The evaluation of gemcitabine in resistant or relapsing multiple myeloma, phase II: a Southwest Oncology Group study

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Summary

Gemcitabine is a cytosine arabinoside (Ara-C) analog with activity in many human tumor systems. We evaluated the drug's activity in resistant or relapsing multiple myeloma. Gemcitabine 1000 mg/m^2 was administered as a 30 minute infusion on days 1, 8, and 15 of a 28-day cycle. No dose escalations were permitted and dose reductions were scheduled for hematologic toxicity. Twenty-nine eligible patients were entered into Southwest Oncology Group (SWOG)-9803. One patient received no treatment and 5 patients had inadequate response assessments. The major toxicity was hematologic with grade 3/4 neutropenia in 9 and grade 3/4 thrombocytopenia in 15 patients. No responses were seen. Stable disease was confirmed in sixteen patients (57%). Median survival was eight months. Gemcitabine as utilized in this trial has shown little activity and is not to be strongly considered for future multiple myeloma trials.

Introduction

Multiple myeloma accounts for approximately 10 percent of all hematologic malignancies and 1 percent of all malignancies [1–3]. Despite the emergence of data supporting aggressive therapies of multiple myeloma with chemotherapy including high-dose treatments with stem cell support, most patients ultimately become resistant to this therapy and/or relapse after treatments [4]. Response rates to second and subsequent chemotherapy regimens have been reported, but new drugs are certainly needed [5–7].

Gemcitabine is a fluorine-substituted Ara-C analog, which requires intracellular phosphorylation to the active form of the drug. Nucleoside kinases metabolize gemcitabine intracellularly to active diphosphate and triphosphate nucleosides. The resultant diphosphate inhibits ribonucleoside reductase which is responsible for generating deoxynucleoside triphosphates for DNA synthesis. Further, a reduced concentration of dCTP enhances the incorporation of gemcitabine triphosphate into DNA (self potentiation) and DNA polymerase is unable to repair growing DNA strands (masked chain termination) [8]. It is likely that gemcitabine also induces apoptosis in certain tumor targets [9]. In experimental antitumor models, this agent has a much broader spectrum of activity against solid tumors than does Ara-C, encouraging further drug development [10–11]. Phase I trials found a maximum tolerated dose (MTD) to be between 790 and 1,370 mg/m^2 per week with bone marrow suppression being the dose-limiting toxicity [12]. Antitumor activity was found in a variety of solid tumors, including pancreas, lung, ovary, bladder, breast, head and neck, Hodgkin's, and cutaneous T-cell lymphoma [13–20].

In these early Phase II trials, there was minimal toxicity when the starting dose was between 800 and 1,250 mg/m^2 [21–22]. Grade 4 neutropenia occurred in only 6 percent of patients and grade 3 neutropenia in 19 percent of patients.

Similarly, thrombocytopenia was noted only occasionally. Mild liver abnormalities and nausea/vomiting occurred in two-thirds of patients, but was never a reason for discontinuation of therapies. Mild proteinuria and hematuria developed in approximately 50 percent of patients, but was clinically insignificant. A few cases of renal failure of undetermined etiology were reported as were 4 cases of hemolytic-uremic syndrome. Less often seen were flu-like symptoms, peripheral edema, and dyspnea as well as alopecia, diarrhea, constipation, somnolence, and oral toxicities. When tried in multiple myeloma, small trials of gemcitabine utilized doses of 800 mg/m^2 over 30 minutes and revealed little activity [M. Voi, personal communication]. Conversely, the suggested Phase II doses of 1,250 mg/m^2 are probably excessive for multiple myeloma patients with prior chemotherapy regimens and thus the lower starting dose for the following study, 1000 mg/m^2 days 1, 8, and 15, every 28 days. Despite the demonstrated activity in a number of solid tumors and because lower doses were ineffective in multiple myeloma, the Southwest Oncology Group undertook the study #S9803 in an attempt to reevaluate the activity of this agent at an increased dose. Patients were accrued on this study between August 1998 and March 2000. Patient accrual ceased in April of 1999, for review of the data and the study was permanently closed in March 2000.

Patients and methods

Patients with all stages of proven multiple myeloma (stages I, II, and III at the time of diagnosis) were eligible. Protein criteria were present and patients with no quantifiable monoclonal proteins were ineligible. Patients must have received at least one prior regimen for multiple myeloma including chemotherapy, bone marrow transplant, biologic therapy, and/or radiation therapy. Patients must have shown indicators of disease progression.

Additional eligibility requirements included a pretreatment granulocyte count of equal to or greater than 1500/microliter, normal platelet count, and creatinine and bilirubin levels within institutional normal limits. If prior radiation therapy were delivered, at least 21 days must have elapsed since completion of this treatment. Performance status of SWOG 0–2 criteria were required. No concomitant radiation therapy, hormonal therapy, or other chemotherapy was permitted and patients with prior malignancy, except adequately treated skin cancer or any other cancer from which the patient had been disease-free for five years were excluded. Pregnant or nursing women were ineligible and persons of reproductive potential may not have participated unless an effective contraceptive method was approved.

The objective of the trial was to evaluate the confirmed response rates in patients with myeloma as well as to evaluate quantitative and qualitative toxicities of gemcitabine in a Phase II Study. Pretreatment determinations and laboratory determinations included CBC, serum chemistries, total serum protein electrophoresis as well as urine protein and electrophoresis, a bone marrow specimen, and a skeletal survey.

Gemcitabine was administered at a starting dose of 1,000 mg/m^2 intravenously over 30 minutes on days 1, 8, and 15 of a 28-day cycle. Complete blood counts and toxicity notations were performed weekly and doses were adjusted for subsequent treatments.

No dose escalations were permitted and dose reductions were accomplished for hematologic toxicity as follows: For an absolute neutrophil count (ANC) greater than 1×10^9/L and platelets over 100×10^9/L, 100 percent of the dose was given; for an ANC of $0.5–1.0 \times 10^9$/L and/or platelets of $50–100 \times 10^9$/L, a 75 percent dose was permitted, and for values under these minimums, the drug was omitted. Similarly, full-dose chemotherapy was given for non-hematologic toxicities of NCI grade 0–2, whereas 50 percent of the dose was given for grade 3 toxicities, and the drug was omitted for grade 4 toxicities. Courses were repeated every four weeks for an ANC greater than 1.5×10^9/L, platelets greater than 100×10^9/L and non-hematologic toxicity improved to grade 0–1. If these parameters were not met and if treatment were delayed more than three weeks from the planned date of re-treatment, the patient was removed from the study.

Responses were determined after 3 courses (12 weeks) of therapy. The Southwest Oncology Group (SWOG) follows one set of criteria for both Phase II and Phase III myeloma studies: Remission is defined as a 50% or greater reduction in serum myeloma production for Phase II studies and further characterized as complete and partial remissions for Phase III studies. Stable disease is anything less than a 50 percent reduction in the protein determination. Progressive disease is defined by an increase of more than 100 percent of the lowest level of protein production seen.

Table 1. Patient characteristics

Characteristic	Median	Minimum	Maximum
Age	68.0	45.0	81.0
Hemoglobin	9.6	6.0	12.0
Platelets $\times 10^9$/L	1.59	1.05	3.09
B2M (17 patients)	13.6	0.5	29.8
% plasma cells	41	13	95
M-component	3.1	1.6	7.1

Table 2. Toxicity

Toxicity	0	1	2	3	4	5
Anemia	5	3	7	10	3	0
Granulocytopenia	14	1	4	6	3	0
Thrombocytopenia	7	0	6	14	1	0
Fatigue/malaise	7	8	8	5	0	0

Results

A total of 30 patients from 22 institutions were registered to SWOG-9803 between August 15, 1998 and March 27, 2000. Twenty-nine patients were eligible and one patient received no treatment. All 28 patients are evaluable for toxicity, although 5 patients had inadequate response assessment (considered to be nonresponders). Patient characteristics are listed in Table 1: The median age of registrants was 68 years (range 45 to 81). 16 males and 12 females are represented with 22 white non-Hispanics and 4 black non-Hispanics, 1 Hispanic, and 1 Asian or Pacific Islander. At the time of this report, no patients are receiving protocol treatments and are off protocol for the following reasons: Toxicity was responsible in 5 patients, refusals unrelated to toxicity in 3 patients, progression in 11 patients, death in 3 patients, and not specified in 6 patients. No major protocol deviations were discovered. Hematologic toxicity was dose-limiting. Table 2 lists toxicities and shows grade 3 and 4 neutropenia in 9 cases, grade 3 and 4 thrombocytopenia in 15 patients, and anemia of grade 3 or 4 severity in 13 patients. Fatal toxicity was seen in 1 patient with grade 3–4 neutropenia, 1 patient with renal failure, and in a third patient with respiratory infection with grade 3–4 neutropenia. The only recurring non-hematologic toxicity was that of fatigue or malaise seen in 21 patients (grade 1–3).

No responses of greater than 50% reduction were seen in the study. Stable disease was determined in 16 patients (57 percent), increasing disease in 6 patients (21 percent), early death in 1 patient (4 percent), and inadequate assessment in 5 other patients (18 percent), for a total of 28 patients. Patients considered to have stable disease were treated from a minimum of 1 dose of gemcitabine to a maximum of 14 doses before therapies were discontinued. In this "stable" population, 4 persons had reductions in myeloma proteins of 10%, 17%, 21%, and 31 percent. Twelve patients had an increase in protein of less than 100% required to fulfill the criteria of progression; these increases average 25 percent (range 3–75%).

Figure 1 details the survival patterns, showing median of 8 months; to date 18 deaths have occurred in the 28-patient population.

Discussion

That the patients entered into this chemotherapy trial had received an average number of prior therapies with 2.5 different regimens (range 1–9) speaks to the desirability and necessity of new treatment programs. Comparisons of combination chemotherapy programs for initial and re-treatment therapies have consistently demonstrated response rates of 50 to 60 percent with no significant differences in overall survival ascribed to one best schema [23]. Studies continue to show excellent response of myeloma patients treated with either autografting or allografting, but neither of these modalities are curative. Obstacles to better results have included toxicities to grafting procedures (allograft) contaminating tumor cells (autograft), and persistent residual disease (allografting and autografting). Major efforts are being undertaken by laboratories to date to improve the outcome using immune-based strategies.

New agents are continually being investigated for the treatment of resistant or recurrent myeloma. Topotecan was the most recent candidate drug investigated by SWOG and the first reported instance of topoisomerase activity in multiple myeloma [7]. Our current attempts using conventional doses of chemotherapy as salvage therapy utilize DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin) with or without thalidomide in a Phase III trial.

The observation that anti-angiogenesis may be seen in human tumors and that anti-angiogenesis therapy is effective therapy in both murine models and human tumors has been well-demonstrated [24].

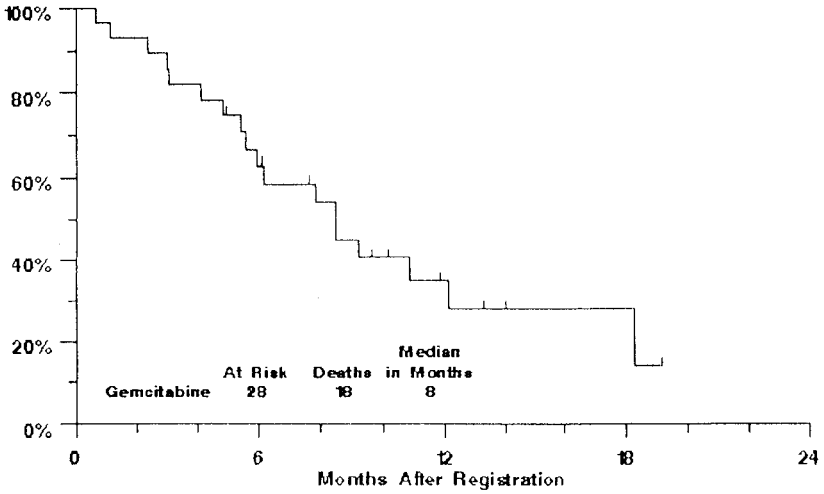

Figure 1. Overall survival

Thalidomide responses were seen in 32% of patients with advanced refractory myeloma [25].

Additional treatment options being investigated today include Phase II trials of arsenic trioxide, suramin, tyrosine kinase inhibitors, and farnesyl transferase inhibitors [26,27]. The initial reports of trials with these biologic response modifiers are encouraging and results of Phase II trials are eagerly anticipated.

The reports of efficacy of gemcitabine, an analog of cytarabine, in solid tumors and hematologic malignancies was the impetus for the current clinical trial in plasmacytic myeloma. Recent reports of response in refractory Hodgkin's disease (39%) and cutaneous T-cell lymphoma (69%) contribute to the anticipated benefits. Unfortunately, the results of single agent gemcitabine from this SWOG trial are disappointing. It is possible that the dose of 1000 mg/m^2/wk was insufficient to achieve the desired biological effect. Higher doses of 1250 mg/m^2 are common in solid tumor studies, but the heavy pre-treatment and the intrinsic marrow abnormalities suggested that the lesser dose be chosen. Minor responses in four evaluable patients confirm the activity of this agent in myeloma, but the data does not support the inclusion of gemcitabine in future myeloma trials.

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