increased the complete remission rate, but the survival benefit over conventional treatment remains unclear [1].

Another approach to overcome the inherent resistance of multiple myeloma is to explore new agents with novel mechanisms of action. When activity can be demonstrated, such agents could be included in new combinations or sequences of treatments that may be more effective. Paclitaxel is a taxane derivative, isolated from the bark of the western yew tree (*Taxus brevifolia*). The drug has a novel mechanism of action promoting microtubule assembly and stabilizing tubulin polymers [4]. Cell death occurs when division is attempted, although the precise mechanism has not been defined. Paclitaxel has demonstrated activity against a variety of solid tumors including breast and ovarian cancer [5, 6]. Therapeutic activity has been described in some patients with resistant lymphoma [7].

We administered paclitaxel to 33 previously untreated patients with multiple myeloma. Neutropenia of short duration was the dose limiting toxicity, mild alopecia was common, and there was a high frequency of myalgia. In only 15% of patients was the myeloma responsive, with both dose regimens equally effective. One-half of the unresponsive patients responded subsequently to melphalan-dexamethasone affirming the expected inferiority of paclitaxel as a single agent to standard combination regimens. Whether higher doses of paclitaxel with colony stimulating factor or a longer infusion schedule might be more effective requires further study. Our experience was sufficiently promising to justify further trials of new analogues that may be more active against multiple myeloma.

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