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Phase II trial of amonafide in advanced colorectal cancer: a SouthWest Oncology Group study

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Amonafide is a substituted benzisoquinolinedione that exerts its cytotoxicity through effects on macromolecular synthesis and intercalation of DNA. In this trial, 44 patients with advanced colorectal cancer and without prior chemotherapy received amonafide at a starting dose of 300 mg/m^2 intravenously over one hour, on a daily × 5 schedule every 3 weeks. Toxicities of grade 3 or above included granulocytopenia, thrombocytopenia, sepsis, anaphylaxis and transient aphasia. Forty-seven % of patients had grade 3 or higher toxicity of any type. There were no complete or partial responses for an overall response rate of 0%, with a 95% confidence interval of 0–9%. The level of toxicity observed on this trial suggests an appropriate dose intensity of amonafide, despite lack of knowledge of patients' acetylator phenotypes.

Key words: Amonafide, colorectal cancer, phase II trial.

Amonafide is a five-substituted benzisoquinolinedione, synthesized in an effort to incorporate the active moieties from several cytotoxic compounds.[1] Amonafide appears to exert its cytotoxicity through effects on macromolecular synthesis and intercalation of DNA.[2,3] This agent was selected for clinical development based on its activity against murine implants of L1210 leukemia, P388 leukemia, M5076 sarcoma and B16 melanoma. Preclinical studies with amonafide in L1210 murine leukemia did not clearly demonstrate schedule dependency of the observed antitumor activity. Phase I trials utilizing daily ×5 schedule of amonafide have been conducted, with dose-limiting toxicity consisting of myelosuppression.[4] The maximally tolerated dose on this schedule has been defined at 350–400 mg/m^2. The SouthWest Oncology Group (SWOG) performed a phase II trial to determine the clinical response and toxicity of amonafide in patients with advanced colorectal cancer. Eligibility criteria included: a pathologically verified diagnosis of advanced adenocarcinoma arising from the colon or rectum; bidimensionally measurable disease; SWOG performance status of 0–2; no prior chemotherapy; prior radiotherapy limited to <25% of bone marrow volume; adequate organ function with PMN ≥ 1500/μl, platelets ≥100 000/μl, creatinine ≤1.5 mg%, SGPT within normal limits (SGPT ≤ 5 × upper limits of normal if liver involved with tumor), total bilirubin ≤1.5 mg/dl; institutional review board approval and written informed consent.

Amonafide was given as an intravenous infusion in 100 cm^3 normal saline over 1 h, daily ×5, every 3 weeks. The starting dose was 300 mg/m^2 with dose escalation and de-escalation based on observed interval toxicity. Dose de-escalation by 25 or 50% was performed for SWOG grade III or IV myelosuppression, respectively. In the absence of myelosuppression or grade >2 non-hematologic toxicity, the dose of amonafide was escalated by 25%. Subsequent doses of drug were delayed for granulocytes <1500 or platelets <100 000. Responses were classified by the standard SWOG definitions.[5]

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Table 1. Characteristics of eligible patients

Characteristic	No. of patients
Sex	
male	27
female	11
Median age in years (range)	64 (36–81)
Median SWOG performance status (range)	1 (0–2)
Prior therapy	
none	30
chemotherapy	0
radiotherapy	8

Table 2. Toxicities in eligible patients (SWOG grade 3 or higher)

Toxicity	No. of patients
Leukopenia	14
Granulocytopenia	9
Thrombocytopenia	5
Sepsis	3
Anaphylaxis	1
Transient aphasia	1
Fever/chills	1
Hypertension	1
Nausea/vomiting/anorexia	1

Forty-four patients from 23 SWOG institutions were entered on this study. Patient characteristics for the 38 eligible patients were as shown in Table 1. Thirty-seven patients were eligible and fully evaluable for toxicity and response. The median number of courses administered per patient was 2, with a range of 1–11. There were no complete or partial responses, for an overall response rate of 0% with a 95% confidence interval of 0–9%. The median survival for patients on this study was 8.5 months. The most common toxicities were leukopenia (27 patients), granulocytopenia (22 patients), nausea/vomiting/anorexia (19 patients), anemia (12 patients), local reaction with phlebitis/urticaria/pruritus (11 patients), thrombocytopenia (nine patients), facial flush (four patients), hepatotoxicity (four patients), fevers/rigors (three patients) and systemic allergic reactions (two patients). Toxicities of grade 3 or above, as shown in Table 2, included leukopenia (14 patients), granulocytopenia (nine patients), thrombocytopenia (five patients), sepsis (three patients), anaphylaxis (one patient) and transient aphasia (one patient). Other toxicities were of grade 2 or less and involved no more than three patients each, and included diarrhea, dizziness, headache, nephrotoxicity, mucositis, hypertension, abnormal taste, tinnitus, constipation and alopecia. One patient had their first infusion of amonafide discontinued due to anaphylaxis after 45 min, with the onset of diaphoresis, unresponsiveness and hypotension (blood pressure 60/40 mm Hg). The drug was immediately discontinued and normal saline infused, with recovery of the patient within minutes. One patient had the drug discontinued during their second course of treatment due to transient fever and an expressive aphasia. This occurred with 12 h of drug administration with fever up to 40°C. Symptoms and signs resolved within 24 h but occurred with retreatment. One additional patient developed urticaria over their torso, which was controlled with diphenhydramine.

Based on this trial amonafide is not felt to have significant antitumor activity against advanced adenocarcinoma of the colon and rectum. Twenty-four percent of patients had grade 3 or higher granulocytopenia, 47% of patients had grade 3 or higher toxicity of any type and 71% of patients had grade 2 or higher toxicity of any type.

Acetylator phenotype has been suggested as a determinant of toxicity, with rapid acetylation of amonafide associated with a greater risk of drug induced toxicity.[6] The level of toxicity observed on this trial suggests an appropriate dose intensity of amonafide, despite lack of knowledge of patients' acetylator phenotypes.

References

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