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Rapid Communication

AUGMENTATIVE EFFECT OF LENTINAN ON IMMUNE RESPONSES OF PELVIC LYMPH NODE LYMPHOCYTES IN PATIENTS WITH UTERINE CERVICAL CANCER

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Introduction

Lentinan, a $\beta(1\rightarrow3)$ glucan with average molecular weight of 500,000 daltons, shows a prominent anti-tumor activity in syngeneic and even autochthonous tumor-host models (3). The recent studies have revealed that lentinan can augment IL-1 production by activating macrophage function (1,2), which might subsequently lead to an enhanced IL-2 production as a cascade. Under defined conditions, lentinan has shown therapeutic efficacy in clinical trials on various cancers (1), though its mechanism in humans remains to be elucidated.

Thus, the present study was designed to analyze whether lentinan could augment IL-2 production and lymphokine-activated killer (LAK) cell activity of lymphocytes in pelvic lymph nodes (PLNs) in patients with uterine cervical cancer.

Materials and Methods

Lentinan was i.v. administered 2mg (group B) or 4mg (group C) one day before the operation. In group D, 2mg and 4mg of lentinan were i.v. administered 7 days and 1 day before the surgery, respectively. PLNs, including external iliac, internal iliac, and obturator nodes, were biopsied in stage 0 cervical cancer patients (33 cases) or radically dissected in stage Ib cervical cancer patients (12 cases). Fresh lymphocytes of PLNs, all of which were negative for cancer metastases, were assayed for IL-2 production and LAK cell activity.

IL-2 production: A 5×10^5 cells/ml sample of lymphocytes was stimulated with 0.5μg/ml PHA-P for 48 hrs at 37℃ in 5% CO_2. Afterwards, the supernatant was removed and co-cultured with 1.5×10^3 cells/well IL-2 dependent cytotoxic T lymphocytes in microtiter plates (Falcon, 3072, Bectone Dickinson Labware, USA) in a total volume of 200μl/well for 24 hrs. At 6 hrs prior to harvesting, the microcultures were pulsed with 0.5 μCi H^3 thymidine. The IL-2 concentrations were calculated by probit analysis using standard IL-2 preparations.

LAK cell activity: LAK cells were induced in PLN lymphocytes by 3-day culture with 10 U/ml of recombinant IL-2 (rIL-2, Takeda Chem., Ind.) at 37℃ in 5% CO_2. A standard 4-hr ^{51}Cr release assay was used to measure LAK cell activity against Daudi target cells.

Results and Discussion

Lentinan administered i.v. showed no side effects by these doses. As shown in Table 1, lentinan significantly augmented IL-2 production of PLN lymphocytes as compared with the controls. Furthermore, LAK cell activity, which is considered to be dependent on the existence of IL-2, was also significantly enhanced by preoperative lentinan as shown in Table 1.

PLN lymphocytes may play major roles in

Table 1. Effect of lentinan on IL-2 production and LAK cell activity of lymphocytes in pelvic lymph nodes in patients with cervical cancer

Group	No. of patients	Lentinan (i.v.)[a]	IL-2 production[b] (units/ml)	LAK cell activity[c] % Specific lysis (E/T=20)
A	20	Ope. ⇩	16.3±21.2	5.41±5.74
B	7	2mg ↓ Ope. ⇩ 1d	164.0±81.1**	18.0±12.2*
C	13	4mg ↓ Ope. ⇩ 1d	81.1±28.3***	17.0±10.3**
D	5	2mg ↓ 7d 4mg ↓ Ope. ⇩ 1d	97.1±34.5***	15.0±7.43***

[a] : Patients classified into 4 groups were injected i.v. with lentinan one day before the operation as indicated.

[b,c] : Fresh lymphocytes in pelvic lymph nodes obtained during surgery were assayed for IL-2 production using IL-2 dependent cell line (b) and for LAK cell activity against Daudi target cells by the 4-hr ^{51}Cr release assay (c).

Statistical significance of difference from group A : *$p<0.05$, **$p<0.01$, ***$p<0.001$

protecting against lymphatic metastasis of cervical cancer. The results described in this communication are the first to demonstrate that lentinan can augment IL-2 production of PLN lymphocytes in cervical cancer patients. Whether augmented IL-2 is a cascade of events following increased IL-1 from macrophages activated by lentinan (1,2) or results of a direct impact on helper T cells requires further studies. The effect was not dose dependent, in fact, the lowest dose (2mg) seemed to be most efficient, though the differences among various doses were not significant. IL-2 is considered to be a crucial lymphokine inducing in vivo anti-tumor effector cells, among which LAK cells have been received much attraction because of its potential use of adoptive immunotherapy. Lentinan could also augment LAK cell activity possibly through increased IL-2. Besides LAK cells, other effector cells including cytotoxic T cells and NK cells might also be activated by IL-2. Therefore, it is likely that lentinan is feasible as an immunomodulator for cervical cancer patients, especially for inhibiting metastasis.

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