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**DESIGN AND METHODOLOGY OF META-ANALYSIS TO SHOW THE
EFFICACY OF OK-432**

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For The Japanese Meta-Analysis Group in Cancer in the
Japanese Society of Strategies for Cancer Research and Therapy.

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Introduction

The Japanese Meta-Analysis Group in Cancer was formed in the Japanese Society of Strategies for Cancer Research and Therapy to evaluate the effect of adjuvant therapy of cancer using meta-analysis. Performance of a meta-analysis to review all relevant trials is considered to be one of the best methods with a reasonable chance of detecting small, but worthwhile, clinical benefits.

We previously reported the therapeutic efficacy of oral 5-FU and related agents against curatively resected colorectal cancer (Sakamoto, Hamada *et al.*, 1999).

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Object

OK-432 (Picibanil) is a lyophilized preparation of a low-virulence group A *Streptococcus pyogenes* (Su strain) of human origin that has been inactivated by treatment with benzyl-penicillin and heat. In 1975, The Japanese Ministry of Health and Welfare approved the use of OK-432 as an anticancer agent (Kurokawa, Hattori *et al.*, 1972).

The therapeutic efficacy of immunochemotherapy with OK-432 is reassessed in patients with curatively resected gastric cancer using a meta-analysis based on individual patient data from randomized clinical trials. In this analysis, the administration of OK-432 is systemic, i.e. intra-muscular or intra-dermal.

Materials and Methods

1) Literature search

A search will be performed of the MEDLINE data base and presentations at meeting, and inquiries will be made to industry, for the following items: OK-432 (Picibanil), randomized trial, gastric cancer, published since 1980 with an English or Japanese abstract. The reports found are summarized independently by two of the investigators, using a standardized summary form. The information is provided about the number of trials identified, included, and excluded and the reasons for excluding them (Moher, Cook *et al.*, 1999).

2) Funnel plot

Publication bias is assessed using the funnel plot approach recommended for meta-analysis with few studies. The funnel plot is drawn up with sample size and odds ratios of individual trials (Felson, 1992).

Statistical analysis

a) Primary analysis

The endpoint of interest is the overall 5-year survival on an intent-to-treat basis. To assess the quality of trials, the analysis was carried out for trials using central randomization or envelope-method randomization. Individual patient data were collected from inquiries for trialist of each study. Analyses were performed using SAS procedure, including LIFETEST and PHREG. The relative risk ratios and their 95% confidence

intervals were calculated by Cox's proportional hazard model, with treatment effect being stratified by study

b) Prospective analysis in selected subgroups

Subgroup analysis of individual prognostic factors will be performed. The beneficial effect of immunochemotherapy with OK-432 was particularly relevant in patients with advanced gastric cancer patients. The trials that reported the efficacy were either oral administration (Kyoto research group for digestive organ surgery, 1992) or intratumoral administration (Tanaka, Gouchi *et al.*, 1994) of OK-432 in patients with positive lymph node metastasis. The effect of intra peritoneal administration of OK-432 was reported in malignant ascites (Torisu, Katano *et al.*, 1983), and peritoneal infiltration of immunological effector cells after the preoperative systemic administration of OK-432 was demonstrated (Omote, Fujimoto *et al.*, 1990). Therefore, a subgroup of patients who had advanced tumors with histological tumor invasion to serosal wall could be a good candidate to assess the beneficial effects of OK-432 and will be analyzed in a meta-analysis of systemic OK-432 treatment. The effect of splenectomy (Kyoto research group for digestive organ surgery, 1992) or delayed-type hypersensitivity, e.g. skin test with bacterial antigen (Watanabe, Iwa *et al.*, 1984), must also be examined to improve the evaluation of immunochemotherapy.

Conclusion

Our group has started to analyze the treatment efficacy of adjuvant immunochemotherapy with OK-432 for resected gastric cancer patients. The results of those meta-analysis will be published after the completion of all the planned study.

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