A Phase II Study of Idarubicin in the Treatment of Measurable Gastric Cancer

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Idarubicin is one of the new anthracycline analogues. It has a higher therapeutic index than either doxorubicin or daunorubicin in a variety of murine leukemias and solid tumors. The authors performed a multicenter Phase II trial of idarubicin in patients with advanced gastric cancer. Seventeen patients with measurable metastatic disease were entered into the trial and treated with idarubicin at a starting dose of 15 mg/m^2. This dose was escalated or reduced according to toxicity. There were no documented responses. The dose-limiting toxicity was myelosuppression. These data did not compare favorably with the data on doxorubicin in the treatment of gastric carcinoma. A conclusion could not be reached on whether idarubicin has minimal activity in the treatment of gastric carcinoma. ***Cancer*** **67:2988–2989, 1991.**

IDARUBICIN is one of the new anthracycline analogues. It differs from daunorubicin because it lacks the methoxy group in the C4 position of the aglycone.[1] Idarubicin has a higher therapeutic index than either doxorubicin or daunorubicin in a variety of murine leukemias and solid tumors.[2] Animal studies have also shown that it is significantly less cardiotoxic than either doxorubicin or daunorubicin.[3] The dose-limiting toxicity in Phase I trials was myelosuppression.[4] Therapeutic efficacy has been shown in a Phase I study.[5] Activity has also been demonstrated in hematologic malignancies.[6] However, the activity of solid tumors in Phase II studies has been less impressive.[7] The activity of idarubicin has been compared with the activity of doxorubicin in the treatment of solid tumors and idarubicin appears to be less effective.[8] We report the results of a multicenter Phase II trial of idarubicin in patients with measurable gastric cancer.

Patients and Methods

Seventeen patients with histologic proof of primary adenocarcinoma of the stomach and either disseminated or residual local disease after surgery were entered into this study. Disease had to be bidimensionally measurable by radiograph, computed tomographic (CT) scan, ultrasound, or physical examination. Criteria for entry into the study included the following: performance status of 2 or less (Eastern Cooperative Oncology Group); no prior chemotherapy or radiation therapy directed at the site of measurable disease; leukocyte count greater than or equal to 4.0 $\times$ 10^9/l; platelet count greater than 100 $\times$ 10^9/l; bilirubin level less than 2.0 mg/dl or 35 μmol/l; creatinine level less than 2.5 mg/dl or 220 μmol/l; and signed informed consent.

The site of major measurable disease included the liver in ten patients (59%), the lymph nodes in three patients (18%), and the gastric bed in four patients (24%).

Patients were treated with idarubicin at a starting dose of 15 mg/m^2 intravenously every 3 weeks. Dose adjustments were based on treatment day and nadir granulocyte and platelet counts. Interval counts were assessed at days 8 and 14 of each treatment cycle. When the nadir granulocyte count was greater than 2000 and the nadir platelet count was greater than 70,000 $\times$ 10^9/l, the dose was increased by 2.5 mg/m^2. When the nadir granulocyte count was less than 200 and the nadir platelet count was less than 40,000 $\times$ 10^9/l, the dose was decreased by 2.5 mg/m^2. Using this criteria, three patients were escalated to a dose of 17.5 mg/m^2 and in four patients the dose was reduced to 12.5 mg/m^2 every 3 weeks.

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TABLE 1. Patient Characteristics

Characteristic	No. of patients
Total	17
Median age in yr (range)	59 (31–76)
Median performance status	1
Sex	
Male	13
Female	4
Response	
CR	0
PR	0
Stable disease	5
Disease progression	12
Toxicity median (range) $\times 10^9$/l	
Leukocytes	1.8 (0.8–4.0)
Granulocytes	0.7 (0.2–1.9)
Platelets	177 (74–424)

CR: complete response; PR: partial response.

Seventeen patients took part in this study (Table 1). The median age of the patients was 59 years (age range, 31 to 76 years) and there were 13 men and 4 women. The median performance status was 1.

Results

There were no documented responses in 17 treated patients. Five patients had stable disease after two cycles of therapy and 12 patients had disease progression after one or two cycles of therapy. The main toxic side effect was myelosuppression with median nadir counts occurring on day 14. The median nadir leukocyte, granulocyte, and platelet counts were 1.8×10^9/l, 0.72, and 177×10^9/l, respectively (Table 1). Nausea and vomiting was the most commonly reported nonhematologic toxicity and was easily controlled with antiemetics. There was no demonstrated cardiac toxicity. No other significant nonhematologic toxicity was observed.

Conclusion

With no observed responses in 17 patients, the probability of idarubicin having at least a 20% response rate is less than 5%.[9] These data do not compare favorably with the data for doxorubicin showing that doxorubicin has response rates of 22% to 50% when used as a single agent in the treatment of gastric carcinoma.[10]

REFERENCES

1. Casazza AM, Partesi G, Giuliani F *et al.* Antileukemic activity of 4-demethoxydaunorubicin in mice. *Tumori* 1980; 66:547–565.
2. Dimarco AL *et al.* Effects of various substitutions in position 1, 2, 3 and 4 of 4-demethoxydaunorubicin and 4-demethoxyadriamycin. *Cancer Chemother Pharmacol* 1978; 1:249–254.
3. Casazza AM *et al.* Anti-leukemic activity and cardiac toxicity of 4-demethoxydaunorubicin. *Proc Am Soc Clin Oncol.*
4. Berman E, Wittes RE, Leyland-Jones B *et al.* Phase I and clinical pharmacology studies of intravenous and oral administration of 4-demethoxydaunorubicin in patients with advanced cancer. *Cancer Res* 1983; 43:6096–6103.
5. Bonfante V, Ferraril, Villani F *et al.* Phase I study of 4-demethoxydaunorubicin. *Invest New Drugs* 1983; 1:161–168.
6. Carrela AM *et al.* Idarubicin in the treatment of acute leukemias: An overview of preclinical and clinical studies. *Haematologica* 1990; 75(2):159–169.
7. Umsawasdi T, Holoye P, Jeffries D, Carr D. Phase II study of Idarubicin in extensive disease non-small cell lung cancer. *Am J Clin Oncol* 1989; 12(6):519–520.
8. Lopez M *et al.* A perspective randomized trial of Doxorubicin *vs.* Idarubicin in the treatment of advanced breast cancer. *Cancer* 1989; 64(12):2431–2436.
9. Gehan EA. The determination of the number of patients required in a preliminary and follow-up trial of a new chemotherapeutic agent. *J Chronic Dis* 1961; 13:346–353.
10. Moertell CG, Lavin PT. Phase II–III chemotherapy trials of advanced gastric cancer. *Cancer Treat Rep* 1979; 63.