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Phase III double-blind randomized trial of radiation therapy for stage IIIb cervical cancer in combination with low- or high-dose Z-100: Treatment with immunomodulator, more is not better

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Abstract

Background. To evaluate the efficacy of low or high-dose immunomodulator, Z-100, in combination with radiotherapy for cervical cancer.

Methods. Between 1995 and 1999, 221 patients with stage IIIb squamous cell carcinoma of the cervix were randomly assigned to treatment with Z-100 either at 0.2 μg or 40 μg in a double-blind manner in combination with radiotherapy.

Results. The 5-year survival of patients with high-dose and low-dose Z-100 was 41.5% (95% CI: 31.7–51.3%) and 58.2% (95% CI: 48.7–67.7%), respectively, showing a 30% reduction in the death rate (hazard ratio: 0.670 [95% CI: 0.458–0.980], $P = 0.039$). Survival of high-dose group was equivalent to the 4-year survival of the radiotherapy plus hydroxyurea arm (49.7%) of GOG120 study, and that of low-dose group was similar to the survival of the cisplatin-based chemoradiation arm. The progression-free survival was also significantly improved in favor of low-dose group (hazard ratio: 0.667 [95% CI: 0.447–0.997], $P = 0.048$). The survival of low-dose group was similar to the survival of the cisplatin-based chemoradiation arms of the GOG120 study.

Conclusions. Unexpectedly, the survival of patients with advanced cervical cancer treated by lower dose of Z-100 in combination with radiotherapy was significantly better than those treated with higher dose Z-100, which was equivalent to the survival with radiotherapy alone. The hypothesis that lower dose of Z-100 enhances the efficacy of radiation therapy is now being tested by placebo-controlled randomized trial.

Keywords: Immunomodulator; Cervical cancer; Radiotherapy; Z-100; SSM

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Introduction

Cervical cancer has been treated with multidisciplinary therapies, and radiation therapy has played an important role [1,2]. For advanced cancers, however, radiation therapy alone has limited therapeutic efficacy. Since preventing the spread of the disease is critical to improving prognosis of patients, it is important to confine the tumor and to suppress recurrence/relapse following irradiation. Investigations are ongoing on radiosensitizing agents and maintenance therapies, and the concomitant use of radiation therapy and chemotherapy or immunotherapy has also been investigated. The clinical usefulness of non-specific immunotherapies, predominantly with biological response modifiers (BRM), is being investigated for their ability to enhance the efficacy of radiotherapy by activating the immune system, thereby resulting in a decrease in systemic immunosuppression [3,4].

The specific Substance of Maruyama (SSM) is a carcinostatic immunotherapeutic agent first prepared from human tubercle bacilli by Dr. Chisato Maruyama (Nippon Medical University) in 1944. SSM has been used as an unapproved therapy for the treatment of patients with a variety of terminal cancers at many private and public hospitals in Japan. In 1981, the Japanese Ministry for Health and Welfare (MHW) exceptionally approved the sale of SSM without clinical authorization trials, and, to date, more than 240,000 patients have been treated. SSM has been used in the treatment of cancer in accordance with the regimen of Nippon Medical University Vaccine Therapy Institution (SSM Solutions A and B containing 2 μg/ml and 0.2 μg/ml of tubercle bacillus extracts, respectively, are subcutaneously injected alternatively every other day), and several reports have demonstrated the therapeutic efficacy of SSM [5,6]. As a result, SSM has been attracting attention overseas [7]. Z-100 (ZERIA Pharmaceutical Corporation, Ltd.) is a formulation that is prepared by the same method as Solutions A and B, but the content of tubercle bacillus extracts is different from SSM. In addition, Z-100 contains a number of additives, with polysaccharides such as arabinomannan and mannan being the main additives [8]. In animal experiments, Z-100 has been shown to enhance hematopoiesis via activation of colony stimulating factor (CSF) [9]. The manufacture and use of 20 μg/ml Z-100 solution for injection were approved in Japan in 1991, and the product was marketed with the brand name 'Ancer 20 Injection®' as an agent for improving the irradiation-induced leukocytopenia.

Z-100 has been reported to provide an immunostimulatory effect in humans and mice [10,11] and an anti-tumor effect in various experimental tumors [12]. It was reported that interleukin (IL)-12 and interferon (IFN)-γ, induced by Z-100, lead to an improvement of type 1/2 T cell responses from type 2-dominated states to the normal states, resulting in suppression of tumor metastasis in mice bearing highly metastatic B16F10 melanoma cells [12,13] (Table 1).

In the previous dose-finding phase II study using three doses of Z-100 (2, 20, and 40 μg/patient) for patients with uterine cervical cancer in combination with radiation therapy, the tumor regression was higher in the 20 μg and 40 μg groups than in the 2 μg group, and 40 μg was determined to be the most effective dose (unpublished data). Since the incidence of adverse events in this study was similar in the 20 μg and 40 μg groups, 40 μg was recommended for further trials. Based on this result, we have conducted a phase III double-blind randomized trail to investigate the clinical usefulness of Z-100 to compare the efficacy of low dose and high dose of Z-100, focusing on tumor response, overall survival, and progression-free survival as the clinical endpoints.

Table 1
Pharmacology of Z-100

In vivo	Prolongation of survival time and anti-tumor activity by combination with radiation
	Suppression of lung metastasis
In vitro	Increase of interleukin (IL)-12 and interferon (IFN)-γ
	Improvement of type 1/2 T cell responses from type 2-dominated states to the normal states

Patients and methods

Patients

Patients with histologically confirmed International Federation of Obstetrics and Gynecology (FIGO) Stage IIIb squamous cell carcinomas of the uterine cervix were enrolled into this study. The patients, aged between 20 and 80 years, must receive the treatment as a primary treatment, and they must have appropriate bone marrow function (WBC count: $\geq$3000/mm^3, platelet count: $\geq$90,000/mm^3, and hemoglobin: $\geq$9.5 g/dl). The patients must be judged suitable for brachytherapy. Patients with metastasis, patients with additional cancers other than cervical cancer, pregnant women, nursing mothers, and patients suspected of having para-aortic lymph node metastasis, as assessed by CT scan, were excluded from the study. Stratification was made by degree of the parametrium, low/medium or high. Pelvic wall invasion is unilateral, and its degree is from low to medium. Low/medium was classified when parametrial invasion was unilateral, and its degree was low/medium. When parametrial invasion was unilateral and it is unknown if its degree is moderate or severe, this case is classified into low/medium. When parametrial invasion was bilateral, or unilateral with high degree invasion, it was classified to be high. This study obtained the approval of the institutional review boards of each participating institution, and written informed consent was obtained from each patient.

Treatments

Z-100 administration

The patients were randomly assigned to the high-dose or low-dose Z-100 groups in a double-blind manner. The allocation was conducted by the central registration system using facsimile, and a modified minimization technique was applied using parametrium invasion, use of adjuvant chemotherapy and institutions as adjusting factors. In preparation for this trial, the protocol committee discussed the possibility of using placebo, but we reached an agreement not to use it because a double-blind placebo randomized trial might have been considered not feasible from the point of participating patients in Japan.

Instead, Z-100 at a dose of 0.2 μg/2 ml was chosen as a control arm because none of the existing reference drugs had been approved for long-term administration to cervical cancer patients. This dose (0.2 μg/2 ml) corresponds to SSM Solution B and had been previously administered to many cancer patients. Although the effectiveness of this dose had not yet been verified, its safety had been documented [5]. Thus, the group to be treated with this safe and possibly effective dose was set as the control for these studies. Therefore, during the radiation therapy and until 4 weeks after radiation therapy, Z-100, either at 40 μg/2 ml/ampoule (high-dose group) or at 0.2 μg/2 ml/ampoule (low-dose group), was administered subcutaneously twice weekly every 3 to 4 days. Administration of Z-100 started within 3 days after the start of radiation