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Neoadjuvant radiochemotherapy for locally advanced gastric cancer: a phase I–II study

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Background: To study in a phase I–II trial the maximum tolerated dose, the toxicity, and the tolerance of adding radiotherapy to systemic chemotherapy administered preoperatively in patients with locoregionally advanced gastric adenocarcinoma.

Patients and methods: Patients with adenocarcinoma of the stomach ($T_{3–4}N_{any}$ or $T_{any}N+$), performance status ≤1, normal hematological, hepatic and renal functions received two cycles of cisplatin 100 mg/m^2 on day 1, 5-FU 800 mg/m^2 on days 1 to 4 and leucovorin 60 mg b.i.d. on days 1 to 4 q3w, concomitantly with radiation therapy escalated in three dose tiers (31.2, 38.4 and 45.6 Gy).

Results: Nineteen patients were accrued and 18 completed neoadjuvant therapy. Major toxicity consisted of grade 3/4 leucopenia and mucositis in 89% and 36% of the patients, respectively. Only one episode of febrile neutropenia was recorded. Dose level number 2 (38.4 Gy) with the chemotherapy given q4w is the recommended dose level. All patients were subsequently operated and no fatalities occurred. Pathological assessment showed one complete and eight partial responses. Two- and 3-year relapse-free survival rates were 57% and 50%, respectively. Only one patient relapsed locally. The peritoneum was the most frequent site of relapse.

Conclusions: This neoadjuvant therapeutic program is relatively well tolerated, does not seem to increase the operative risk, and might increase the locoregional control of the disease. The frequency of peritoneal involvement in relapsing patients underscores the need for a more effective systemic treatment.

Key words: gastric cancer, neoadjuvant radiochemotherapy, peritoneal relapse

Introduction

Despite a significant decrease in its incidence over the last 70 years, gastric cancer remains a significant health problem worldwide [1]. In Western countries, the disease is diagnosed mostly at an advanced stage, and the cure rate of locoregionally advanced disease remains dismal even with extensive surgery [2, 3]. Adjuvant chemotherapy has been tested in numerous randomized trials, but its effectiveness has not been convincingly established thus far [4]. Furthermore, it is very likely that the patients enrolled in these studies were highly selected. From a nutritional point of view, it has been shown that patients often recover slowly from total gastrectomy and are therefore unfit to start adjuvant systemic treatment 4–6 weeks after surgery [5, 6].

Locoregional relapse is also a major problem after curative surgery in gastric cancer. According to some series, the first site of relapse is local or regional in up to 50% of curatively-operated patients [7–9]. The incorporation of radiotherapy into (neo)-adjuvant therapeutic programs might decrease the locoregional relapse rate and thereby improve long-term results. A number of randomized trials studying preoperative or postoperative radiotherapy have been published, some with encouraging results [10–15]. However, most of the studies suffered from methodological problems, making them inconclusive [16]. Recently, a large trial in the USA comparing adjuvant radiochemotherapy plus chemotherapy with surgery alone has clearly shown an advantage for the adjuvant arm [17]. However, the results of this well-designed and well-conducted trial were mitigated by the suboptimal surgery performed in >50% of the patients enrolled. Furthermore, this adjuvant program was relatively toxic, with grade 3 and 4 toxicities observed in 41% and 32% of the patients, respectively.

Problems associated with postsurgical recovery can be avoided by the administration of systemic therapy and/or radiation prior to the surgical procedure. Furthermore, preoperative therapy has the theoretical advantage of treating an untouched tumor (lack of treatment-induced resistance), with intact vascularization and without fibrotic remodeling of the tumor bed due to surgical trauma. These considerations might account for the higher response rates observed when systemic therapy is administered preoperatively [18–20].

In contrast to adenocarcinoma of the esophagus, where neoadjuvant radiochemotherapy has been extensively investigated, very little has been done so far in gastric cancer with a combined-

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modality approach [21, 22]. Therefore, we conducted a phase I–II trial to study the maximum tolerated dose (MTD), the toxicity and the tolerance of the addition of radiotherapy to systemic chemotherapy administered preoperatively in patients suffering from locoregionally advanced gastric carcinomas.

Patients and methods

Consecutive patients with locally advanced adenocarcinoma of the stomach ($T_{3-4}N_{any}$ or $T_{any}N+$) amenable to curative resection were enrolled in this study. Patients were required to have a performance status ≤1, age ≤70 years old, normal blood counts, creatinine clearance ≥60 ml/min, normal liver function and no other serious illness or medical history.

The treatment consisted of two courses of chemotherapy combined with radiation therapy, followed by surgery performed 50 days after the start of the treatment program. The treatment schedule, including the radiotherapy dose escalation, is summarized in Figure 1. Chemotherapy consisted of cisplatin 100 mg/m^2 on day 1 in a 4-h i.v. infusion, followed by 5-FU 800 mg/m^2/day on days 1 to 4 in 24-h i.v. infusion and leucovorin 60 mg twice daily on days 1 to 4, to be repeated once on days 22 to 25. All patients received a standard supportive regimen consisting of hyperhydration and antiemetics during each course of treatment.

Radiotherapy was escalated by starting it earlier in the neoadjuvant treatment plan as follows: for the first radiotherapy dose level, 31.2 Gy in 26 fractions (two daily fractions of 1.2 Gy at least 6 h apart, 5 days a week) was given to six patients starting on day 22. Dose escalations to 38.4 Gy (in 32 fractions) starting on day 16, and then to 45.6 Gy (in 38 fractions) starting on day 11 were then carried out according to tolerance. The target volume included the tumor bed and the regional lymph nodes, adapted according to tumor location. Before each dose escalation, at least five patients in the previous dose tier had to have completed the treatment program with at least 28 days' postoperative follow-up. Toxicity was assessed according to WHO grading.

Responses were assessed by pathological examination of the resected specimens by an experienced pathologist (M-A.B.). If grossly residual tumor was present, the specimen was sampled according to standard procedures. While in cases with no or only small foci of residual tumor, the presumed tumor area was sampled *in toto*. A complete pathological response (pCR) was defined by the total absence of detectable viable tumor. A partial pathological response (pPR) was defined as residual viable tumor of a total size of ≤10 mm. Specimens not satisfying these criteria, i.e. with residual tumor of >10 mm, were considered as not showing a significant response (pNR) and the patients considered as non-responders (NR).

Results

Nineteen consecutive patients with clinical stage II, IIIA, IIIB and IV (five, ten, two and two patients, respectively) were entered in the study. All patients had had a full pretreatment work-up, including thoraco-abdominal CT scan, bone scintigraphy, upper gastrointestinal (GI) series and endosonography.

The results of the study are summarized in Table 1. Six, nine and four patients were enrolled in dose tiers 1, 2 and 3, respectively. In the first dose tier, all patients but one received their treatment on schedule. In the second dose tier, six patients had their second cycle delayed by 1 week and one by 2 weeks. In the third dose tier, one patient had the second cycle of chemotherapy delayed by 1 week, another by 3 weeks (febrile neutropenia), and one refused it. Most delays were due to late hematological recovery. Per protocol, white blood cell and platelet counts had to be at least 3000/mm^3 and 100 000/mm^3, respectively, before the next cycle of chemotherapy. Grade 3/4 hematological toxicity was observed in all but two patients, and led to only one episode of febrile neutropenia in the third dose tier. Grade 3/4 mucositis was observed in two of six, two of nine and three of four patients in dose tiers 1, 2 and 3, respectively. Three of these patients (one per dose tier) experienced concomitant grade 3 fatigue. One patient in dose tier 2 had grade 3 nausea–vomiting. Other toxicities were mild or moderate, not exceeding grade 2. Based on the high incidence of grade 3/4 toxicity in the four patients included in the last dose tier, this dose tier was considered to be the MTD. Dose tier number 2, with the chemotherapy recycled at 4 week intervals, is the recommended dose level for future phase II studies.

After completion of the neoadjuvant treatment program and before surgery, all patients underwent a work-up with a thoraco-abdominal CT scan, a gastroscopy and an upper GI series. None of the patients were found to have progressed. However, bidimensionally measurable disease was not available to allow a reliable clinical assessment of tumor response.

All patients underwent a total or subtotal gastrectomy with D2 lymph node resection. No postoperative deaths were observed. One patient suffered an anastomotic leak requiring surgical drainage and prolonged hospital stay. A second patient had a biliary peritonitis secondary to a probable duodenal leak, managed conservatively. Both patients recovered fully thereafter. Three patients were found during surgery to have minimal peritoneal carcinomatosis (patients 7, 12 and 18). Pathological examination of the resected specimens showed one pCR and eight pPRs.

Overall survival and relapse-free survival curves are presented in Figures 2 and 3, respectively, with a median follow up of 81 months. Two- and 3-year relapse-free survival rates were 57% (95% CI 35% to 77%) and 50% (95% CI 26% to 71%), respect-

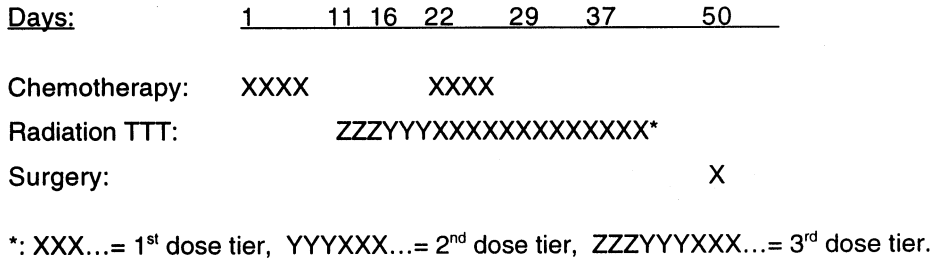

Figure 1. Treatment scheme.

Table 1. Results summary

Patient number	Dose tier	Maximal hemato-toxicity	Grade 3/4 non-hematological toxicity	TTT delays	Pathological response	First site of relapse	Outcome (months) cut off : 30.09.2001
1	1	4	Mucositis + fatigue	–	pPR	–	NED (84+)
2	1	4	–	–	pPR	–	NED (83+)
3	1	3	–	–	NR	–	NED (81+)
4	1	4	–	–	pCR	–	NED (81+)
5	1	4	Mucositis	1 week	NR	Peritoneum	DOD (12)
6	1	3	–	–	NR	Retroperitoneum + peritoneum	DOD (59)
7	2	4	–	1 week	NR	Peritoneum	DOD (6)
8	2	3	Mucositis + fatigue	1 week	pPR	–	DOOC (42)
9	2	3	–	1 week	pPR	–	NED (71+)
10	2	4	–	1 week	NR	Peritoneum	DOD (17)
11	2	2	–	–	pPR	Retroperitoneum + liver	DOD (24)
12	2	3	Nausea/vomiting	2 weeks	NR	Peritoneum	DOD (29)
13	2	3	–	–	NR	–	NED (53+)
14	2	4	Mucositis	1 week	NR	Peritoneum	DOD (27)
15	2	3	–	1 week	NR	Anastomosis	DOD (39)
16	3	4	Mucositis + fatigue	2nd cycle refusal	pPR	–	NED (47+)
17	3	4	Mucositis	3 weeks	pPR	–	NED (37+)
18	3	2	–	–	NR	Peritoneum	DOD (13)
19	3	3	Mucositis	1 week	pPR	Peritoneum	AWD (28+)

pPR, partial pathological response; NR, pathological 'No Response' when criteria for pPR are not reached (see text); pCR, complete pathological response; TTT, treatment; NED, no evidence of disease; DOD, dead of disease; DOOC, dead of other cause; AWD, alive with disease.

ively, while the overall 2- and 3-year survival rates were 71% (95% CI 47% to 87%) and 59% (95% CI 36% to 79%). Ten patients have died, nine of them after progression of their gastric cancer. One patient died of acute erythroleukemia (AML M6) three and a half years after inclusion in the study, without evidence of gastric cancer relapse. The sites of relapse or residual disease after gastrectomy are detailed in Table 1.

Discussion

Despite the small number of patients enrolled in the present study, its results indicate that radiotherapy can be safely combined with neoadjuvant chemotherapy in locally-advanced gastric cancer patients. Furthermore, neoadjuvant chemoradiation seems to be effective, as suggested by the number of pathological reponses observed. This approach may thus be able to decrease the high rate of locoregional relapse typically observed in this unfavorable patient population.

The main aim of this study was to determine the dose of radiotherapy that could be added to a relatively standard drug combination in gastric cancer. The rationale was that potential improvement in locoregional control by the addition of radiation therapy should not be obtained to the detriment of systemic therapy. Therefore, a conventional chemotherapy regimen for gastric cancer was chosen and given at a fixed standard dosage. The radiation was then escalated, indicating that 38.4 Gy could be combined safely with this regimen. However, all but two patients treated at this dose level had their second cycle of chemotherapy delayed by 1 week (2 weeks in one case). This is the reason why dose tier 2, with the chemotherapy recycled at 4 week intervals, is the recommended treatment program in this setting. Dose tier 3 was considered the MTD, since all patients but one endured significant toxicity and had prolonged delays in chemotherapy.

This relatively intensive neoadjuvant treatment program did not seem to increase operative risks significantly. One of the 19 patients presented with a serious complication requiring re-operation, but no fatality was recorded. One can only speculate whether this anastomotic leak was due to the neoadjuvant chemo-radiation, or whether it just occurred by chance. The fistula took several weeks to heal, and irradiation may have been partly responsible for this delay. Surgery in an irradiated field can be more difficult because of tissue fragility, with compromised anastomotic healing and a higher risk of anastomotic leakage. During our study, the surgeon and the radiation oncologist maintained close contact, and the planning of radiation fields regularly took into account the surgeon's input. In addition, the operative approach was modified according to the neoadjuvant therapy,

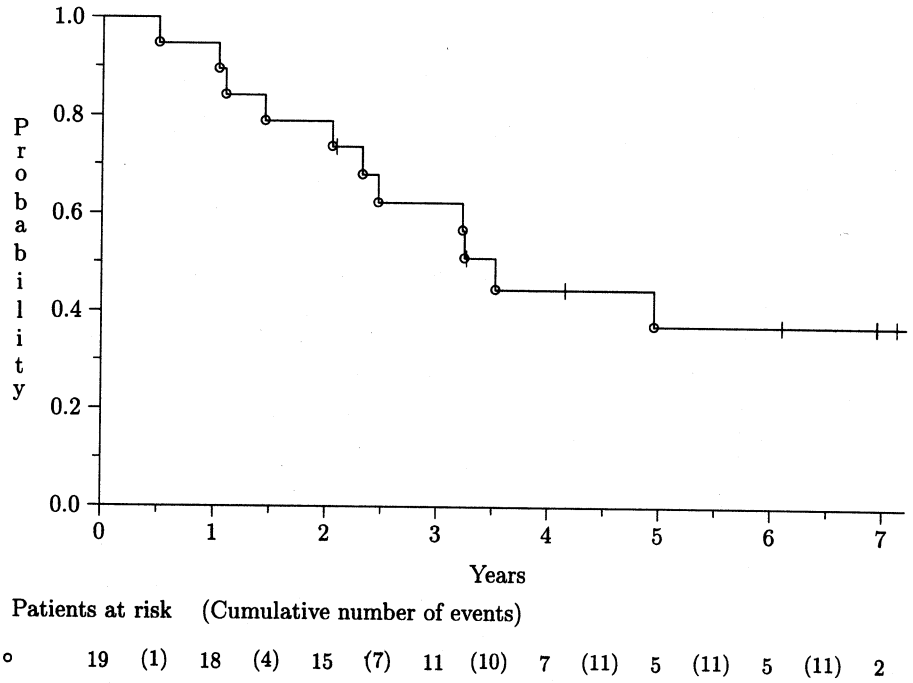

Figure 2. Overall survival.

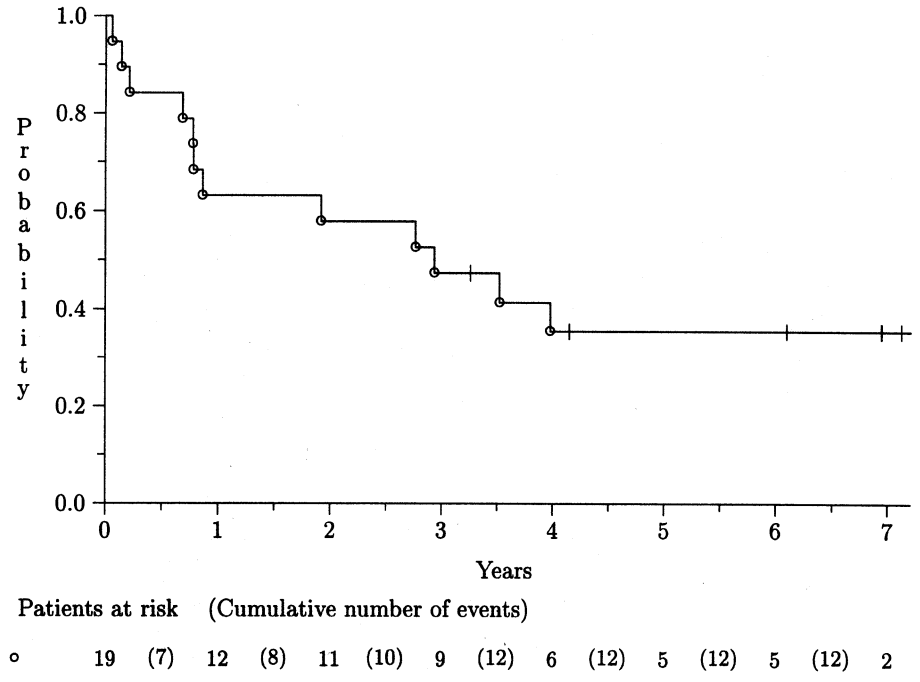

Figure 3. Event-free survival.

aiming to locate the anastomosis in a non-irradiated zone. In two cases of proximal tumor, thoracotomy was needed. In three other patients, distal gastrectomy had to be converted to total gastric resection.

Several encouraging conclusions can be drawn from these results regarding the efficacy of this treatment program. Nine out of 19 patients presented with major responses to preoperative therapy. It is of interest to note that seven of them are still relapse-free 37+ to 84+ months after inclusion. This contrasts with the 10 patients considered as non-responders or poor responders to the neoadjuvant treatment program, only two of whom are still relapse-free 55+ and 81+ months later. In esophageal carcinoma, it is known that pCR or near pCR to neoadjuvant therapy indicates a good prognosis [23, 24]. The observation that most sur-

vivors in our study were found among responders leads us to suspect that this might also be valid for gastric cancer, as already reported by others [22].

The median disease-free survival of 35.5 months (CI 95% 9.5 months to not reached), and the median survival of 42.5 months (CI 95% 18 months to not reached) are of interest, considering the locoregionally-advanced status of the patients enrolled. However, this is certainly not conclusive because of the small size of the population considered, which explains the very wide 95% confidence intervals observed. Among the other encouraging features, we can note that only one of the relapsing patients did so locally (patient number 15). This contrasts significantly with the high locoregional relapse rate reported by other authors, leading us to believe that this treatment program is effective for locoregional disease control [7, 8].

On the downside, however, it is of concern that the great majority of the relapsing patients did so in the peritoneum, and that for seven of them it was the sole site of clinically-detectable disease at first relapse. This finding implies that the impact of this treatment program is mostly locoregional. We are still in need of more effective chemotherapeutic regimens to decrease the incidence of distant relapse, especially in the peritoneal cavity, which seems to be a very common target for recurrence in locoregionally advanced disease [25]. Promising newer chemotherapeutic regimens incorporating taxanes or topoisomerase I inhibitors may be worth testing in this setting [26–30].

In conclusion, we show that radiation therapy can be safely combined to 5-FU–cisplatin in a neoadjuvant setting in locoregionally advanced gastric cancer, and that it seems to have an encouraging impact on the incidence of local relapse. However, distant failures, especially in the peritoneal cavity, remain a major issue, underscoring the need for more effective systemic therapy in this disease.

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References

1. Parkin DM. Epidemiology of cancer: global patterns and trends. Toxicol Lett 1998; 102–103: 227–234.
2. Hansson LE, Sparen P, Nyren O. Survival in stomach cancer is improving: results of a nationwide population-based Swedish study. Ann Surg 1999; 230: 162–169.
3. Hundahl SA, Menck HR, Mansour EG et al. The National Cancer Data Base report on gastric carcinoma. Cancer 1997; 80: 2333–2341.
4. Shimada K, Ajani JA. Adjuvant therapy for gastric carcinoma patients in the past 15 years: a review of western and oriental trials. Cancer 1999; 86: 1657–1668.
5. Braga M, Zuliani W, Foppa L et al. Food intake and nutritional status after total gastrectomy: results of a nutritional follow-up. Br J Surg 1988; 75: 477–480.
6. Hebuterne X, Vaillon F, Peroux JL et al. Correction of malnutrition following gastrectomy with cyclic enteral nutrition. Dig Dis Sci 1999; 44: 1875–1882.
7. Gunderson LL, Sosin H. 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 1982; 8: 1–11.
8. Landry J, Tepper JE, Wood WC et al. Patterns of failure following curative resection of gastric carcinoma. Int J Radiat Oncol Biol Phys 1990; 19: 1357–1362.
9. Wisbeck WM, Becher EM, Russell AH. Adenocarcinoma of the stomach: autopsy observations with therapeutic implications for the radiation oncologist. Radiother Oncol 1986; 7: 13–18.
10. Dent DM, Werner ID, Novis B et al. Prospective randomized trial of combined oncological therapy for gastric carcinoma. Cancer 1979; 44: 385–391.
11. Hallissey MT, Dunn JA, Ward LC et al. The second British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: five-year follow-up. Lancet 1994; 343: 1309–1312.
12. Shchepotin IB, Evans SR, Chorny V et al. Intensive preoperative radiotherapy with local hyperthermia for the treatment of gastric carcinoma. Surg Oncol 1994; 3: 37–44.
13. Mahadevan A, Carey D. The role of radiotherapy in the surgical management of gastrointestinal cancer. Surg Oncol 1997; 6: 201–208.
14. Zhang ZX, Gu XZ, Yin WB et al. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of gastric cardia (AGC): report on 370 patients. Int J Radiat Oncol Biol Phys 1998; 42: 929–934.
15. Skoropad VY, Berdov BA, Mardynski YS et al. A prospective, randomized trial of pre-operative and intraoperative radiotherapy versus surgery alone in resectable gastric cancer. Eur J Surg Oncol 2000; 26: 773–779.
16. Bleiberg H, Jeziorsky K, Hendlisz A et al. Role of radiotherapy in cancers of the stomach. Bull Cancer 1997; 84: 913–916.
17. Macdonald JS, Smalley SR, Benedetti J et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001; 345: 725–730.
18. Wilke H, Preusser P, Fink U et al. Preoperative chemotherapy in locally advanced and nonresectable gastric cancer: a phase II study with etoposide, doxorubicin and cisplatin. J Clin Oncol 1989; 7: 1318–1326.
19. Rougier P, Mahjoubi M, Lasser P et al. Neoadjuvant chemotherapy in locally advanced gastric carcinoma—a phase II trial with combined continuous intravenous 5-fluorouracil and bolus cisplatinum. Eur J Cancer 1994; 30A: 1269–1275.
20. Ajani JA, Mayer RJ, Ota DM et al. Preoperative and postoperative combination chemotherapy for potentially resectable gastric carcinoma. J Natl Cancer Inst 1993; 85: 1839–1844.
21. Minsky BD. Carcinoma of the esophagus. Part 2: adjuvant therapy. Oncology 1999; 13: 1415–1427.
22. Lowy AM, Mansfield PF, Leach SD et al. Response to neoadjuvant chemotherapy best predicts survival after curative resection of gastric cancer. Ann Surg 1999; 229: 303–308.
23. Law S, Fok M, Chow S et al. Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus: a prospective randomized trial. J Thorac Cardiovasc Surg 1997; 114: 210–217.
24. Forastiere AA, Heitmiller RF, Lee DJ et al. Intensive chemoradiation followed by esophagectomy for squamous cell and adenocarcinoma of the esophagus. Cancer J Sci Am 1997; 3: 144–152.
25. Otsuji E, Yamaguchi T, Sawai K et al. Regional lymph node metastasis as a predictor of peritoneal carcinomatosis in patients with Borrmann type IV gastric carcinoma. Am J Gastroenterol 1999; 94: 434–437.
26. Roth AD, Maibach R, Martinelli G et al. Docetaxel (Taxotere)-cisplatin (TC): an effective drug combination in gastric carcinoma. Swiss Group for Clinical Cancer Research (SAKK), and the European Institute of Oncology (EIO). Ann Oncol 2000; 11: 301–306.

27. Roth AD, Maibach R, Fazio N et al. 5FU as protracted continuous IV infusion (5FUpiv) can be added to full dose Taxotere-cisplatin (TC) in advanced gastric carcinoma (AGC). Eur J Cancer 1999; 35 (Suppl. 4): S139–S130.
28. Bleiberg H. CPT-11 in gastrointestinal cancer. Eur J Cancer 1999; 35: 371–379.
29. Pozzo C, Szanto J, Peschel C et al. Irinotecan (Iri) in combination with CDDP (C) or with 5-FU and folinic acid (FU/FA) is active in patients (pts) with avanced gastric or gastroesophageal junction adenocarcinoma (AGC). Ann Oncol 2000; 11 (Suppl 4): 63–60.
30. Ajani JA. Current status of therapy for advanced gastric carcinoma. Oncology 1998; 12: 99–102.