Langenbecks Arch Surg (2006) 391: 124–129
DOI 10.1007/s00423-006-0022-z

ORIGINAL ARTICLE

Antonios-Apostolos K. Tentes
Sotirios K. Markakidis
Charisios Karanikiotis
Aliki Fiska
Ioannis K. Tentes
Vangelis G. Manolopoulos
Thespis Dimitriou

Intraarterial chemotherapy as an adjuvant treatment in locally advanced gastric cancer

Received: 24 May 2005
Accepted: 21 December 2005
Published online: 14 March 2006

A.-A. K. Tentes (✉) ·
S. K. Markakidis · C. Karanikiotis
Surgical Department,
Didimotichon General Hospital,
68300 Didimotichon, Greece
e-mail: atentes@did-hosp.gr
Tel.: +30-25530-44100
Fax: +30-25530-25652

A. Fiska · I. K. Tentes ·
V. G. Manolopoulos · T. Dimitriou
Laboratories of Clinical Anatomy,
Biochemistry & Clinical Pharmacology,
Demokritus University of Thrace,
Alexandroupolis, Greece

Abstract *Background and aims:* D_2 gastrectomy has improved survival in gastric cancer. Adjuvant intravenous chemotherapy, radiotherapy, or multimodal therapy has failed to demonstrate improved survival. The results of intraarterial chemotherapy (IARC) as an adjuvant have been encouraging in a few studies. A prospective randomized trial was designed to evaluate the toxicity and survival in locally advanced gastric cancer using IARC as an adjuvant after potentially curative gastrectomy. *Patients and methods:* Forty patients with locally advanced gastric cancer were randomly selected to undergo either potentially curative gastrectomy and receive IARC (study group) or gastrectomy only (control group). Clinical and histopathologic data were analyzed and the toxicity related to IARC was recorded. *Results:* The groups were comparable ($p>0.05$). Three patients in the study group had minor toxicity. Five-year survival rate for the study and the control group was 52 and 54%, respectively ($p>0.05$). Mean survival for the study and the control group was 50±8 and 62±10 months, respectively ($p>0.05$). The number of recurrences and the failure sites were comparable ($p>0.05$). *Conclusion:* Intraarterial chemotherapy can be safely applied to gastric cancer patients. As proposed by the protocol, the method cannot be recommended as an adjuvant treatment for locally advanced tumors because it appears that there is no survival benefit compared to potentially curative gastrectomy alone.

Keywords Gastric cancer · Curative gastrectomy · Intraarterial chemotherapy

Introduction

The long-term results of treatment in resectable gastric cancer have not been significantly improved in recent decades [1]. Adjuvant intravenous chemotherapy [2], radiotherapy [3], or multimodal therapy [4] have failed to demonstrate improved survival. The combination of chemotherapy and radiotherapy in an adjuvant setting after potentially curative gastrectomy has shown to improve survival but further studies are required to document these findings [5]. Survival has undoubtedly been significantly prolonged in Japan where radical lymph node dissection has been extensively used [6]. The Japanese results have been reproduced by several European multicentric studies [7–9]. Nevertheless, other studies have questioned the effectiveness of D_2 lymph node dissection [10, 11]. The sites of failure play a prominent role in poor survival. In approximately 50% of the cases, the major sites of failure in resectable gastric cancer are the liver and the peritoneal surfaces that ultimately lead to death [12]. The patterns of treatment failure using adjuvant [13] or neoadjuvant [14] chemotherapy are essentially the same as after surgery alone and only extended lymph node dissection has been proven to prolong survival and decrease locoregional relapses [6] compared to those seen with limited surgery [12].

Intraarterial chemotherapy has been successfully used in cancer treatment [15, 16] reaching a high first-pass extraction of the drug to the tumor. The method has been used in gastric cancer in a few trials [17, 18] in an adjuvant setting to prevent the development of liver metastases [19] or in a neoadjuvant setting with encouraging results [20]. It has also been used in the treatment of pancreatic cancer as an adjuvant and it has been shown that liver metastases have been decreased [21], or even as palliation in nonresectable pancreatic cancer and suppression of liver metastases have also been observed [22]. There is no prospective randomized study investigating the effect of IARC after potentially curative gastrectomy. The study was designed to evaluate the toxicity and the long-term effects on survival of intraarterial chemotherapy in patients with locally advanced gastric tumors undergoing potentially curative resection.

Materials and methods

From January 1992 to January 1998, 40 patients with locally advanced gastric tumors without distant metastases according to routine preoperative staging (physical examination, chest X-ray, CT scan, and bone scan) were enrolled in the study. Advanced gastric tumors were considered the T_3 and T_4 tumors as assessed by preoperative examination. The study was approved by the ethical committee of the hospital and was carried out in accordance with the Helsinki Declaration. Exclusion criteria were prior antitumor therapy or prior malignancy except for basal cell carcinoma of the skin or carcinoma in situ of the cervix and pregnancy. Eligible patients had a Karnofsky performance status of more than 50%, an ASA class I and II without severe comorbidity, a white blood cell count of at least 4,000/ml or more, a platelet count of more than 150.000/ml, a blood urea level of less than 40 mg/dl, and a creatinine level less than 1.5 mg/dl.

The age, sex, tumor location, procedures, T, N, stage (pTNM), Lauren, Ming, and Bormann classification, degree of differentiation, residual tumor, complications, hospital deaths, recurrences, and the anatomic sites of failure were analyzed. Toxicity related to intraarterial chemotherapy was recorded. The patients were randomly enrolled in the control or the study group intraoperatively after induction of anesthesia.

The proportions of patients with a given characteristic were compared by chi-square analysis. Differences in the means of continuous measurement were tested by the Student's *t* test. The survival curves were obtained using the Kaplan–Meier method and comparison of survival was calculated using the log-rank test. A two-tailed p value<0.05 was considered statistically significant.

Surgery

The patients in both groups underwent total or subtotal gastrectomy with D_2lymph node dissection depending on location and macroscopic type of the tumor. The left gastric artery was routinely dissected in subtotal gastrectomy and a short stump was always left. Through the stump of the left gastric artery the arterial catheter was introduced in the celiac artery. In D_2 lymph node dissection, the lymph node groups 1–12 were resected en block with the specimen. Lymph node group 10 was preserved if splenectomy was not performed. Splenectomy was always performed for tumors located at the great curvature of the gastric body and the pancreas was always preserved. The reconstruction of the alimentary tract was made using hand-sewn Roux-en-Y esophago-jejunostomy or Roux-en-Y gastro-jejunostomy. The resected specimens were studied according to the Japanese Classification of Gastric Carcinoma [23]. The study group (14 males and six females) underwent gastrectomy and received intraarterial chemotherapy. The control group (11 males and nine females) underwent resection only.

Intra-arterial chemotherapy

Intraarterial chemotherapy (IARC) was infused via a completely implantable device subcutaneously (infuse-a-port) that was connected to the arterial catheter. The catheter was inserted intraoperatively in the celiac artery via the stump of the left gastric artery after completion of the resection. The study group received three cycles of IARC with 1-month interval of rest between each cycle. The administration of IARC was initiated 20 days after surgery. One cycle consisted of the administration of IARC once weekly for four consecutive weeks. On day 1, 600 mg/m^2 of 5-FU were infused in approximately 1 h, on day 2, 15 mg/m^2 of doxorubicin, and on day 3, 7 mg/m^2 of Mitomycin-C were infused in the same way. The device was systematically heparinized between each cycle once a week.

Pathologic examination and classifications

Histopathologic type, TNM category, and stage were assigned using criteria provided by the Fourth Edition of the International Union against Cancer classification [24]. Resections were classified as R_0 when there was a complete resection and histologically proven negative margins and as R_1 when the margins of resection were shown by pathology to be infiltrated. Location of the tumors and lymph node stations were described according

to the Japanese Classification of Gastric Carcinoma [23]. Examination of the specimens included evaluation of the lymph nodes in each station by number of lymph nodes dissected and number of positive lymph nodes. All patients with pathologic stages II–IV were included in the final analysis.

Follow-up

No patient was lost during follow-up. The patients were assessed in 3–6 months intervals with physical examination, hematological, and biochemical examinations, tumor markers (CEA, CA 19–9, and CA-125), abdominal CT scan, upper gastrointestinal tract endoscopy, and chest X-ray. Whole body bone scan was performed only in cases in which osseous metastases were suspected. Recurrences and the sites of failure as well as deaths and their cause were recorded.

Results

As listed in Table 1, approximately equal number of patients underwent total and subtotal gastrectomies. All the specimens were classified according to Lauren, Ming, and Bormann classification. The degree of differentiation was also evaluated. The operation was classified as R_1 in two cases (one in each group). Three patients in the study group were classified as stage IV as group 12 lymph nodes were infiltrated. The mean number of retrieved lymph nodes was 27.8 (16–49). Although all the tumors were preoperatively assessed as T_3 and T_4 histopathology revealed that three specimens in the study group and one specimen in the control group were classified as T_2 tumors.

Morbidity and mortality

Three patients in the study group and six in the control group had postoperative complications (Table 2). Only three patients in the study group (15%) had transient complications during IARC treatment. One patient presented grade 1 anemia, and each one of the others presented grade 1 and 2 leukopenia, and neutropenia respectively. Growth factors were supplied to reverse the hematological profile when it was required. No other complication related to IARC was recorded. There was no hospital death in both groups.

Survival

The overall 5-year survival rate was 53% and mean survival 60±7 months (CI 95%=46–74). The 5-year survival rate in the study group was 52%. Mean survival

Table 1 Characteristics of patients treated with surgery plus IARC or surgery alone

Characteristics	Study group (surgery±IARC)	Control group (surgery)	*p* value
Male/female	14/6	11/9	0.327
Mean age	65.3±10	64.9±11	0.4
Location			0.503
Fundus	2	3	
Body	6	5	
Antrum	10	11	
Mixed	2	0	
Gastric remnant	0	1	
Performance status			0.22
90–100%	19	18	
70–80%	0	2	
50–60%	1	0	
Procedures			0.752
Total gastrectomy	9	11	
Subtotal gastrectomy	10	10	
Residual tumor			1.000
R_0	19	19	
R_1	1	1	
T category			0.323
T_2	3	1	
T_3	16	19	
T_4	1	0	
N category			0.145
N_0	7	5	
N_1	8	9	
N_2	2	6	
N_3	3	0	
Stage			0.349
II	5	5	
IIIA	8	10	
IIIB	4	5	
IV	3	0	
Lauren classification			0.492
Ming classification			0.677
Bormann classification			0.321
Degree of differentiation			0.766
G_1	1	2	
G_2	3	2	
G_3	16	16	

Table 2 Morbidity

Complication	Study group	Control group
Respiratory	1	3
Cardiac failure	1	0
Anastomotic leak	0	0
Prolonged ileus	0	1
Trauma related	1	2

p value=0.497

in the same group was 50±8 months (CI 95%=34–66). The 5-year survival rate in the control group was 54% and mean survival was 62±10 (CI 95%=42–81). The difference in survival was not significant (p=0.9005) (Fig. 1).

Patterns of recurrence

The mean follow-up time was 52±14 months (24–102). Within 3 years after the initial operation, 11 recurrences in the study group and nine in the control group were recorded (p=0.527). Three patients in the study group and four in the control group were recorded as having distant metastases. Eight patients in the study group and five in the control group were recorded as having loco-regional recurrences but the difference again was not significant (p=0.423) (Table 3).

Discussion

Most cytotoxic drugs have a steep-dose dependent response curve. Increased response rates can be achieved by increasing the drug delivery to tumors [25]. Intraarterial chemotherapy is successfully used in cancer treatment [15, 16] reaching a high first-pass extraction of the drug to the tumor. Therefore, intraarterial chemotherapy has a relative theoretical advantage over systemic chemotherapy, as high local drug concentrations with reduced toxicity can be achieved [26]. The purpose of intraarterially infused chemotherapy in locally advanced gastric cancer is to reduce the probability of secondary tumor growth by destroying cancer cells directed to the liver or those entrapped on the peritoneal surfaces of the pancreas by acting longer on them when blood flow is not high.

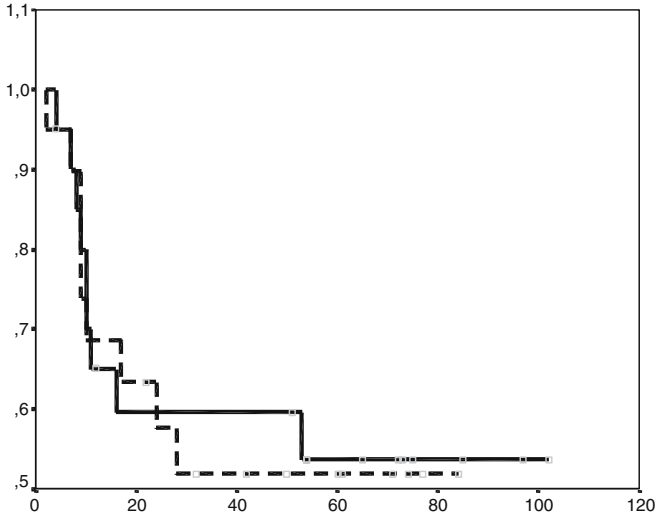

Fig. 1 Survival rate for the study (*dotted line*) and the control (*continuous line*) group

Toxicity of systemic chemotherapy is well established. Systemic side effects, including bone-marrow depression and gastrointestinal manifestations, are less frequent and less severe when the chemotherapeutic regimen is given intraarterially as compared to same doses of agents given intravenously [27]. The results of the present study showed that intraarterial chemotherapy was not followed by severe toxicity probably because the doses were lower than those used in systemic chemotherapy. Easily reversible anemia, leukopenia, and neutropenia during IARC treatment were recorded in 15% of the patients in the study group. The doses of the cytostatic drugs that were used were not high. Lower doses (250 mg of 5-FU, 8 mg of Doxorubicin, and 7 mg of Mitomycin-C) had been used with encouraging results in one nonrandomized study [17], which demonstrated that survival in patients receiving IARC was significantly higher compared to survival of patients that received surgery only. It was also observed that the rate of locoregional failures was lower compared to the rate of failures in the group that received surgery only.

No hospital death was recorded in both groups. Hospital morbidity rate was low and no complication related to the arterial catheter or the infuse-a-port device was recorded. Therefore, it appears that IARC is an easy and simple method that can be safely used in gastric cancer.

The analysis of the data regarding the effect of IARC showed that the study group had no survival benefit over the control group. The overall 5-year survival rate was high (more than 50%). This was expected because D_2 gastrectomy was routinely performed [6]. Recent studies from Western countries comparing D_1 and D_2 gastrectomy showed that there is a significant survival benefit in D_2 gastrectomy with 5-year survival rates over 50% [28, 29]. The recurrence rate was approximately 50% for both groups and the anatomic sites of failure were the same and similar to those demonstrated by other studies using other regimens of systemic chemotherapy [13, 14, 30]. It has

Table 3 Sites of recurrence

Site	Study group	Control group
Distant	3	4
Loco-regional	8	5

p value=0.423

been demonstrated that patients receiving IARC after D_2 gastrectomy have the same survival compared to those with D_2 gastrectomy alone, the sites of failure are almost equal, and loco-regional recurrences cannot be avoided [17].

The pathophysiology of high incidence of loco-regional failure developing after gastrectomy has not been completely clear. Clinical data support the concept that cancer cells originating from traumatized interstitial tissues, particularly when surgery is performed in narrow limits of resection, from the severed lymphatic network and from spilled venous blood, are entrapped with fibrin and blood clots in peritoneal surfaces [31]. During wound healing, as inflammatory cells infiltrate fibrin depositions, growth factors are released to stimulate fibroplast proliferation and collagen production, promote cancer proliferation and differentiation [32], and eventually give growth to loco-regional secondary tumors approximately 2–3 years after initial operation [33]. If this concept is true, the most likely explanation for the lack of increased survival benefit after IARC is that even when higher concentrations in the tumor are achieved, the chemotherapeutic agents cannot reach the entrapped cancer cells that are devastated of adequate blood supply. In case that this concept is not accurate, a possible explanation of the failure of IARC is that the use of cytostatic drugs in lower doses than those used in systemic chemotherapy as an adjuvant in gastric cancer are inadequate to prevent both loco-regional and hepatic metastases despite encouraging preliminary reports [17, 33].

Conclusion

The results of the study show that intraarterial chemotherapy is a safe and easy to perform method in patients with locally advanced gastric cancer undergoing potentially curative gastrectomy. However, IARC, as proposed by the protocol of the present study, cannot be recommended as an adjuvant treatment for locally advanced gastric tumors because there is no survival benefit for these patients compared to those treated by surgery alone. Further studies with more patients are required to document or reject these results.

References

1. Akoh J, and Mc Intyre I (1992) Improving survival in gastric cancer: review of 5-year survival rates in English language publication from 1970. Br J Surg 79:293–299
2. Hermans J, Bonenkamp JJ, Boon MC, Ohyama S, Sasako M, van de Velde CJ (1993) Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. J Clin Oncol 11:1441–1447
3. Hallisey MT, Dunn JA, Ward CL, Allum WH (1994) The second British stomach cancer group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: five-year follow-up. Lancet 343:1309–1312
4. Wanebo H, Kennedy B, Chmiel J, Steele G Jr, Winchester D, Osteen R (1993) Cancer of the stomach: a patient care study by the American College of Surgeons. Ann Surg 218:583–593
5. Mac Donald JS (2005) Role of post-operative chemoradiation in resected gastric cancer. J Surg Oncol 90:166–170
6. Maruyama K, Okabayashi K, Kinoshita T (1987) Progress in gastric cancer surgery in Japan and its limits of radicality. World J Surg 11:418–425
7. Siewert J, Bottcher K, Roder J, Busch R, Hermanek P, Meyer H, and the German Gastric Carcinoma Study Group (1993) Prognostic relevance of systematic lymph node dissection in gastric carcinoma. Br J Surg 80:1015–1018
8. Pacelli F, Doglietto F, Bellantine R, Alfieri S, Sgadari A, Crucitti F (1993) Extensive versus limited lymph node dissection for gastric cancer: a comparative study of 320 patients. Br J Surg 80:1153–1156
9. Jatzko G, Lisborg P, Denk H, Klimpfinger M, Stettner H (1995) A 10-year experience with Japanese type radical lymph node dissection for gastric cancer outside of Japan. Cancer 76:1302–1312
10. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, Sydes M, Fayers P (1999) Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized trial. Surgical Co-operative Group. Br J Cancer 79:1522–1530
11. Hartgrink HH, van de Velde CJH, putter H, Bonenkamp JJ, Kranenbarg EK, Songun I, Welvaart K, van Kriecken JHJM, Plukker JTM, van Elk PJ, Obertop H, Gouma DJ, van Lanshot JJB, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H, Sasako M (2004) Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch Gastric Cancer Group Trial. J Clin Oncol 22:2069–2077
12. Gunderson L, Sosin H (1992) Adenocarcinoma of the stomach: Areas of failure in a re-operation series (second or symptomatic look), clinicopathologic correlation and implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 8:1–11
13. Bruckner H, Stablein D (1983) Sites of treatment failure: gastrointestinal tumor study group analyses of gastric, pancreatic and colonic trials. Cancer Treat Symp 2:199–202
14. Wils J, Meyer H, Wilke H (1994) Current status and future directions in the treatment of localized gastric cancer. Ann Oncol 5(Suppl 3):69–71

15. Kemeny N, Fata F (2001) Hepatic arterial chemotherapy. Lancet Oncol 2:418–428
16. Tsukamoto S, Ishikawa S, Tsutsumi M, Nakajima K, Sugahara S (2002) An organ-sparing treatment using combined intra-arterial chemotherapy and radiotherapy for muscle-invading bladder carcinoma. Scand J Urol Nephrol 36:339–343
17. Blatzas G, Setzis K, Hatzigeorgiou N, Economou S, Zafiriou G, Dimasis A, Chrisafis G, Tsoukalas T (1996) Intraaretrial regional chemotherapy (IARC) with FAM after D_2 gastrectomy for advanced gastric cancer. Reg Cancer Treat 9:107–109
18. Stephens F (1988) Management of gastric cancer with regional chemotherapy preceding gastrectomy—5 year survival results. Reg Cancer Treat 1:80–82
19. Takahashi Y, Mai M, Fujimoto T, Ohta H, Ogino T (1989) Preventive hepatic arterial infusion in high risk cases of liver metastasis from gastric cancer. Gan To Kagaku Ryoho 18:2756–2759
20. Stephens F, Adams B, Crea P (1986) Intra-arterial chemotherapy given preoperatively in the management of carcinoma of the stomach. Surg Gynecol Obstet 162:370–374
21. Papachristou E, Link KH, Schoenberg MH (2003) Regional celiac artery infusion in the adjuvant treatment of pancreatic cancer. Anticancer Res 23:831–834
22. Link KH, Gansauge F, Gorich J, Leder GH, Rilinger N, Beger HG (1997) Palliative and adjuvant regional chemotherapy in pancreatic cancer. Eur J Surg Oncol 23:409–411
23. Japanese Classification of Gastric Carcinoma (1995) Japanese Research Society for Gastric Cancer. Kanehara, Tokyo (1st English edition)
24. American Joint Committee on Cancer (1992) Manual for Staging of Cancer, 4th edn. Lippincott, Philadelphia
25. Ensminger W (2002) Intrahepatic arterial infusion of chemotherapy: pharmacologic principles. Semin Oncol 29:119–125
26. Howell J, Warren H, Anderson J, Kerr D, McArdle C (1999) Intra-arterial 5-fluorouracil and intravenous folinic acid in the treatment of liver metastases from colorectal cancer. Eur J Surg 165:652–658
27. Stephens F, Harker G, Crea R (1980) The intraarterial infusion of chemotheraputic agents as “basal” treatment of cancer: evidence of increased drug activity in regionally infused tissues. Aust N Z J Surg 50:597–602
28. Edwards P, Blackshaw GR, Lewis WG, Barry JD, Allison MC, Jones DR (2004) Prospective comparison of D1 vs modified D2 gastrectomy for carcinoma. Br J Cancer 90:1888–1892
29. Sierra A, Regueira FM, Hernandez-Lizoain JL, Pardo F, Martinez-Gonzalez MA, Cienfuegos JA (2003) Role of extended lymphadenectomy in gastric cancer surgery: experience in a single institution. Ann Surg Oncol 10:219–226
30. Ajani J, Mayer R, Ota D, Steele G, Evans D, Roh M (1993) Preoperative and postoperative chemotherapy for patients with potentially resectable gastric carcinoma. J Natl Cancer Inst 85:1839–1843
31. Cunliffe W, Sugarbaker P (1989) Gastrointestinal malignancy: Rationale for adjuvant therapy using early postoperative intraperitoneal chemotherapy (EPIC). Br J Surg 76:1082–1090
32. Eggermont A, Steller E, Sugarbaker P (1987) Laparotomy enhances intraperitoneal tumor growth and abrogates the antitumor effects of interleukin-2 and lymphokine activated killer cells. Surg 102:71–78
33. Sato M, Terashima M, Takagane A, Saito K, Okada Y, Oikawa K (1989) Clinical effectiveness of arterial infusion chemotherapy in advanced and recurrent gastric cancer. Gan To Kagaku Ryoho 16:2927–2931