Int J Clin Oncol (1998) 3:370–373

ORIGINAL ARTICLE

Minoru Mukai · Shinroku Morita

Phase II study of combination therapy of radiation and local administration of OK-432 for esophageal cancer

Received: October 14, 1997 / Accepted: May 29, 1998

Abstract

Background. From 1993 to 1996, 38 patients (32 men and 6 women) with T1-4NxM0 esophageal cancer (International Union Against Cancer [UICC], 1987) entered into a phase II study of combination therapy of radiation and local administration of the biological resporse modifier, OK-432. The average age of the patients was 64 years. The average tumor length was 7.9 cm. Seven patients were T1; 12, T2-3; and 19, T4.

Methods. OK-432 (0.5 mg) was administered endoscopically around the cancerous lesion at the beginning of radiotherapy, and the same dose of OK-432 was given in the same manner 2 weeks later. X-ray irradiation was given at a daily dose of 1.6–1.8 Gy, five fractions a week. The mean total dose was 62 Gy.

Results. Complete response (CR) was achieved in 23 of the 38 patients (60.5%) and partial response (PR) was achieved in the remaining 15 patients. The 3-year cause-specific survival rate was 39.6% (overall, 29.4%). The 3-year survival rates of CR and PR patients were 74%, and 0.0%, respectively, and the 2-year survival rate of PR patients was 7.8%, a significant difference ($P < 0.001$). The 3-year survival rates of the T1-3 and T4 patients (UICC, 1987) were 73.0% and 14.0%, respectively, a significant difference ($P < 0.001$). The 3-year survival rates of the 9 patients with tumors less than 5 cm in length, and of the 18 patients with tumors 5–10 cm long were 80% and 54.2%, respectively. In the 11 patients with tumors more than 10 cm in length, the 2-year survival rate was 9.0%. The 3-year survival rate of the 18 patients with tumors less than 7 cm was 92.3%, and the 2-year survival rate of the 20 patients with tumors over 7 cm long was 16.7%, a significant difference ($P < 0.001$). All 38 patients were discharged in good condition and were able to take food orally.

Conclusion. This combination therapy could contribute not only to improving the survival rate, but also to improving the patients' quality of life.

Key words Esophageal cancer · Combination therapy · Radiation · OK-432

Introduction

Despite advances in surgical techniques, radiation procedures and chemotherapy, the prognosis for patients with esophageal cancer is still very poor. We have developed a combination therapy of radiation and local administration of OK-432 (Picibanil; Chugai Pharmaceutical Tokyo, Japan), a heat- and penicillin-treated lyophilized powder preparation of *Streptococcus pyogenes* A3 that acts as a biological response modifier, affecting the immure system. We employed this Combination therapy in a phase I/II study for patients with esophageal cancer between 1987 and 1992, and reported the results of the study that showed improvement in both the local contral rate and the 5-year survival rate without severe toxicity, except for high fever. The details of OK-432 have been described elswhere.[1,2] However, there was transient exacerbation of brain infarction symptoms in 2 patients (aged 78 and 83 years, respectively) 3 days after the administration of 1 mg of OK-432. Therefore, we examined blood coagulation factors in 20 patients after that study and found that the level of plasma fibrin/fibrinogen degradation products (FDP) increased to more than 40 μg/ml in 3 of ten patients 3 days after they were injected with 1.0 mg of OK-432. The level of plasma FDP returned to normal after 2 weeks at most. In the 10 patients given 0.5 mg of OK-432, there was no increase in FDP level after the injection of OK-432.[3]

M. Mukai[1] (✉) · S. Morita
Division of Radiation Medicine, National Institute of Radiological Sciences, 4-9 Anagawa 4-chome, Inage-ku, Chiba 263-8555, Japan

Present address:
[1] Kamogawa City Hospital, 233 Miyayama, Kamogawa, Chiba 296-0112, Japan
Tel. +81-470-97-1221; Fax +81-470-97-0157

According to the data obtained from that study, we began a phase II study in 1993 to confirm the efficacy of the combined treatment with a decreased dose of OK-432 in terms of effect on both T classification, and tumor length, in patients with esophageal cancer. We report here the local control rate and 3-year survival rate in this study.

Patients and methods

From 1993 to 1996, 38 patients with T1-4NxM0 (International Union Against Cancer, 1987) esophageal cancer were entered into this study. All had biopsy-proven squamous cell carcinoma and all were aged less than 80 years. Twenty patients were referred to us as locally advanced inoperable cases. Fourteen patients were inoperable because of other diseases. Four patients were operable but refused surgery. Informed consent was obtained from the patients and thier families. The clinical characteristics of the patients are shown in Table 1. The in average age was 64 years (range, 36–79 years). There were 32 men and 6 women. According to the T classification, 19 (50.0%) were T4. The mean tumor length was 7.9 cm (range, 2.0–16.5 cm), and 11 of the 38 patients (28.9%) had tumors more than 10 cm in length. Regarding the location of tumors, 20 (52.6%) had tumors in the middle thoracic portion of the esophagus.

OK-432 (0.5 mg) was dissolved in 5 ml of 0.5% xylocaine and administered endoscopically into the normal submucosal tissue, at five to ten points as closely as possible around the cancerous lesion, with an injection needle (NM-22L; Olympus, Tokyo, Japan) at the beginning of the radiotherapy course. Two weeks later, the patients received a second dose of 0.5 mg OK-432 given in the same manner. If the tumor completely obstructed the esophagus, OK-432 was given at proximal sites only.

X-ray (10-MV) irradiation was given at a daily dose of 1.8 Gy to T1-3 patients and at 1.6 Gy to T4 patients; five fractions a week were given, up to an initial total dose of 43.2 Gy, from two opposing fields that also covered the second group of regional lymph nodes (according to the Japanese guidelines on carcinoma of the esophagus[4]). The radiation field size was usually 8 cm in width and 14–22 cm (mean, 18 cm) in length. The lesions were then irradiated to a final total dose of 52.2–64.8 Gy (mean, 62 Gy), using two oblique shrinkage fields for the main tumors.

The effect of this combination therapy was evaluated by esophagography and fiberscopic examination with biopsy at the end of radiotherapy and 1 month after the end of the radiotherapy. Thereafter, patients were followed-up by esophagogram every month for the first 2 years and every 2 months after 2 years, and by fiberscopic examination and computed tomography every 6 months.

The response criteria were: complete response (CR), total disappearance of the tumor radiologically, endoscopically, and histologically for a minimum of 1 month; partial response (PR), greater than 50% but less than 100% reduction in the tumor volume of every measurable lesion. Statistical significance was determined by the χ^2 test. Survival rate was calculated by the Kaplan-Meier method and statistical significance was evaluated by the log rank test. The median follow-up time was 14 months (range, 3–43 months). The follow-up rate was 100%. The 3-year survival rate is shown with the SE.

Table 1. Clinical characteristics of 38 patients with esophageal cancer treated with combined radiotherapy and OK-432

Category	No. of patients (%)
Age (years)	
30–39	1 (2.6)
40–49	3 (7.9)
50–59	8 (21.1)
60–69	12 (31.6)
70–79	14 (36.8)
Sex	
Male	32 (84.2)
Female	6 (15.8)
T classification (UICC, 1987)	
T1	7 (18.4)
T2	3 (7.9)
T3	9 (23.7)
T4	19 (50.0)
Tumor length (cm)	
<5	9 (23.7)
5–10	18 (47.4)
>10	11 (28.9)
Location	
Cervical	6 (15.8)
Upper	5 (13.2)
Middle	20 (52.6)
Lower	7 (18.4)

UICC, International Union Against Cancer

Results

CR was achieved in 23 of the 38 patients (60.5%), and PR in the remaining 15 (39.5%). The average tumor length of CR patients was 5.8 cm, and that of PR patients 11.1 cm. According to the T classification, we achieved CR in all 10 patients with T1 or T2, in 8 of 9 (88.9%) with T3, and in 5 of 19 (26.3%) with T4. The average tumor length in these three groups was 4.2, 7.2, and 10.1 cm, respectively. Regarding the length of tumors, CR was achieved in 8 of 9 patients (88.9%) with tumors less than 5 cm in length, in 14 of 18 (77.8%) with tumors of 5–10 cm, and in 1 of 11 (9.2%) with tumors longer than 10 cm. When a tumor length of 7 cm was taken as a dividing line, CR was obtain in 17 of 18 patients (94.4%) with tumors less than 7 cm in length, and in 6 of 20 (30.0%) with those over 7 cm. Of the 23 patients with CR 5, (21.7%) had local recurrences within a year.

The 3-year cause-specific and overall survival rates of the 38 patients was 39.6% (SE, 0.098) and 29.4% (SE, 0.085), respectively (Fig. 1). Among CR patients, five have survived for more than 3 years; 4 are tumor-free and 1 has a locally recurrent tumor. Fourteen patients survived for periods of 3–29 months, and 3 had locally recurrent tumors. Four patients died of other diseases.

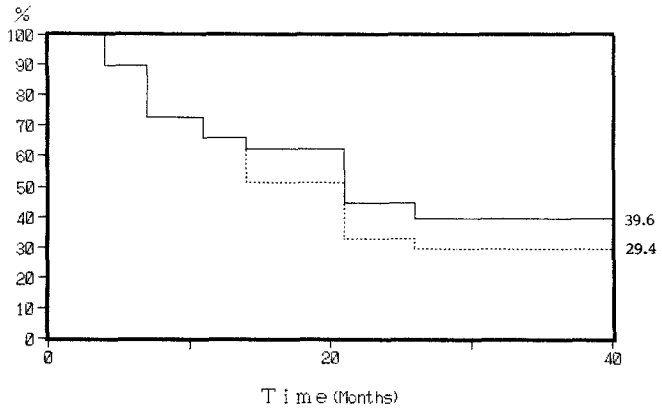

Fig. 1. Three-year cause-specific (—) and overall (...) survival rates for 38 patients with esophageal cancer treated with combined radiotherapy and OK-432. (See text for details)

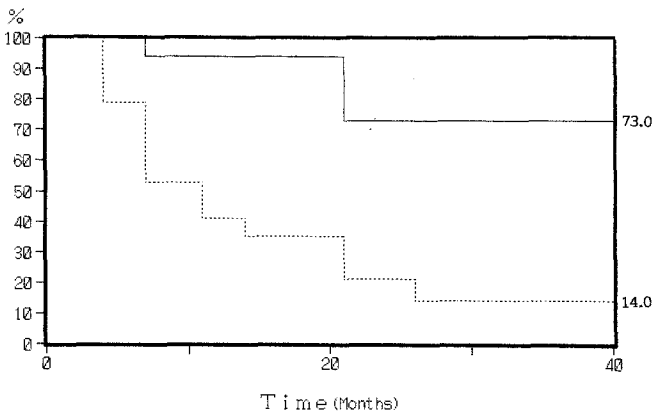

Fig. 3. Three-year cause-specific survival rate according to T classification. — T1-3 (n = 19); ...T4 (n = 19)

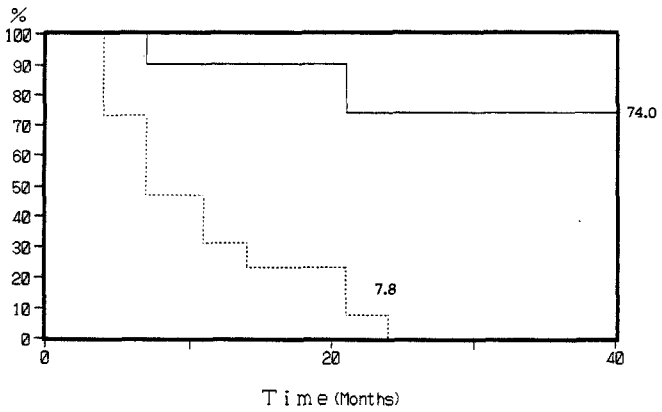

Fig. 2. Three-year cause-specific survival rates according to local response. —, complete response (n = 23);...partial response (n = 15)

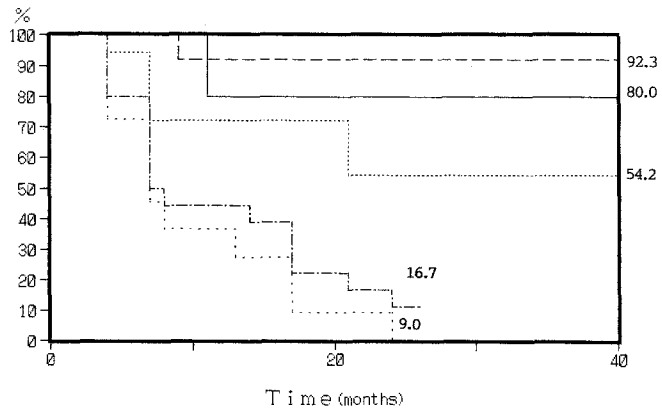

Fig. 4. Three-year cause-specific survival rate according to tumor length. —< 5 cm; ... 5–10 cm; . . > 10 cm; – – 7 cm; –· > 7 cm

The 3-year cause-specific survival rate of the 23 CR patients according to local response was 74% (SE, 0.118) (Fig. 2). No patients with PR survived for more than 3 years, and their 2-year survival rate was 7.8% (SE, 0.074). There was a significant difference (χ^2, 22.690; $P < 0.001$) between CR and PR groups.

In terms of T classification, the 3-year cause-specific survival rate of the 19 patients with T1-3 was 73.0% (SE, 0.138) (T1, 100%; T2-3, 55.0%), and that of the 19 T4 patients was 14.0% (SE, 0.089) (Fig. 3). The difference was significant (χ^2, 11.796; $P < 0.001$). The average tumor length of patients with T1-3 and T4 were 5.6 and 10.1 cm, respectively. Four patients with T1-3 (3 tumor-free, 1 with a tumor) and 1 T4 patient (tumor-free) have survived for more than 3 years.

In terms of tumor length, the 3-year cause-specific survival rate of the 9 patients with tumors less than 5 cm long was 80% (SE, 0.179), and that of the 18 patients with tumors 5–10 cm was 54.2% (SE, 0.136). In the 11 patients with tumors more than 10 cm long, the 2-year survival rate was 9.0% (SE, 0.087) (Fig. 4). There were significant differences between the first and third groups (χ^2, 6.098; $P < 0.05$) and between the second and third groups (χ^2, 6.641; $P < 0.01$). The 3-year survival rate of the 18 patients with tumors less than 7 cm in length was 92.3% (SE, 0.074), and the 2-year survival rate of the 20 patients with tumors more than 7 cm long was 16.7% (SE, 0.272), and the difference was significant (χ^2, 15.321; $P < 0.001$) (Fig. 4).

After the local administration of OK-432, all 38 patients developed a high fever (>38°C), but this was effectively controlled with an antifpyretic. No other side effects were observed during the study.

All 38 patients were discharged in good general condition and were able to take food orally after this combination therapy.

Discussion

This Phase II study was performed to confirm the efficacy of the combination therapy of radiation and local administra-

tion of OK-432, at a dose of 0.5 mg, considered to be an appropriate dose for avoiding the side effects of OK-432, except for fever.

In our pilot phase I/II study[1], the CR rate was 70.0% while in the present study it was 60.5%. However, the CR rates were similar in the two studies when tumors were less than 10 cm in length. When the tumor length was more than 10 cm, the CR rate was higher in the earlier study, but the difference was not significant. The average tumor length was 7.0 cm in the earlier study[1] and 7.9 cm in this study. In terms of T classification, the CR rate in this study was similar to that in the earlier study.[1]

When we compared the 3-year survival rates in this study and our earlier one, the results in terms of both tumor length and T classification were similar. Therefore, we consider that 0.5 mg of OK-432 was an appropriate dose to inject locally in combination with radiation. In addition, the results of this study showed not only a higher local control rate, but also a better survival rate than the results with conventional radiotherapy alone.[5–9]

It is unfortunate that the factor of tumor length was excluded from the TNM classification (UICC, 1987), because tumor length proved to be an important prognostic factor for CR rate and survival rate in both our studies. In particular, the survival rate for patients with tumors less than 7 cm in length in this study was significantly higher. On reviewing the earlier study,[1] we also observed a significantly higher survival rate in the group with tumors shorter than 7 cm.

Studies of the combination of radiation and chemotherapy have reported improvements in 1- and 2-year survival rates compared with rates with radiation alone.[10–12] Herskovic et al.[12] reported the efficacy of chemoradiotherapy compared with radiation alone for esophageal cancer. However, they observed severe and life-threatening side effects in 40% and 20% of the patients, respectively. With our combined therapy, we observed notable improvements in the patients' general condition within 2 weeks after injection of OK-432, (except for transient fever), as dysphagia was alleviated in 2 weeks, except in those patients with an invasive type of carcinoma accompanied by stenosis. In fact, in both studies, we observed tumor shrinkage almost to the extent of PR at the time of the second injection of OK-432. There appears to be a profound difference between chemotherapy and immunotherapy combined with radiation.

Our experimental data for the combination of radiation and local injection of OK-432, in mice, showed the optimal dose of OK-432 to be around 0.4 mg^2. This optimal dose was almost the same as that in humans. Thus, body weight does not appear to be related to dosage quite different from the situation in chemotherapy.

We have also reported the effcet of this combination therapy, with or without mild chemotherapy, in patients with dyspnea caused by obstruction of bronchus or trachea by post-surgical recurrent tumor.[13] Such patients, who have until now received only palliative treatment, can now be treated with curative intent by this combination therapy.

We can say with certainty that both radiotherapy and chemotherapy play a role as attackers as well as suppressors on the human immune system. On the other hand, the local injection of biological response modifiers such as OK-432 play a role as sweepers as well as activators in the human immune system.[1] In other words, the combination therapy of radiation as an attacker and local injection of OK-432 as sweeper is a well-balanced therapy. This concept of a finely balanced therapy for cancer may be a helpful approach in the development of new multidisciplinary treatments.

We are planning a phase III study now, and believe that the combination therapy of radiation and local administration of OK-432 may become the standard treatment for esophageal cancer in the near future.

References

1. Mukai M, Kubota S, Morita S, Akanuma A. (1995) A pilot study of combination therapy of radiation and local administration of OK-432 for esophageal cancer. Cancer 75:2276–2280
2. Mukai M, Ando K, Koike S, Nagao K. (1992) Effect of combination therapy of radiation and local administration of OK-432 on a murine fibrosarcoma (NFSa). Int J Radiat Oncol Biol Phys 22:1047–1050
3. Mukai M, Kubota S, Kato H, et al. (1992) Abstract, The fifth meeting of the Jap Sci Ther Radiol Oncol 64, Sendai
4. Japanese Society for Esophageal Diseases. (1992) Guideline for the clinical and pathological studies on carcinoma of the esophagus. 8th edn. Kanehara, Tokyo
5. Earlam J, Cunha-Melo Jr. (1980) Oesophageal squamous cell carcinoma: II. Critical review of radiotherapy. Br J Surg 67:457–461
6. Newaishy GA, Read GA, Duncun W, Kerr GR. (1982) Results of radical radiotherapy of squamous cell carcinoma of the esophagus. Clin Radiol 33:347–352
7. Nishio H, Morita K, Yamada T, et al. (1992) Clinical results of radiotherapy for M0 esophageal cancer in Japan. Jpn J Soc Cancer Ther 27:912–924
8. Sekiguchi K, Nyunoya K. (1989) Results of radiotherapy for esophageal cancer. Nippon Acta Radiol 49:921–928
9. Matsuki K, Koga K, Nishikawa K, et al. (1988) Results of radiotherapy for esophageal cancer. Nippon Acta Radiol 48:594–601
10. Madhu JJ, Marshall SF, Phyllis AM, et al. (1989) Radiotherapy alone and chemoradiation for nonmetastatic esophageal cancer. A critical review of chemo radiation. Cancer 63:2397–2403
11. LePrise EA, Meunier BC, Etienne P-L, et al. (1995) Sequential chemotherapy and radiation for patients with squamous cell carcinoma of the esophagus. Cancer 75:430–434
12. Herskovic A, Martz K, Al-Sarraf M, et al. (1992) Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. New Engl J Med 326: 1593–1597
13. Mukai M, Morita S, Tsujii H. (1996) Multidisciplinary treatment with OK-432 for tracheal or bronchial invasion by post-surgical esophageal cancer recurrences. Int J Clin Oncol 1:185–189