Brief Communication

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Phase I Study of Taxol in Refractory Acute Myelogenous Leukemias Using a Weekly Schedule

Taxol is an antineoplastic drug which targets microtubules and which has significant clinical activity in ovarian and breast cancer, and also in lymphomas and non-small-cell lung cancer [1]. In the early clinical trials, a high incidence of acute reactions (bronchospasm, hypotension and arrhythmias) was observed due to the vehicle Cremophor [2]. For later clinical trials, taxol was administered with antiallergic premedication. In these trials, neutropenia was observed as dose-limiting toxicity. In addition, a sensory neuropathy, nausea, myalgias, mucositis and alopecia were common. For phase II studies in solid tumors, 210 mg/m^2 as a 6-hour infusion and 250 mg/m^2 as a 24-hour infusion were recommended [1]. In refractory ovarian cancer, taxol could be safely administered at up to 250 mg/m^2 with G-CSF support; in this study, sensory neuropathy was the major dose-limiting toxicity [3]. In vitro, several human leukemic cell lines were found to be sensitive to taxol [5]. Taxol induces apoptosis in sensitive myeloid leukemia cell lines [5, 6]. In a phase I study, taxol was used in refractory acute leukemias. At doses of 390 mg/m^2, repeated once every 3 weeks, severe mucositis was observed [7]. At this dose, a clearance of leukemic blasts from blood and bone marrow was observed in 2/6 patients. By analogy to vincristine, another agent targeting microtubules, we hypothesized that weekly administration of a lower dose repeated 3 times might lead to reduced side effects and enhanced antileukemic activity. We therefore designed a phase I study, in which taxol was administered to patients with relapsed or refractory acute myelogenous leukemia (AML) starting with a dose of 80 mg/m^2 repeated in 3 weekly intervals.

Adults (aged >16 years) were eligible for this phase I study if they had relapsed AML or were not in complete remission (CR) after at least 2 courses of induction treatment. In addition, the likelihood of remission with standard salvage regimes (high-dose cytosine-arabinoside) had to be <40% as judged by a duration of first remission of less than 1 year and having received at least one prior salvage regimen. Other eligibility criteria were: serum creatinine and bilirubin each <1.6 mg/ml; Zubrod performance status <3; no prior cisplatin, or taxotere; no major cardiac history; at least 2 weeks from last prior therapy and full recovery from any toxic effects. Taxol was supplied by the Division of Cancer Treatment of the National Cancer Institute, Bethesda, Md.

The probability of obtaining CR was calculated according to a statistical model based on 314 patients with relapsed AML [8]. Details of the patients are given in table 1.

Taxol was started in the first 3 patients at a dose of 80 mg/m^2 over 24 h by intravenous infusion on days, 1, 8, and 15. Premedication consisted of dexamethasone 20 mg i.v. 14 and 7 h prior to beginning taxol and diphenhydramine and ranitidine 50 mg 30 min prior to taxol. A dose escalation was planned in the steps of 100, 125, 160 and 200 mg/m^2 (3 doses each) if no excessive toxicity developed in the first 3 patients treated at the previous dosage level. A patient was to be removed from the study

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Table 1. Patient characteristics, taxol dose, side effects and clearance of leukemic blasts

Pat.	Age years	Cytogenetics	Duration CR 1, weeks	Salvage n	Pred. prob. CR, %	Taxol dose, mg/m^2	Toxicity	Blasts % in PB[a]
1	53	i.m.	33	2	1	80 × 3	0	9/100
2	77	diploid	8	3	1	80 × 3	1 (N, P)	10/15
3	59	diploid	22	1	20	80 × 3	0	15/55
4	35	diploid	43	2	1	100 × 3	0	59/90
5	64	–5,–7	20	2	1	100 × 3	2 (U)	72/9[b]
6	38	diploid	8	1	1	100 × 3	0	5/nt
7	20	diploid	NA[c]	2	1	100 × 2[d]	0	93/96
8	59	i.m.	35	3	10	100 × 2[d]	0	10/45
9	77	diploid	0	2	1	100 × 3	0	28/88
10	50	t(9;11)	43	2	1	125 × 3	1 (P)	nt/nt
11	42	diploid	9	2	1	125 × 3	1 (D)	91/98
12	73	+8	0	3	1	125 × 2[e]	3 (U)	51/95
13	39	–5,–7	6	2	1	125 × 3	2 (N)	9/63

CR = Complete remission; PB = peripheral blood; N = nausea; U = ulcer; D = diarrhea; i.m. = insufficient metaphases; nt = not tested.

[a] Blasts before/after one course of taxol (percentage).

[b] In this patient, a concomitant decrease in bone marrow blasts from 60 to 15% was noted.

[c] Underwent bone marrow transplantation and relapsed 4 weeks thereafter.

[d] Patient died before 3rd dose could be given.

[e] 3rd dose not given because of grade 3 toxicity (stomatitis).

if his marrow was not hypoplastic after 1 course of taxol (3 doses) or if he or she was not in CR after 2 courses of taxol (6 doses) with >1 week separating courses and no more than 3 doses given per course or if the patient developed ≥ grade 2 extramedullary toxicity with a <50% decrease in the marrow leukemic infiltrate. Toxicity was evaluated according to common NCI criteria.

A total of 13 patients with relapsed or refractory AML was treated with taxol. All patients were heavily pretreated. Most patients had failed several salvage regimens and had a low probability of obtaining CR (<1%) [8]. At 80 mg/m^2 × 3 (3 patients) only minor toxicities were encountered. Six patients were treated at 100 mg/m^2; in 1 of 3 evaluable patients a grade 2 stomatitis was recorded. Four patients were treated at 125 mg/m^2. All had major toxicity: 1 patient had a severe buccal ulcer (stomatitis, grade 3), and 1 patient each had grade 2 nausea, grade 1 peripheral neuropathy and grade 1 diarrhea. All patients were severely immunosuppressed: 3/13 had fever of undetermined etiology, 1 patient each had pneumonia and herpes zoster infection and 5 patients were treated for septicemia and/or fungemia. No patients entered CR. Only in 1 of 11 patients some antileukemic activity (decrease of blasts in blood and bone marrow) could be observed. Taking into account the definite toxicity observed at the dose level of 125 mg/m^2 × 3, a further dose escalation does not appear feasible in this group of patients with AML who are heavily pretreated. Taking into account the modest antileukemic activity observed at this dose level, a further dose escalation also would not appear to enter patients into CR. We conclude from this study that the schedule proposed here for taxol (three 24-hour infusions at 1-week interval) is no improvement as far as toxicity and antileukemic activity are concerned.

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