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ORIGINAL ARTICLE

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Recombinant human interleukin-11 improved carboplatin-induced thrombocytopenia without affecting antitumor activities in mice bearing Lewis lung carcinoma cells

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Abstract *Purpose:* Interleukin-11 (IL-11) is a stromal cell derived multifunctional cytokine, which plays important roles in the hematopoietic and nonhematopoietic systems. Recombinant human IL-11 (rhIL-11) is used in the treatment of chemotherapy-induced thrombocytopenia. We have investigated the effects of rhIL-11 on the antitumor activity of chemotherapeutic agents and on thrombocytopenia in myelosuppressed mice bearing tumor cells. *Methods:* We tested the effect of rhIL-11 on Lewis lung carcinoma (LLC) cell proliferation when used alone or in combination with three antitumor agents in vitro. Also, a newly developed chemotherapy-induced myelosuppressed mice model bearing LLC cells was used to study the effects of rhIL-11 on the antitumor activity and on thrombocytopenia. *Results*: On its own, rhIL-11 (1–100 ng/ml) did not stimulate cell proliferation, and did not alter the antitumor activities of carboplatin, mitomycin C, or etoposide in vitro. In mice implanted with LLC cells (1×10^4), carboplatin (50 mg/kg/day for 2 consecutive days, i.p.) inhibited tumor growth and caused thrombocytopenia. Treatment with rhIL-11 (500 μg/kg/day, from the day following the last dosing with carboplatin for 14 days, s.c.) successfully prevented thrombocytopenia without affecting the antitumor activity of carboplatin. With rhIL-11 there was no obvious effect on the red blood cell count, white blood cell count, or body weight. *Conclusion*: These results support the assertion that rhIL-11 may be a significant therapeutic agent for thrombocytopenia following cancer chemotherapy, and that it need be associated with little fear of tumor proliferation.

Keywords rhIL-11 · Thrombocytopenia · Lewis lung carcinoma · Tumor-bearing mice

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Introduction

Interleukin-11 (IL-11) belongs to a family of cytokines that includes interleukin-6, leukemia inhibitory factor, ciliated neurotropic factor, oncostatin M, and cardiotrophin, which share a common signal transducer, gp130 [1, 2, 3]. IL-11 is a pleiotropic cytokine [4] affecting the hematopoietic and nonhematopoietic systems. Thus, IL-11 stimulates megakaryocytopoiesis, neuronal differentiation, osteoclastogenesis, and the inhibition of adipocyte differentiation as described elsewhere [5]. Although IL-11 shows diverse biological activities, subcutaneous administration of recombinant human IL-11 (rhIL-11) rather preferentially shows a thrombopoietic effect in normal mice and nonhuman primates [6, 7]. Furthermore, rhIL-11 treatment accelerates the recovery of thrombocytopenia in mice and monkeys with chemotherapy [7, 8, 9, 10, 11, 12]. In clinical trials, rhIL-11 has shortened the duration of thrombocytopenia and decreased the need for platelet transfusion in patients receiving chemotherapy [13, 14, 15], demonstrating that rhIL-11 treatment is effective in ameliorating thrombocytopenia induced by chemotherapy.

IL-11 binds to the α-chain receptor (IL-11Rα) on the cell surface, and the IL-11–IL-11Rα complex then acti-

vates gp130 [16]. IL-11Rα is expressed in both normal and cancer cells, that is, megakaryocytes, colon epithelium, breast cancer, colon carcinomas, myeloma, and acute myeloid leukemia cells [17, 18, 19, 20]. The expression of gp130 is seen in most cancer cells [21]. The effect of rhIL-11 on the growth of cancer cells has been investigated in several in vitro studies, which have demonstrated that rhIL-11 could affect the growth of certain types of cancer cells. For example, studies using cell lines have shown that rhIL-11 inhibits the growth of breast cancer cells [17], while it can stimulate, alone or in synergy with IL-3, part of leukemia cell lines [22, 23] and the human myeloma cell line [24]. It has no effect, however, on the growth of fresh myeloma cells [24], melanoma [18], or fresh solid tumor cells [25]. On the other hand, the effect of rhIL-11 on the anticancer activity of chemotherapy in vitro or in vivo has not been investigated, except in one study [26], which demonstrated that rhIL-11does not significantly change the cytotoxic effects of several chemotherapeutic agents on EMT-6 murine mammary carcinoma in mice. For clinical use of rhIL-11, it would be desirable if a thrombopoietic effect can be demonstrated, without the tumor proliferation and cytotoxic activities of the anticancer therapies being affected. In this assay, we established a chemotherapy-induced myelosuppressive model using tumor-bearing mice, and evaluated, in this model, the simultaneous effects of rhIL-11 on the growth of tumor cells and platelet counts.

Materials and methods

Cell line

Murine Lewis lung carcinoma (LLC) cells were obtained from Riken Cell Bank (Ibaraki, Japan). Cells were cultured in Dulbecco's modified Eagle's medium (DMEM; Dainippon Pharmaceutical, Osaka, Japan) with 10% fetal bovine serum (FBS; Dainippon Pharmaceutical) for the in vitro study. For the in vivo study, cells were subcultured in the subcutaneous tissue of male C57BL/6 Cr mice aged 6 weeks (Japan SLC, Shizuoka, Japan). The cells were isolated 12 days after implantation, homogenized with glass homogenizer (Iwaki Glass, Chiba, Japan), and diluted with saline for implantation, to establish the tumor-bearing model.

Drugs

The Genetics Institute (Boston, Mass.) provided rhIL-11 purified to homogeneity from *Escherichia coli*. For the in vitro study, a solution of rhIL-11 at a concentration of 1000 μg/ml was prepared in phosphate-buffered saline (PBS) containing 0.1% bovine serum albumin (BSA; Dainippon Pharmaceutical), and stored at –80 °C until use. For the in vivo study, rhIL-11 was dissolved in a solution containing 0.004 M $NaH_2PO_4{\cdot}2H_2O$, 0.006 M $Na_2HPO_4{\cdot}12H_2O$, 0.3 M glycine, and 0.01% (w/v) polyoxyethylene (20) sorbitan monooleate.

Carboplatin (Paraplatin, Bristol-Myers Squibb, Tokyo, Japan), mitomycin C (Kyowa Hakko Kogyo, Tokyo, Japan), and etoposide (Sigma Chemical, St.Louis, Mo.) were used as the chemotherapeutic agents. Carboplatin injection was diluted with medium or saline for the in vitro and in vivo studies, respectively. Mitomycin C was dissolved with distilled water and diluted with saline. Etoposide was dissolved and diluted with culture medium containing 0.2% dimethyl sulfoxide (DMSO).

Effect of rhIL-11 on antitumor activity of chemotherapeutic agents in vitro

LLC cells (5×10^4 cells/well) were seeded in a 24-well plate (Dainippon Pharmaceutical) and incubated under conditions of 5% CO_2 and 37 °C. Six hours after the seeding, rhIL-11 and/or the anticancer agents were added, and the culture was incubated for 3 days. The cells were isolated with trypsin-EDTA (Dainippon Pharmaceutical) and the viable cells were counted by trypan blue staining. The IC_{50} value, the concentration required to inhibit tumor proliferation by 50%, and the 95% confidence limit were calculated by the logic method for each chemotherapeutic agent in the presence or absence of rhIL-11.

Effect of rhIL-11 on carboplatin-induced myelosuppression model in tumor-bearing mice

LLC cells (1×10^4 cells/0.05 ml) were implanted subcutaneously at the right abdomen of male C57BL/6 Cr mice (7 weeks old). Beginning on the following day, carboplatin was administered intraperitoneally to the mice at a dose of 50 mg/kg/day for 2 consecutive days. The last day of carboplatin dosing was considered as day 0. From days 1 to 14, rhIL-11 (500 μg/kg/day) or the vehicle was administered subcutaneously. The body weight and the tumor volume were measured at the indicated time points. The tumor volume was calculated by the following formula:

$$\text{Tumor volume}\left(\text{mm}^3\right) = (\text{Longest diameter of tumor, mm}) \times (\text{Shortest diameter of tumor, mm})^2 \times 1/2.$$

On day 15, the mice were killed and the wet tumor weight was measured. Each experiment group consisted of 20 animals. The peripheral blood counts were measured by a blood cell counter (Microcell Counter F-820, Sysmex, Hyogo, Japan) in all the animals of each group before tumor implantation (day –2), and in half the animals of each group on days 5 and 11, and in the other half of each group on days 8 and 15. The dose of rhIL-11 was chosen as described previously [27], and the dosing schedule was designed on the basis of the clinical usage.

During the experiment, the animals were housed in conventional holding rooms and were given commercial rodent feed and water ad libitum. The rooms were ventilated 13–17 times per hour, maintained at a temperature of 20–24 °C and at a relative humidity of 40–68%, and illuminated in a 12-hour light/dark cycle (lighting: 8:00 to 20:00). Animal procedures were approved by the Animal Ethical Committee of Yamanouchi Pharmaceutical.

Statistical analysis

The results are expressed as the mean ± SEM. The effect of rhIL-11 was tested by Student's t test or Dunnett's multiple range test. A P value below 0.05 was considered significant.

Results

Effect of rhIL-11 on antitumor activity of chemotherapeutic agents in vitro

Alone, rhIL-11 (1–100 ng/ml) inhibited LLC cell proliferation concentration-dependently, with a maximum inhibition rate of 20.7% at 100 ng/ml (Table 1). The antitumor activities of three anticancer agents were examined in the presence and absence of rhIL-11 at a dose of 100 ng/ml (Table 2). In the absence of rhIL-11, carboplatin, mitomycin C and etoposide inhibited LLC cell proliferation with IC_{50} values of 4.18, 0.0805, and 0.134

Table 1 Effect of rhIL-11 on murine LLC cell proliferation in vitro

rhIL-11 concentration (ng/ml)	Viable cells ($\times 10^6$ cells/well)	Proliferation (%)
0	1.61 ± 0.01	100.0 ± 0.06
1	1.60 ± 0.02	99.2 ± 1.1
10	1.43 ± 0.02*	88.8 ± 1.4
100	1.28 ± 0.03*	79.3 ± 1.7

*$P < 0.01$ (Dunnett's multiple range test). Indicates the significance versus the group receiving no rhIL-11 treatment

Table 2 Effect of rhIL-11 on the antitumor activity of carboplatin, mitomycin C, and etoposide on LLC cells in vitro

Chemotherapeutic agent	IC_{50} (μg/ml) [95% confidence limit]	
	–rhIL-11	+ rhIL-11 (100 ng/ml)
Carboplatin	4.18 [3.17–5.90]	2.51 [2.01–3.33]
Mitomycin C	0.0805 [0.0725–0.0926]	0.0691 [0.0630–0.0784]
Etoposide	0.134 [0.108–0.206]	0.100 [0.090–0.112]

μg/ml, respectively. None of the IC_{50} values for the inhibition of these anticancer agents were significantly changed by rhIL-11.

Effect of rhIL-11 on myelosuppression in LLC cell-bearing mice

In preliminary experiments, we investigated the adequate dose regimen of tumor cells and carboplatin. LLC cells with 1×10^3, 1×10^4, and 1×10^5 cells/body were implanted in mice. Mice implanted with 1×10^3 LLC cells had no tumor growth. Tumor cells grew well in mice of the 1×10^5 cells/body group, but one of the five animals died 11 days after the cell implantation (data not shown). In mice implanted with 1×10^4 LLC cells, progressive tumor proliferation was observed, with an isolated tumor weight of 1040 ± 132 mg (Fig. 1). Hematological analysis revealed that the platelet counts, red blood cell counts (RBC), and white blood cell counts (WBC) did not change greatly during the observation period (Fig. 2).

Intraperitoneal administration of carboplatin, in a regimen of 50 mg/kg/day for 2 days, inhibited tumor growth by 41% (Fig. 1), without inducing any animal deaths. This regimen of carboplatin induced myelosuppression concurrently. Carboplatin decreased the platelet counts and RBC on days 5, 8 and 11, with the nadir on day 8, and decreased WBC on day 11 (Fig. 2).

Administration of rhIL-11 was done subcutaneously, at a dose of 500 μg/kg/day, from the day following the last dosing with carboplatin, to day 14 in this model. The antitumor activity of carboplatin was not significantly affected by rhIL-11 (Fig. 1). Treatment with rhIL-11 attenuated the nadir of thrombocytopenia on day 8 and accelerated the recovery of the platelet count to the pretreatment level on day 15 (Fig. 2). The effects of rhIL-11 on RBC and WBC were inconsistent. Carboplatin and rhIL-11 did not affect the body weight significantly (data not shown).

Discussion

Lung stromal cells have the ability to produce IL-11 in response to various stimuli [28, 29, 30, 31, 32, 33], and IL-11 may have some functions in human lung functioning. IL-11 or IL-11Rα are produced or expressed in a variety of tissues/cells, including some kinds of carcinoma cells [17, 18, 34, 35]. Since rhIL-11 is becoming a therapeutically important molecule in supportive care for patients who receive cancer chemotherapy, it is important to be certain that rhIL-11 exerts a thrombopoietic effect on chemotherapy-induced thrombocytopenia without affecting the tumor growth. Thus, the effects of rhIL-11 on tumor growth and the cytotoxic activity of several anticancer drugs were investigated in murine lung carcinoma cells both in vitro and in vivo.

In vitro, rhIL-11 did not stimulate the growth of murine LLC cells. More specifically, it slightly inhibited the growth of this cell line. Soda et al. reported that rhIL-11 inhibited the growth of fresh cancer cells, including non-small-cell lung cancer cells, by 24.2% [25]. Our finding was considered to correspond to their result. In the present study, the cytotoxicities of three antitumor agents in the presence or absence of rhIL-11 were estimated. Carboplatin and mitomycin C cause cytotoxicities by the formation of DNA interstrand cross-links, similar to antitumor alkylating agents. Etoposide arrests cells in the late S or G2 phases of the cell cycle. The anticancer activity of these chemotherapeutic agents, which have different mechanisms of action, were not significantly altered by rhIL-11. Teicher et al. reported that upon exposure of human CEM lymphoblastic leukemia cells in culture to rhIL-11 along with cytotoxic antitumor agents, there is no effect on the response of the cells to radiation therapy or to antitumor agents, except for the cell-cycle dependent antimetabolites 5-fluorouracil and ara-C [26]. However, they have also reported that there was no protection by rhIL-11 against the cytotoxicity of these drugs in vivo. The reason for this difference between their and our results is unknown. We counted the viable cells after 3 days of co-culture with anticancer agents and rhIL-11, whereas Teicher et al. counted the colony formation after 24 h co-culture with anticancer agents and rhIL-11, followed by seeding the cells on the soft agar. It might be due to the aforementioned differences, the cell lines, the antitumor mechanisms used, and the experimental conditions.

To evaluate the effects of rhIL-11 on tumor growth and blood cell counts concomitantly, we examined the effects of rhIL-11 on a newly developed chemotherapy-

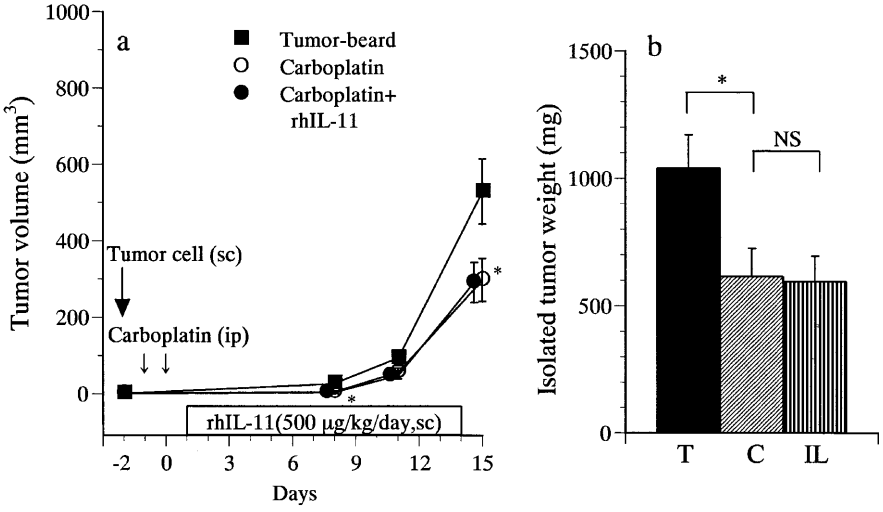
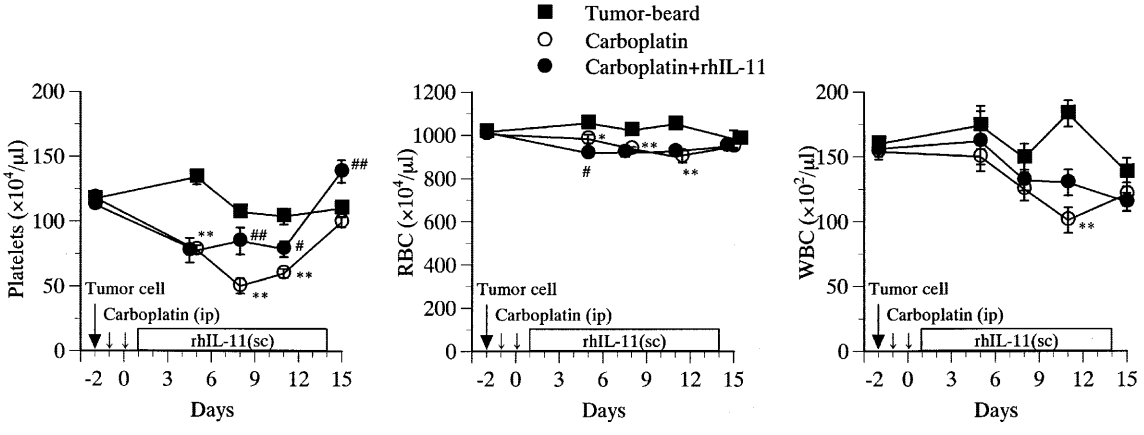


Fig. 1 Changes in tumor volume (**a**) and isolated tumor weight (**b**) in mice bearing LLC cells. Mice were subcutaneously implanted with 1×10^4 LLC cells on day –2. Carboplatin was administered intraperitoneally at 50 mg/kg on days –1 and 0. rhIL-11 (500 μg/kg/day) was administered subcutaneously from day 1 for 14 days. On day 15, the tumor was isolated and the wet weight was measured. T, C, and IL are the tumor-bearing, carboplatin-treated, and carboplatin- and rhIL-11-treated groups, respectively. The results are expressed as the means ± SE of 20 animals. The *asterisks* (*) indicate $P < 0.05$ (*t* test), i.e., a significant difference between the tumor-bearing and carboplatin-treated groups

induced thrombocytopenic model using LLC-cell-bearing mice. In these tumor-bearing mice, tumor proliferation was seen to begin 10 days after tumor implantation. In addition, these mice showed normal hematopoiesis, and no body weight loss or animal death, indicating that the present model would be a relatively early stage of tumor proliferation. Carboplatin was selected as an anticancer therapy because carboplatin is known to cause thrombocytopenia and to be clinically used for lung cancer therapy [36, 37]. Carboplatin produced antitumor activity and thrombocytopenia concomitantly, showing that the present thrombocytopenia model is suitable for assessing the effects of the drugs on both antitumor activity and thrombocytopenia. In this model, rhIL-11 did not alter the cytotoxicity of carboplatin. When rhIL-11 was administered with chemotherapeutic agents after tumor establishment, it did not diminish the murine mammary EMT-6 cell growth delay produced by chemotherapeutic agents in vivo [26]. Our results, together with previous reports, support the idea that rhIL-11 does not affect the cytotoxic activity of chemotherapeutic agents, regardless of whether the chemotherapeutic agents were administered just after tumor implantation or after tumor establishment.

The thrombopoietic effects of rhIL-11 have been confirmed in various thrombocytopenic models and clinical studies [7, 8, 9, 10, 11, 12, 13, 14, 15]. In the present model, rhIL-11 prevented the nadir and accelerated recovery from thrombocytopenia induced by carboplatin in mice in a tumor-bearing condition. In

Fig. 2 Changes in peripheral blood counts of mice bearing LLC cells. Mice were subcutaneously implanted with 1×10^4 LLC cells on day –2. Carboplatin was administered intraperitoneally at 50 mg/kg on days –1 and 0. Twenty animals were divided into two groups; in the one, blood was drawn from the tail vein on days –2 (pre), 5, and 11, and in the other, on days –2, 8, and 15. The platelet, erythrocyte (RBC), and leukocyte (WBC) counts are expressed as the means ± SE of 20 animals for day –2 and of 10 animals for the remainder. The following indicate significant differences between the tumor-bearing and carboplatin-treated groups: $*P < 0.05$, $**P < 0.01$ (*t* test). The following indicate significant differences between the carboplatin-treated and carboplatin- and rhIL-11-treated groups: # $P < 0.05$, ## $P < 0.01$ (*t* test)



clinical chemotherapies, drugs with which the bleeding resulting from severe thrombocytopenia can be avoided and the recovery from thrombocytopenia be ameliorated, would be desirable. With rhIL-11, the nadir was improved, and the effects of thrombocytopenia in the recovery phase were ameliorated. Accordingly, this cytokine could be a feasible drug in clinical use.

In the present study, administration of rhIL-11 from one day after the last dosing of carboplatin could not prevent the initial drop in platelets seen at day 5. Therefore, it would be interesting to investigate whether the administration of rhIL-11 prior to or from the same day of carboplatin treatment could prevent the initial drop in platelet count.

In summary, rhIL-11 improved carboplatin-induced thrombocytopenia without suppressing the antitumor effect, suggesting that rhIL-11 could be a clinically significant drug for cancer chemotherapy.

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