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Phase II study of tallysomycin $S_{10}b$ in patients with advanced colorectal cancer

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Summary. A total of 16 patients with histologically confirmed colorectal cancer were entered into this phase II trial, designed to evaluate the efficacy and safety of tallysomycin $S_{10}b$. The compound was given i.v. weekly at a dose of 2.5 mg/m^2 by push injection. Pulmonary toxicity was the most significant side effect; it was observed in three patients and required treatment discontinuation in one. Skin lesions occurred in three patients. Other side effects were mild and their relationship to drug administration was ill-defined. No responses were observed in this group of patients, most of whom had received prior therapy.

Introduction

Bleomycin is an antibiotic that has been predominantly used in patients with lymphoma as well as in those with a variety of solid tumors, including head and neck and lung cancers. Its clinical use has been limited by its cumulative pulmonary toxicity [3, 4]. Other common side effects include fever and skin changes. A search for analogs with improved antitumor activity and/or reduced toxicities led to the discovery of tallysomycin $S_{10}b$.

Tallysomycin $S_{10}b$ is active against a variety of murine tumors, including P388/J leukemia, B16 melanoma, and Lewis lung and Madison 109 carcinomas [6]. In the subrenal capsule assay, tallysomycin $S_{10}b$ also exhibits antitumor activity against human lung and colon xenografts. Toxicologic studies in mice and dogs have indicated that nephrotoxicity, mainly renal tubular damage, is dose-limiting; in both species, pulmonary toxicity was noted at the highest doses [2].

Two phase I studies exploring weekly and twice-weekly schedules have been conducted [5, 7]. In both trials, cumulative pulmonary toxicity was determined to be dose-limiting. Decreases in pulmonary diffusion capacity and changes on chest X-rays were observed at various dose levels, but primarily in patients who received cumulative doses of >60 mg/m^2. Skin changes were infrequent and, unlike those observed with bleomycin, consisted of edema of the fingertips. Based on these data, a weekly dose of 2.5 mg/m^2 was recommended for further investigations. We initiated a phase II study in patients with measurable metastatic colorectal carcinoma.

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Patients and methods

The study was open to patients with histologically confirmed adenocarcinoma of the colon or rectum that was not (or no longer) suitable for surgery and/or radiotherapy. Eligibility criteria included an age of ⩾15 years, an ECOG performance status of 2 or better, and a life expectancy of at least 12 weeks. An absolute granulocyte count of >1,500/μl and a platelet count of >75,000/μl were required as well as adequate renal function tests [blood urea nitrogen (BUN), <20 mg/ml; serum creatinine, <2.0 mg%; creatinine clearance, >60 ml/min]. Patients had to have a measurable indicator lesion, which had to be enlarging if located in previously irradiated fields. Patients with a history of previous exposure to bleomycin, those with prior lung irradiation, and those with chronic obstructive pulmonary disease were not eligible.

Prior to entry, each patient underwent a complete history and physical examination, with tumor measurements. Prestudy tests comprised a complete blood count (CBC), including differential and platelet counts; determination of SGOT, total bilirubin, alkaline phosphatase, BUN, and serum creatinine levels, as well as creatinine clearance; measurement of Na^+, K^+, CL^-, and glucose values; CO_2 analysis; and urinalysis. Pulmonary function was assessed by pulmonary diffusion capacity (DLCO), forced expiratory volume (FEV), and forced vital capacity (FVC). Other pretreatment evaluations consisted of chest X-rays and computerized tomographic (CT) scans of the chest and abdomen. Toxicity data, CBCs, and platelet counts were recorded every week; tumor measurement and pulmonary function tests were assessed every 4 weeks. Antitumor activity was evaluated according to WHO criteria [8].

Tallysomycin $S_{10}b$ was supplied by Bristol-Myers Company in 5-mg vials for i.v. use; it was given as a rapid i.v. injection at a weekly dose of 2.5 mg/m^2. Treatment was discontinued when tumor progression was documented or after a maximum cumulative dose of 60 mg/m^2. When myelosuppression (granulocyte count, <1,500/μl; platelets, <75,000/μl) or hepatotoxicity (SGOT and bilirubin, >2.5 times the upper normal limit) were noted on scheduled days for retreatment, chemother-

Table 1. Pretreatment characteristics of 16 patients

	Patients (*n*)
Sex: M/F	11/5
Median age (range)	56 (35–67) years
Performance status (WHO)	
0	6
1	10
Prior therapy:	
Chemotherapy	10
Chemotherapy + radiotherapy	3
None	3
Indicator lesions:	
Lung and liver	6
Liver	4
Lung	3
Other sites	3

Table 2. Nonhematologic toxicities in 16 evaluable patients

Toxicity	Patients (*n*)
Pulmonary	3
Skin	3
Diarrhea	2
Anorexia	2
Leukopenia	2
Constipation	1
Dysgeusia	1
Fatigue	1
Weakness	1
Malaise	1

apy was delayed until recovery. Chemotherapy was discontinued in patients with a creatinine clearance of <40 ml/min, pulmonary toxicity (30% reduction in DLCO as compared with baseline values), and/or severe proteinuria. Toxicity was graded according to the criteria used at M. D. Anderson Cancer Center [1].

Results

In all, 16 patients were entered (Table 1); all had an ECOG performance status of 0 or 1. All but three patients had been pretreated with radiotherapy and/or chemotherapy, which usually included fluorouracil. Four patients had previously been exposed to either mitomycin C (three cases) or nitrosourea (one patient), one of whom had also undergone extensive radiotherapy to the pelvis and had a WBC count of 2,800/μl at entry. The indicator lesions primarily consisted of liver, lymph node, and lung metastases.

The number of weekly injections of tallysomycin $S_{10}b$ ranged from 1 to 17, with a median cumulative dose of 20 mg/m^2. One patient who showed marginally altered pulmonary function tests at entry received a single infusion of tallysomycin $S_{10}b$ and was taken off study because of rapidly growing tumor.

Pulmonary toxicity was the most significant adverse experience observed (Table 2); it was noted in three patients and was severe in one. After a cumulative dose of 20 mg/m^2, one patient developed bilateral rales coincidental with a decrease in DLCO. Although no changes were noted in the chest X-ray, the latter abnormalities were considered to be strong evidence of pulmonary toxicity. In the other two patients, changes in pulmonary function tests were minimal and their relationship to drug administration was ill-defined. Cutaneous toxicity was observed in three patients, consisting of disseminated rash and local induration in one case, soreness of scar tissue in another, and peripheral edema in yet another. Other nonhematologic symptoms were mild and questionably related to the administration of tallysomycin $S_{10}b$; it is noteworthy that no renal toxicity was observed.

A WBC count of <4,000/μl was noted in three patients, one of whom had an initial count of 2,900/μl, which further dropped to 2,200/μl. The other two patients had a WBC nadir of 3,900 and 3,600/μl, respectively, with prompt recovery to values of >4,000/μl. None of these three patients had thrombocytopenia (platelets, <100,000/μl). There were no complete or partial responses; however, in one patient tumor size remained stable for 4+ months.

Discussion

In this phase II trial, tallysomycin $S_{10}b$ did not exhibit significant therapeutic activity against adenocarcinoma of the colon. Most patients had been heavily pretreated, and a better result might have been obtained with a group of previously untreated patients. Significant pulmonary toxicity was observed at a cumulative dose of 20 mg/m^2, corresponding to 8 weekly doses. These data suggest that at the dose and with the schedule used in this trial, tallysomycin $S_{10}b$ has a toxicity profile similar to that of bleomycin; it is therefore not recommended for further investigation in patients with advanced colorectal cancer.

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