Early postoperative chemotherapy following noncurative resection for patients with advanced gastric cancer

Y. Maehara1, K. Sugimachi1, M. Akagi2, T. Kakegawa3, H. Shimazu4 & M. Tomita5

1Department of Surgery II, Faculty of Medicine, Kyushu University, Fukuoka; 2Department of Surgery II, Faculty of Medicine, Kumamoto University, Kumamoto; 3Department of Surgery I, Faculty of Medicine, Karume University, Karume; 4Department of Surgery I, Faculty of Medicine, Kagoshima University, Kagoshima; 5Department of Surgery I, Faculty of Medicine, Nagasaki University, Nagasaki, Japan.

Summary We studied the effect of early postoperative chemotherapy, including 5-fluorouracil (5-FU) for 5 days for patients with gastric cancer following noncurative resection. The study was prospectively randomised and controlled, and 162 (87.1%) of 186 were eligible candidates for statistical assessment. Patients randomised to group A received therapy that is used widely to treat patients with gastric cancer in Japan: mitomycin C (MMC), OK-432, UFT and PSK. Patients randomised to group B received the same drugs given to group A plus 5-FU bolus injections for 5 days, beginning on postoperative day 2. There were no differences in prognostic factors and doses of the drugs prescribed, except for 5-FU. There was no difference in the toxicity rate between the groups. Generalised Wilcoxon test revealed a P value of 0.169, and the 50% survival rate improved 1.4-fold in patients with gastric cancer treated with early postoperative chemotherapy of MMC, OK-432 plus 5-FU injection.

The early detection of gastric cancer by upper G.I. series, endoscopy, extensive lymph node dissection (Kodama et al., 1981; Boku et al., 1989) and postoperative adjuvant chemotherapy (Kano et al., 1981; Gastrointestinal Tumor Study Group, 1982; Inokuchi et al., 1984) have led to a longer survival time for approximately 60% of curatively resected patients. Patients with a far advanced cancer are usually treated by palliative resection. As tumour foci remain in these patients, antitumour drugs are required to suppress tumour growth. Kano et al. (1982) reported that postoperative long-term cancer chemotherapy (PLCC) with a combination of mitomycin C (MMC), 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur) and PSK led to life-prolongation for patients with noncuratively resected stage IV gastric cancer, however, the clinical effects are not satisfactory. The doubling time of tumour cells in a small population focus is often shorter than in a larger population focus (Schabel, 1975; Gunduz et al., 1979), hence, tumour foci remaining after a noncurative resection are expected to be more sensitive to cell-cycle specific drugs. For these reasons, intensive remission-induction followed by maintenance therapy should be given due consideration. 5-Fluorouracil (5-FU) administration has been prescribed for 5 days for the patients with advanced gastric cancer, in combination with MMC and other drugs (Haller, 1988). In 162 patients, we examined the effect of adding 5-FU bolus injections for 5 days during induction therapy with MMC and OK-432 (Maehara et al., 1990a).

Materials and methods

Patients

All patients included in the prospectively randomised and controlled trial underwent a macroscopic noncurative gastric resection. The 186 patients were entered into this study between July 1986 and June 1988. The patients were assigned, at random, to either group A or B on the day of operation. The protocol (Figure 1) was as follows. The inductive regimen for group A included mitomycin C (MMC) (Inokuchi et al., 1984) 20 mg intravenous (i.v.) injection on the day of operation, 10 mg on postoperative day 1, and 10 mg every month thereafter for 1 year. and OK-432 (Uchida & Hoshino, 1980), 20 KE intraperitoneal (i.p.) injection on the day of the operation and 5 KE i.ntradermal (i.d.) injections on postoperative days 3, 5, 7, 9, 11. 1 KE of OK-432 is equivalent to a 0.1 mg lyophilised preparation of heat-killed Streptococeus hemolyticus. For maintenance therapy, group A received UFT (Ota et al., 1988; Maehara et al., 1989; Maehara et al., 1990b), a combination of tegafur and uracil in a molar ratio of 1:4, 400 mg orally daily, and PSK (Tsukagoshi et al., 1984), 3 g orally daily beginning 2 weeks after the operation. For 1 year. PSK is a protein-bound preparation, extracted from Coriolus versicolor which belongs to Basidiomycetes. The regimen for group B included regimen A plus 5-FU 250 mg i.v. bolus injections on postoperative days 2–6. Patients were selected on the basis of: (1) histological diagnosis of gastric cancer; (2) macroscopic diagnosis as a noncurative case, on completion of surgical procedures; (3) age less than 76 years; (4) performance status grade of 0–3; (5) no evident synchronous or metachronous double cancer; (6) adequate organ system function (leucocytes >4,000 mm−3, platelets >100,000 mm−3, GOT and GPT <100 U). Pathological diagnosis and classifications were evaluated according to the General Rules for the Gastric Cancer Study in Surgery and Pathology in Japan (Japanese Research Society for Gastric Cancer, 1981).
Table I  Comparison of clinicopathological characteristics between patients in groups A and B

| Factor                              | Category     | Group A (n = 82) | Group B (n = 80) | P value |
|-------------------------------------|--------------|------------------|------------------|---------|
| Sex                                 | Male         | 53               | 55               | NS      |
|                                     | Female       | 29               | 25               |         |
| Age                                 |              | 60.2 ± 11.3*     | 59.1 ± 11.6*     | NS      |
| Location of tumour                  | Upper (C)    | 18               | 19               | NS      |
|                                     | Middle (M)   | 31               | 32               |         |
|                                     | Lower (A)    | 33               | 29               |         |
| Tumour maximal diameter (cm)        |              | 8.4 ± 3.8*       | 8.6 ± 3.5*       | NS      |
| Macroscopic appearance              | type 1       | 0                | 2                | NS      |
|                                     | type 2       | 19               | 15               |         |
|                                     | type 3       | 33               | 35               |         |
|                                     | type 4       | 22               | 21               |         |
|                                     | type 5       | 4                | 4                |         |
|                                     | Unknownb     | 4                | 3                |         |
| Macroscopic stage                   | III          | 4                | 5                | NS      |
|                                     | IV           | 78               | 75               |         |
| Histological stage                  | II           | 0                | 3                | NS      |
|                                     | III          | 7                | 5                |         |
|                                     | IV           | 74               | 69               |         |
|                                     | Unknownb     | 1                | 3                |         |
| Macroscopic curability              | RNC          | 13               | 18               | NS      |
|                                     | ANC          | 69               | 62               |         |
| Histological curability             | RC           | 4                | 3                | NS      |
|                                     | RNC          | 7                | 13               |         |
|                                     | ANC          | 69               | 60               |         |
|                                     | Unknownb     | 2                | 4                |         |
| Macroscopic cancer-infiltration at  |              | 69               | 69               | NS      |
| the resection margin                | (–)          | 7                | 8                |         |
|                                     | (+)          | 6                | 3                |         |
| Histological cancer-infiltration at |              | 60               | 52               | NS      |
| the resection margin                | (–)          | 18               | 20               |         |
|                                     | (+)          | 4                | 8                |         |
| Serosal invasion                    | S0           | 2                | 2                | NS      |
|                                     | S1           | 2                | 2                |         |
|                                     | S2           | 45               | 33               |         |
|                                     | S3           | 33               | 42               |         |
|                                     | Unknownb     | 0                | 1                |         |
| Histological depth of invasion     | No serosal   | 8                | 16               | NS      |
|                                     | invasion     | 54               | 39               |         |
|                                     | Invasion into|                  |                  |         |
|                                     | neighbouring |                  |                  |         |
|                                     | structures   |                  |                  |         |
|                                     | Unknownb     | 8                | 8                |         |
| Macroscopic lymph node metastasis   | N0           | 0                | 3                | NS      |
|                                     | N1           | 9                | 9                |         |
|                                     | N2           | 31               | 19               |         |
|                                     | N3           | 19               | 24               |         |
|                                     | N4           | 23               | 21               |         |
|                                     | Unknownb     | 0                | 4                |         |
| Histological lymph node metastasis | n0           | 1                | 2                | NS      |
|                                     | n1           | 22               | 22               |         |
|                                     | n2           | 29               | 17               |         |
|                                     | n3           | 11               | 15               |         |
|                                     | n4           | 8                | 11               |         |
|                                     | Unknownb     | 11               | 13               |         |
| Peritoneal dissemination            | P(–)         | 37               | 46               | NS      |
|                                     | P(+)         | 45               | 34               |         |
| Liver metastasis                    | H(–)         | 63               | 64               | NS      |
|                                     | H(+)         | 19               | 16               |         |
| Lymph node dissection               | R0           | 15               | 11               | NS      |
|                                     | R1           | 19               | 15               |         |
|                                     | R2           | 38               | 31               |         |
|                                     | R3           | 6                | 8                |         |
|                                     | Unknownb     | 4                | 2                |         |
| Gastrectomy                         | Total        | 43               | 42               | NS      |
|                                     | Partial      | 39               | 38               |         |

NS, no significant difference; RC, relative curative; RNC, relative non-curative; ANC, absolute non-curative. *Mean ± standard deviation. **Unknown cases were excluded from the statistical analysis.
Statistical analysis

Data were analysed using the chi-square test, Mann-Whitney U-test and Student’s t-test. Survival curves were calculated by the method of Kaplan and Meier. Comparisons were made by the generalised Wilcoxon test. A P value of less than 0.05 was considered to be significant.

Results

In the 186 patients, entered into this study, 19 (10.2%) had to be excluded: four had double cancers, eight no surgical resection, two over 76 years of age and five macroscopic cutaneous resections, and five (2.7%) dropped out in the course of treatment; two no injection of any drug and three in group A who were inadequately given 5-FU injections. The patients were followed in the outpatient department at 2 week intervals. Attention was directed to their general condition, bone marrow function, liver function and serum carcinoembryonic antigen levels (Maehara et al., 1990a), and at 6 month intervals imagings were taken.

Clinicopathological features

Clinicopathological details on the 162 eligible cases (87.1%): 82 in group A; 80 in group B, are shown in Table I. There were no significant differences between the groups with regard to the distribution of prognostic factors. With respect to surgical procedures: gastric resection and lymph node dissection, there were no differences between the groups. The clinicopathological factors related to palliative resection are shown in Table II. There was no difference between them.

Doses of drugs

There was no difference in the dose of each drug between groups A and B, as shown in Table III.

Survival rates for patients in groups A and B

Figure 2 shows the survival curves of 82 patients in group A and 80 in group B. Generalised Wilcoxon test of the two survival patterns revealed a P value of 0.196. The 50% survival was 8.9 months for those in Group A and 12.9 months for those in group B. The 1-year survival rate was 35.5% for group A and 49.0% for group B and the 2-year survival rate was 19.9% for group A and 28.1% for group B.

Table II Comparison of factors involved in noncurative resection between patients in groups A and B

| Factor                        | Group A (n = 82) | Group B (n = 80) |
|-------------------------------|-----------------|-----------------|
| Serosal invasion              | 78 (95.1%)      | 75 (93.8%)      |
| Lymph node metastasis         | 55 (67.1%)      | 50 (62.5%)      |
| OW (+)                        | 3 (3.7%)        | 6 (7.5%)        |
| AW(+)                         | 6 (7.3%)        | 4 (5.0%)        |
| Liver metastasis              | 19 (23.2%)      | 16 (20.0%)      |
| Peritoneal dissemination      | 45 (54.9%)      | 34 (42.5%)      |

OW(+) : macroscopic cancer infiltration at the oral margin. AW(+) : macroscopic cancer infiltration at the anal margin.

Table III Doses of drugs

| Drug              | Group A | Group B |
|-------------------|---------|---------|
| MMC (mg)          | 61.0 ± 32.4* | 54.8 ± 35.0 |
| OK-432 (KE)       | 44.2 ± 16.9 | 42.9 ± 10.2 |
| 5-FU (mg)         | 1186.6 ± 226.5 |
| UFT (g)           | 63.1 ± 54.9 | 62.5 ± 51.7 |
| PSK (g)           | 534.6 ± 424.6 | 535.9 ± 412.0 |

MMC: mitomycin C. 5-FU: 5-fluorouracil. UFT: a combined oral preparation of 1,12,11-tetrahydrofuril)-5-fluorouracil and uracil in a molar ratio of 1:4. OK-432 and PSK: immunomodulators. *Mean ± standard deviation.

Figure 2 Survival curves for patients of groups A and B. There were 82 patients in group A (●) and 80 patients in group B (○).

Table IV Toxocities

| Toxicity* | Group A | Group B |
|-----------|---------|---------|
| Leukopenia (<3,000 cells mm−3) | 24.4 | 15.0 |
| Anaemia (<3 x 106 cells mm−3) | 14.6 | 15.0 |
| Thrombocytopenia (<1 x 106 cells mm−3) | 13.4 | 11.3 |
| Liver dysfunction: GOT (>100 U) | 9.8 | 11.3 |
| Anorexia | 15.9 | 25.0 |
| Skin pigmentation | 1.2 | 0.0 |
| Nausea. Vomiting | 12.2 | 11.3 |
| Diarrhea | 4.9 | 12.5 |

*Values = % of patients fulfilling each criterion for toxicity.

Toxicity

Table IV summarises factors related to toxicity. Various side effects occurred in each group, as did hematologic toxicities. The rates of anorexia and diarrhea were higher in treatment group B, but the difference could not be supported statistically. There was no difference between the treatment groups with respect to other side effects.

Discussion

MMC and or fluorinated pyrimidines are prescribed for patients undergoing resection for gastric cancer. These drugs can be given alone and in combination with other antitumour drugs (Kano et al., 1981; Inokuchi et al., 1984). A delay in postoperative treatment can lead to negative results (Higgins et al., 1983; Engstrom et al., 1985). Fielding et al. (1983) found no positive effects of adjuvant chemotherapy with MMC plus 5-FU, but survival time was prolonged when treatment was begun within 1 month. Douglass (1985) reported that postoperative chemotherapy should be initiated at the time of surgical resection. As tumour cells remaining after noncurative resection may grow rapidly in the postoperative period (Schabel, 1975; Gunduz et al., 1979), the potential to control the remaining tumour foci is reduced significantly by delaying chemotherapy further in the postoperative period. The PLCC regimen, which consists of intermittent administration of MMC and long-term continuous administration of tegafur and PSK, has lengthened the survival time of patients with gastric cancer following noncurative resection (Kano et al., 1982). We found that the combination chemotherapy of MMC, tegafur plus PSK improves the 15-year survival of patients with advanced gastric cancer (Maehara et al., 1990c). In an attempt to improve survival by initiating aggressive chemotherapy early, 5-FU bolus injections were added to the chemotherapy regimen. As UFT is more effective than tegafur for patients with stage IV gastric cancer (Maehara et al., 1990b), we prescribed UFT...
and PSK for 1 year, for both groups. 5-FU has been prescribed for 5 days, in combination with other drugs to treat patients with advanced gastric cancer (Gastrointestinal Tumor Study Group, 1988). The rate of myelotoxicity of 5-FU is lower in those treated with continuous infusion, than in those given a bolus injection, in cases of high dose administration (Seifert et al., 1975; Fraile et al., 1980). An adequate anastomotic healing has been ensured. We prescribed a bolus injection of 250 mg of 5-FU for 5 days. The incidence of side effects did not increase in the group B, by adding 5-FU infusion to the same regimen given to group A. This induction chemotherapy with MMC and 5-FU (MF) was safe for the patients. The 1 year survival rate was 35.5% in group A, for whom the drug protocol was similar to that of PLCC (Kano et al., 1982), and the rate was 49.0% in group B on the aggressive chemotherapy.

Although there was no definite statistical difference, the 50% survival rate improved 1.4-fold in cases of aggressive chemotherapy, that is when 5-FU injection was added in the very early postoperative period. Retrospective analysis showed that this protocol is effective for patients with gastric cancer of the differentiated, but not for the undifferentiated type. A prospective study based on the histopathology is in progress.

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