

Disseminated Intravascular Coagulation at Presentation of Advanced Gastric Cancer

Margarita Tokar MD, Dmitri Bobilev MD, Samuel Ariad MD and David B. Geffen MD

Department of Oncology, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

Key words: bone marrow involvement, bone metastases, disseminated intravascular coagulation, 5-fluorouracil, gastric cancer

Abstract

Background: Disseminated intravascular coagulation associated with malignant bone marrow involvement has been described as a rare complication of gastric carcinoma and most patients die within 1–4 weeks. Effective chemotherapy of the underlying malignancy may be the only way to control acute DIC.

Objectives: To assess the benefit of infusional 5-fluorouracil as the primary treatment of metastatic gastric carcinoma and DIC at diagnosis.

Methods: From February 2001 to January 2005, six women (median age 48 years) with gastric carcinoma who presented with diffuse bone metastases and acute DIC were treated in our department. Diagnosis was based on primary gastric and bone marrow biopsies. DIC was confirmed by laboratory findings. Initial treatment consisted of infusional 5FU 200 mg/m²/day. When the bleeding tendency stopped, cisplatin 60 mg/m² and epirubicin 50 mg/m² every 3 weeks were added.

Results: Within one week of starting the treatment, the clinical and laboratory signs of acute DIC were resolved in five of six patients. Upon clinical improvement, five patients subsequently received epirubicin and cisplatin. Survival, however, was short (mean 15 weeks). All patients died with symptoms of bleeding, showing clinical and laboratory signs of DIC.

Conclusions: Based on our experience, infusional 5FU is an effective regimen with negligible myelosuppression; thus, it may be a good choice as initial therapy for this group of patients. The response induced by protracted 5FU was usually short and lasted for only a few weeks. Therefore, once DIC symptoms are controlled, the addition of newer cytotoxic drugs may be necessary to consolidate the remission.

IMAJ 2006;8:853–855

Gastric cancer remains one of the major causes of cancer death worldwide [1]. Despite an improving survival trend through early detection and curative surgery for early-stage disease, the prognosis of patients with metastatic gastric carcinoma remains poor. Randomized trials have demonstrated that 5-fluorouracil-containing regimens provide improved survival in patients with advanced gastric cancer when compared with best supportive care [2–5]. This survival advantage, however, appears to be marginal and no standard regimens have been established.

Disseminated intravascular coagulation is a clinicopathologic syndrome characterized by laboratory evidence of consumption and proteolytic degradation. The clinical expression varies and

may be manifested by laboratory abnormalities only or combined with hemorrhagic and thrombotic complications. The common laboratory abnormalities that are associated with chronic DIC in solid tumors include thrombocytopenia and circulating fibrin degradation products. Microangiopathic hemolytic anemia may occur in the absence of other DIC laboratory abnormalities, usually in association with disseminated mucin-secreting adenocarcinoma.

DIC has been reported in association with gastrointestinal, pancreatic, liver, ovarian, breast, lung and prostate cancers. Acute DIC is a rare but severe complication of gastric cancer with a fatal prognosis and most patients die within 1–4 weeks. Although treatment may be complicated by the presence of DIC and/or reduced bone marrow reserve, effective chemotherapy of the underlying malignancy may be the only way to control acute DIC associated with metastatic disease. We describe our experience with infusional 5FU given as primary treatment of metastatic gastric carcinoma in a series of six young women presenting with DIC.

Patients and Methods

From February 2001 to January 2005, six women with histologically proven gastric carcinoma who presented with diffuse bone metastases and acute DIC were treated in our department. Their median age was 48 years (range 32–56). All patients had an ECOG (Eastern Cooperative Oncology Group) performance status score of 3. None of the patients underwent surgery or had been previously treated with chemotherapy. Multiple ecchymoses and upper gastrointestinal tract bleeding were noted in four of the six patients [Table 1]. The diagnosis of acute DIC was based on the following criteria: evident bleeding symptoms and laboratory findings, which include thrombocytopenia (platelet count < 100 × 10⁹/mm³), prolonged prothrombin time or activated partial thromboplastin time, decreased serum fibrinogen levels (< 150 mg/dl) and elevated D-dimer levels (> 500 ng/ml). The abnormal laboratory findings supporting the diagnosis of DIC are illustrated in Table 2. ⁹⁹Tc bone scan and bone marrow examination were performed in all patients. Bone scan revealed diffuse bone metastases in all patients. Bone marrow and skeletal involvement by metastatic poorly or undifferentiated adenocarcinoma were shown in all cases, while in five of six cases they were the only site of metastatic disease. All patients needed initial blood and platelet transfusions to maintain hemodynamic stability and to correct the bleeding tendency.

DIC = disseminated intravascular coagulation
5FU = 5-fluorouracil

Table 1. Clinical characteristics of patients presenting with advanced gastric cancer and DIC

Patient no.	Age (yrs)	Gender	GI bleeding	Bone marrow	Other metastatic sites	Survival (wks)
1	50	Female	+	+	-	1
2	56	Female	-	+	-	4
3	45	Female	+	+	-	6
4	49	Female	+	+	-	26
5	32	Female	-	+	-	23
6	48	Female	+	+	Pleuropericardial effusion	32

Table 2. Hematologic and biochemical blood studies in patients with advanced gastric cancer and DIC at presentation

Patient no.	Hemoglobin (mg/dl)	Platelets/mm ³	PT INR	aPTT (sec)	D-dimer (ng/ml)	Fibrinogen (mg/ml)	LDH (U/L)	Alk-P (U/L)	Total bil (mg/dl)	Dir. bil (mg/dl)
1	8.5	15 000	1.74	28.4	30050	170	5800	1443	3.5	0.8
2	8.7	10 000	1.38	26.8	2000	450	1100	2301	2.8	1.0
3	8.0	53 000	1.97	24.0	20010	175	2416	1811	1.6	0.2
4	8.1	40 000	1.96	25.0	N/A	290	505	1957	1.9	0.2
5	8.4	39 000	1.52	22.2	24180	70	4729	1048	0.6	0.2
6	7.7	70 000	1.68	22.4	8600	142	708	571	0.8	0.2

PT = prothrombin time, INR = international normalized ratio, aPTT = activated partial thromboplastin time, LDH = lactate dehydrogenase, Alk-P = alkaline phosphatase, Total bil = total bilirubin, Dir. bil = direct bilirubin.

Initial treatment consisted of protracted infusional 5FU, 200 mg/m²/day on a daily basis, until progression of disease via peripheral venous line as in-patient treatment. When the bleeding tendency stopped, an indwelling vascular access device was inserted. Other cytotoxic drugs, usually cisplatin 60 mg/m² and epirubicin 50 mg/m² given every 3 weeks (ECF regimen), were added after the initial treatment successfully controlled the DIC process. The second-line chemotherapy consisted of docetaxel (75 mg/m² over 1 hour), cisplatin (75 mg/m² over 1 hour), both given intravenously on day 1 only and 5FU (750 mg/m²/day as a continuous infusion over days 1–5), with cycles repeated every 3 weeks (DCF regimen). Criteria for response to chemotherapy were based on clinical signs (upper gastrointestinal bleeding, skeletal events, performance status) and laboratory findings of DIC. The decision regarding second-line chemotherapy was based on laboratory evidence of DIC exacerbation.

Five of the six patients rapidly improved on primary chemotherapy in terms of laboratory findings and clinical signs of upper gastrointestinal bleeding. In five patients, clinical status improved dramatically within 2 weeks of chemotherapy. One patient died a week after starting the therapy with uncontrolled bleeding. The five surviving patients received more aggressive combination chemotherapy (ECF) after the acute DIC was brought under control. Four of the five patients (# 3, 4, 5 and 6) had symptomatic and laboratory improvement and three (# 4, 5 and 6) had a relatively long duration of response – 26, 23 and 32 weeks respectively.

ECF = infusional 5FU, cisplatin and epirubicin chemotherapy
DCF = infusional 5FU, cisplatin and docetaxel chemotherapy

Patients 5 and 6 received second-line chemotherapy (DCF). Survival of these patients, however, was short (mean 15 weeks) [Table 1].

Discussion

Acute DIC is a rare but severe complication of gastric cancer with diffuse bone metastases. The prognosis of these patients is poor and most of them die within 1–4 weeks [6,7]. Effective chemotherapy of the underlying malignancy may be the only way to control acute DIC and to correct the thrombocytopenia and bleeding tendency. The myelosuppressive effect of most combination chemotherapy regimens mitigates against their use in the clinical setting of acute DIC because of pancytopenia and the poor general condition of the affected patients.

On reviewing the literature we found several publications, mainly from Japan, on the successful treatment of patients with gastric cancer and DIC using 5FU-containing regimens [7,8]. In contrast to previously reported cases of gastric cancer and DIC, the current cases have several unique features. While gastric cancer is usually more common in men than in women (approximate ratio 2:1) with incidence increasing with age, peaking in the seventh decade, all our patients were young females. Gastric carcinoma at a younger age is relatively rare, accounting for less than 10% of cases. Recently, this group of patients was found to carry molecular changes distinct from gastric cancer occurring at a later age [9].

Despite many advances in the diagnosis and treatment of this disease, the prognosis of gastric cancer remains poor, especially in more advanced stages [1]. Gastric cancer is a relatively chemosensitive disease with a response rate to single agents in the range of 15%–20% and to combination chemotherapy 35%–50% [10]. However, a complete response rate to chemotherapy in the setting of advanced gastric cancer is usually low and generally of short duration. The treatment is often toxic, particularly in terms of myelosuppression. For many years, 5FU-based regimens have been considered the reference treatment. The most commonly used regimens have included infusional forms, which showed superior results compared with best supportive care or even bolus 5FU. Several comparative clinical trials were conducted in attempts to identify the best available combination [2–5]. The combination of cisplatin, epirubicin and infusional 5FU was shown in two prospective randomized trials to be superior in response rate and median survival to other combinations [11,12]. While the issue of standard chemotherapy of advanced gastric cancer remains unresolved, we chose the ECF regimen as first-line chemotherapy for our patients with metastatic gastric cancer.

Infusional 5FU is an effective regimen with negligible myelosuppression; thus, it may be a good choice as initial therapy for this group of patients. In our experience, the response induced by protracted infusional 5FU and the later addition

of epirubicin and cisplatin was usually short and lasted only a few weeks. Therefore, once DIC symptoms are controlled, the addition of newer cytotoxic drugs may be necessary to consolidate the remission. On the other hand, the fact that none of the patients survived may indicate that more intensive up-front combination chemotherapy may have been more effective. The chemotherapy of metastatic gastric cancer has evolved rapidly in the last several years with the introduction of newer agents into clinical practice. The incorporation of docetaxel, paclitaxel, oxaliplatin and irinotecan into the treatment of gastric cancer has resulted in relatively high response rates in phase II trials [10,13]. Recently, the interim results of a randomized phase III trial comparing the DCF combination with a standard reference regimen of cisplatin and 5FU were reported. Patients treated with the docetaxel-containing regimen had a statistically superior response rate, time to disease progression and prolongation of survival [14].

In the future, the treatment of gastric cancer patients presenting with DIC may probably be improved by the addition of the newer generation of cytotoxic agents and targeted therapy.

Acknowledgments. We thank Dr. Elliott H. Birnbaum for editorial assistance.

References

1. Jemal A, Murray T, Ward E et al. Cancer statistics, 2005. *CA Cancer J Clin* 2005;55(1):10-30.
2. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M, Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer* 1995;71(3):587-91.
3. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993;72(1):37-41.
4. Schipper DL, Wagener DJ. Chemotherapy of gastric cancer [Review]. *Anticancer Drugs* 1996;7(2):137-49.
5. Glimelius B, Ekstrom K, Hoffman K, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997; 8(2):163-8.
6. Pasquini E, Gianni L, Aitini E, et al. Acute disseminated intravascular coagulation syndrome in cancer patients. *Oncology* 1995; 52(6):505-8.
7. Yeh KH, Cheng AL, Gastric cancer associated with acute disseminated intravascular coagulation: successful initial treatment with weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin. *Br J Haematol* 1998;100(4):769-72.
8. Chao Y, Teng HC, Hung HC, et al. Successful initial treatment with weekly etoposide, epirubicin, cisplatin, 5-fluorouracil and leucovorin chemotherapy in advanced gastric cancer patients with disseminated intravascular coagulation. *Jpn J Clin Oncol* 2000;30(3): 122-5.
9. Carvalho R, Milne AN, van Rees BP, et al. Early-onset gastric carcinomas display molecular characteristics distinct from gastric carcinomas occurring at a later age. *J Pathol* 2004;204(1):75-83.
10. Sulkes A. Chemotherapy in gastric cancer: a brief chronicle with emphasis on recent developments [Review]. *IMAJ* 2004;6(7):415-19.
11. Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997;15(1):261-7.
12. Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol* 2002;20(8):1996-2004.
13. Shah MA, Schwartz GK. Treatment of metastatic esophagus and gastric cancer [Review]. *Semin Oncol* 2004;31(4):574-87.
14. Van Cutsem E. The treatment of advanced gastric cancer: new findings on the activity of the taxanes [Review]. *Oncologist* 2004;9 (Suppl 2):9-15.

Correspondence: Dr. M. Tokar, Dept. of Oncology, Soroka University Medical Center, P.O. Box 151, Beer Sheva 84101, Israel.
Phone: (972-8) 640-0768
Fax: (972-8) 640-0194
email: ritato@clalit.org.il

When you have only two pennies left in the world, buy a loaf of bread with one, and a lily with the other

Chinese proverb

Capsule

Dealing with DNA damage

For an organism to remain healthy, cells with damaged DNA must either pause in the cell cycle for a repair job or succumb to elimination by apoptosis. Huang et al. provide a mechanism through which cells with genomic damage may switch between these alternative fates. DNA damage activates a checkpoint signaling mechanism that arrests the cell cycle in part by inhibiting activity of cyclin-dependent kinase 2 (CDK2). The authors now find

that CDK2 may also couple to the machinery controlling cell death. Normally, the transcription factor FOXO1 is phosphorylated by CDK2. In cells with extensive DNA damage, reduced phosphorylation of FOXO1 allows its translocation to the nucleus, where it enhances expression of apoptosis-inducing genes.

Science 2006;314:294

Eitan Israeli

