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Correlation of eosinophilia with clinical response in patients with advanced carcinoma treated with low-dose recombinant interleukin-2 and mitomycin C

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Summary. On the basis of our clinical findings that the ability of cancer patients to generate lymphokine-activated killer cells became markedly augmented after mitomycin C administration, we designed a treatment regimen comprising mitomycin C 12 mg/m^2, i.v. on day 1 and recombinant interleukin-2 700 U/m^2 (8000 IU/kg), i.v. every 12 h from day 4 through day 8. The treatment course was repeated at almost 7-day intervals. Altogether 33 patients with advanced carcinoma, including mainly gastrointestinal carcinoma, were treated with this regimen. Of these, 10 had a partial response (PR) and 4 had a minor response (MR). Since eosinophil counts peaked 1 day after either the first or second course of the therapy, the posttreatment values were compared to each pretreatment level, with regard to the clinical antitumor response to this treatment. When patients who showed PR were defined as responders, absolute eosinophil counts and the percentages of eosinophils in responders after both the first and second courses of the therapy were significantly greater than each pretreatment value or the posttreatment level in nonresponders. Further, these findings were almost identical, when both PR and MR were considered to be a true remission and therefore patients who exhibited PR or MR were defined as responders, although the difference between posttreatment levels of eosinophils in responders and nonresponders was not significant at the second course. These results indicate that eosinophilia induced by this treatment correlates with the clinical response to this therapy.

Key words: Eosinophilia – Antitumor response – Interleukin-2 – Mitomycin C – Advanced carcinoma

Introduction

Immunotherapeutic trials with interleukin-2 (IL-2) in various doses and schedules, with or without lymphokine-activated killer (LAK) cell infusion, have been shown to induce tumor regressions of human malignancies including renal cell carcinoma, melanoma or lymphoma [4, 22, 28, 29]. Further, a regimen of low-dose IL-2 preceded by low-dose cyclophosphamide was reported to be effective in the treatment of advanced melanoma [19]. We previously found that the ability of cancer patients to generate LAK cells became significantly augmented after mitomycin C (MMC) administration [20]. On the basis of these clinical findings, we designed a treatment regimen consisting of MMC in combination with low-dose IL-2, to be given when LAK cell generation had been shown to be significantly augmented [2]. This treatment has been found to be effective against advanced carcinoma, particularly carcinoma of the gastrointestinal tract [1, 2].

Administration of IL-2 or IL-2 plus LAK cells has been shown to induce hematological and immunomodulatory changes in patients with malignant diseases [6, 7, 22, 26–29]. It has also been widely observed that patients treated with IL-2 or IL-2 and LAK cells develop variable levels of eosinophilia, with activation of eosinophil functions [24]. Consequently the correlation of the level of increase in eosinophils with clinical efficacy has been investigated [19].

Patients treated with our regime, which consisted of low-dose IL-2 and MMC, also developed a moderate eosinophilia. The present study was undertaken to examine the relationship between the level of eosinophilia and clinical antitumor response in patients treated with our therapy, in order to elucidate how far this parameter can predict therapeutic efficacy and the possible role of IL-2 in the effectiveness of this treatment.

Materials and methods

Patients. A total of 33 patients with advanced carcinoma for which standard therapy had failed or no standard effective therapy was available were entered in this study; 18 had gastric carcinoma, 6 had colon carcinoma, 4 had carcinoma of the biliary tract, 3 had pancreatic carcinoma and 2 had breast carcinoma. All had clinically evaluable or measurable disease and had received no antineoplastic therapy within the 30 days prior to study entry. Eligibility requirements included a total white blood cell count of 2500/mm^3, a platelet count of 100 000/mm^3, adequate renal

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Table 1. Patient characteristics

Characteristic	No. patients		
	PR	MR	SD+PD[a]
Total patients	10	4	19
Male	7	2	14
Female	3	2	5
Age (years; mean ± SE)	59.2±5.8	65.3±2.9	61.2±2.5
Disease			
Gastric carcinoma	8	0	10
Colon carcinoma	0	2	4
Pancreatic carcinoma	2	0	1
Carcinoma of biliary tract	0	1	3
Breast carcinoma	0	1	1
Prior therapy: chemotherapy and/or immunotherapy	6	2	11
No. of courses			
mean ± SE	31±0.6	2.0±0.5	2.8±0.5
Range	1–8	1–3	1–8

[a] Patients who showed partial response (PR), minor response (MR), and stable disease (SD) plus progressive disease (PD)

Table 2. Changes in eosinophil counts in patients who showed PR or MR following this treatment

Patient no.	Response	Absolute eosinophil counts (mm^{-3})			
		1st course		2nd course	
		Pre-treatment[a]	Post-treatment[b]	Pre-treatment[a]	Post-treatment[b]
1	PR	132 (2)[c]	825(15)	180 (3)	1122(22)
2	PR	0 (0)	201 (3)	0 (0)	268 (6)
3	PR	56 (1)	370(10)	138 (3)	516(12)
4	PR	110 (1)	940(20)	1134(14)	1050(15)
5	PR	350 (7)	390(10)	390(10)	1404(27)
6	PR	450 (5)	954(18)	–	–
7	PR	165 (7)	364 (7)	364(10)	640(16)
8	PR	300 (6)	704(16)	931(19)	1161(27)
9	PR	52 (1)	246 (6)	41 (1)	342 (6)
10	PR	92 (2)	864(16)	–	–
11	MR	308 (4)	424 (8)	101 (3)	684(12)
12	MR	225 (3)	496(17)	316 (4)	657 (9)
13	MR	0 (0)	0 (0)	–	–
14	MR	670(10)	1001(18)	–	–

[a] One day before the course of the therapy
[b] One day after the end of the course of the treatment
[c] The percentage of eosinophils

function, and adequate hepatic function. Patients with active systemic infection or major cardiovascular or pulmonary disease were ineligible.

Treatment schedule. The treatment regimen consisted of MMC 12 mg/m^2 given intravenously on day 1. Recombinant IL-2 (rIL-2) at a dose of 700 U/m^2 (8000 IU/kg) was infused intravenously over a 30-min period every 12 h from day 4 through day 8, when the ability of peripheral blood monocytes (PBM) to generate LAK cells had been shown to be significantly augmented. The rIL-2 employed in this study was supplied by Takeda Pharmaceutical Co., Osaka, Japan, and had a specific activity of 3.5×10^4 U/ml as assayed on IL-2-dependent murine NKC_3 [10]. The entire 8-day treatment course was then repeated at almost 7-day intervals in patients who were stable or responding. Standard blood studies, including complete blood counts, hepatic and renal function tests, and

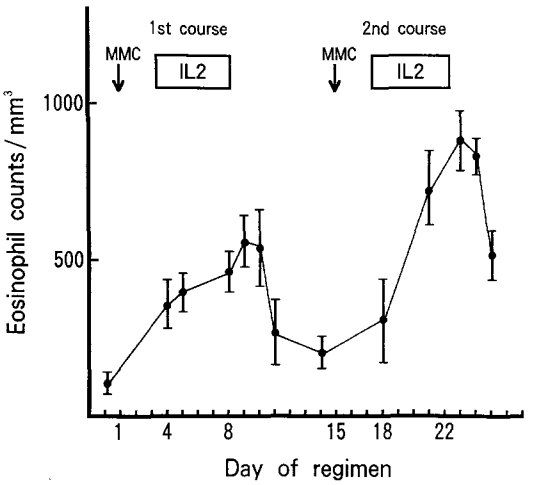

Fig. 1. Changes in eosinophil counts following treatment consisting of low-dose interleukin-2 (*IL2*) and mitomycin C (*MMC*). Mean eosinophil counts (± SE) are given for four representative patients

electrolyte determinations, were frequently performed during the treatments.

Response criteria. Standard response criteria were used. A partial response (PR) was defined as a decrease in the sum of the products of the longest perpendicular diameters of all measurable lesions by at least 50% with no new lesions developing. A minor response (MR) was defined as a decrease in this sum by more than 25% but less than 50%. Tumor regression lasting less than 30 days was not considered to constitute a response. Progressive disease (PD) was an increase of more than 25% in the sum of the products of diameters of measured lesions or the appearance of any new lesions. Stable disease (SD) was defined as a disease not meeting the above criteria for response or progression.

Statistics. Student's *t*-test was used to analyze the responder and the nonresponder group means. Differences from baseline for each parameter were assessed using a paired *t*-test. Significance was determined on the statistical tests at the 0.05 level.

Results

Of 33 patients with advanced carcinoma, 10 patients, including 8 with gastric carcinoma and 2 with pancreatic carcinoma, showed a PR. Further, 2 with colon carcinoma, 1 with carcinoma of the biliary tract and 1 with breast carcinoma exhibited a MR. The patient characteristics of each group of patients who showed PR, MR, SD or PD are shown in Table 1.

The mean absolute eosinophil counts following this treatment for four representative patients are shown in Fig. 1. There was an apparent increase in eosinophils in the first course of the therapy, peaking 1 day after the end of the treatment. By 1 day before the second course the counts had decreased. A marked increase, with a peak 1 day after the treatment, was also observed following the second course of the therapy. We therefore measured the eosinophil counts 1 day before and 1 day after either the first or second course of this treatment.

With regard to the clinical antitumor response to this therapy, changes in both absolute eosinophil counts and the percentages of eosinophils are shown in Tables 2 and 3. When patients whose remission of disease was partial were

Table 3. Changes in eosinophil counts in patients who showed SD or PD following this treatment

Patient no.	Response	Absolute eosinophil counts (mm^{-3})			
		1st course		2nd course	
		Pre-treatment[a]	Post-treatment[b]	Pre-treatment[a]	Post-treatment[b]
1	SD	0 (0)[c]	310(10)	–	–
2	SD	252 (4)	525 (7)	–	–
3	SD	56 (2)	215 (5)	123 (3)	518(14)
4	SD	58 (1)	714(14)	134 (2)	44 (3)
5	SD	372 (4)	312 (4)	–	–
6	SD	240 (5)	255 (5)	534 (6)	360 (8)
7	SD	316 (3)	290(10)	276 (4)	700(10)
8	SD	276 (6)	222 (6)	342 (9)	260 (2)
9	SD	1071 (9)	166 (2)	–	–
10	PD	195 (3)	160 (4)	195 (3)	273 (3)
11	PD	98 (2)	205 (5)	246 (6)	210 (3)
12	PD	74 (2)	336 (8)	–	–
13	PD	56 (2)	198 (6)	156 (3)	1150(23)
14	PD	912 (9)	629 (7)	629(17)	814(22)
15	PD	350 (7)	407(11)	245 (6)	252 (8)
16	PD	715(11)	429(11)	–	–
17	PD	0 (0)	510(10)	352 (6)	224 (5)
18	PD	325 (5)	770(10)	–	–
19	PD	50 (2)	44 (1)	81 (3)	154 (2)

[a] One day before the course of the therapy
[b] One day after the end of the course of the treatment
[c] The percentage of eosinophils

defined as responders, there was no significant difference between pretreatment values before either the first or second course of treatment in responders and nonresponders (Table 4). Before the first course of this therapy, larger numbers of eosinophils (more than 500) were observed in 4 of 23 nonresponders, but none of 10 responders, there being was no significant difference. Following both the first and second courses of the therapy, eosinophil counts and the percentages of eosinophils were increased in both groups of patients. However, the increase in eosinophils was significant only in responders, and not in nonresponders. The posttreatment values in responders after both courses were significantly greater than those in nonresponders.

No significant difference was observed between the pretreatment eosinophil counts or the percentages of eosinophils in responders and nonresponders after either the first or second course of this treatment, when both PR and MR were considered to be a remission and therefore patients who showed PR or MR were defined as responders (Table 4). In this context, eosinophil counts in responders after both the first and second courses of the therapy were significantly greater as compared to each pretreatment value or the posttreatment level in nonresponders. The percentages of eosinophils in responders were significantly increased following both the first and second courses of the treatment, and the posttreatment value after the first course in responders was significantly greater than that in nonresponders, although the difference between the posttreatment values in responders and nonresponders was not significant after the second course of this therapy.

Discussion

The results of the present study demonstrate that eosinophils were significantly increased following both the first and second courses of this therapy in responder patients who showed either PR or PR plus MR, but not in nonresponder patients, indicating that the increase in eosinophils correlated with an antitumor response in this therapy.

Table 4. Relation of absolute eosinophil counts and the percentages of eosinophils with clinical response

Response	1st course			2nd course		
	No. of patients	Absolute eosinophil counts (mm^{-3})		No. of patients	Absolute eosinophil counts (mm^{-3})	
		Pre-treatment[a]	Post-treatment[b]		Pre-treatment[a]	Post-treatment[b]
Remissions of disease (PR)						
Responders	10	171±47 (2.8±0.8)[c]	586±95* (12.1±1.8)*	8	397±149 (7.5±2.4)	813±150** (16.3±3.1)**
Nonresponders	23	288±62 (4.0±0.7)	375±50 (7.8±0.9)	14	268±46 (5.4±1.0)	473±86 (8.9±1.8)
Remissions of disease (PR + MR)						
Responders	14	208±51 (3.2±0.8)	556±86* (11.8±1.6)*	10	360±120 (6.7±2.0)	754±126** (15.2±2.5)***
Nonresponders	19	285±70 (4.0±0.7)	352±44 (7.1±0.8)	12	276±48 (5.7±1.2)	422± 91 (8.6±2.2)

[a] One day before the course of the therapy
[b] One day after the end of the course of the treatment
[c] The percentages of eosinophils, mean ± SE
* The eosinophil counts or the percentages of eosinophils were significantly greater than either the pretreatment value ($P < 0.01$) or the posttreatment value of nonresponders ($P < 0.05$)
** The eosinophil counts or the percentages of eosinophils were significantly greater than either the pretreatment value ($P < 0.05$) or the posttreatment value of nonresponders ($P < 0.05$)
*** The percentage was significantly greater than the pretreatment value ($P < 0.01$), but not significantly different from the posttreatment value of nonresponders ($P < 0.06$)

Compared to the previous studies, a lower systemic dose of IL-2 was utilized in this trial, based on the results of the phase I and II study in Japan [25]. In a group of patients treated with high dose IL-2, IL-2 was given at a dose of 100000 U/kg every 8 h and the median cumulative dose was 1800×10^3 U/kg [22, 29]. In the trials using low-dose IL-2, systemic IL-2 was administered at a dose of 30000 U/kg every 8 h [5, 22]. Since the specific activity of IL-2 per unit employed in our study was almost 400 times higher than that used in the latter study, the dosages given were 5%–15% of those previously administered.

The degree of eosinophilia induced by IL-2 administration was shown to depend on the dose and duration of infusion of IL-2 [6, 7, 26]. High-dose IL-2 produced a marked increase in eosinophils [7]. This treatment induced moderate eosinophilia, which was comparable to that observed in other studies using low-dose IL-2 [6]. MMC administration alone did not affect eosinophil counts in PBM at the dosage used in this trial (data not shown).

Under certain conditions, eosinophils release mediators that increase vascular permeability or leakage. It was therefore postulated that eosinophilia induced by IL-2 might be responsible for fluid retention, which is one of the toxic effects of IL-2 therapy [13]. In our study, however, there was no relationship between eosinophilia and weight gain in cancer patients treated with this therapy.

In a regimen consisting of low-dose IL-2 preceded by low-dose cyclophosphamide, eosinophilia was shown to correlate with antitumor response including PR plus MR, but not a true remission, PR alone [19]. In this study, eosinophilia was considered to correlate with a clinical response of true benefit to patients, since the significant increase following both the first and second courses of this treatment was observed in responder patients who exhibited not only PR plus MR but also PR alone, whereas the increase was not significant in nonresponder patients.

Following IL-2 or IL-2 plus LAK cell therapy, eosinophils were shown to undergo physical changes and become functionally activated. The cytotoxic function of eosinophils was then greatly enhanced [24]. There have been several reports indicating that eosinophil infiltration in carcinoma is associated with increased patient survival [12, 17, 21], therefore the eosinophil cytotoxic function may be directed against tumors [8]. However, in vivo eosinophil killing of tumors may be limited, because the cytotoxic functions of eosinophils require the presence of antibody in vitro [24].

The mechanism by which IL-2 induces eosinophilia may be indirect, because IL-2 has no direct effect on eosinophil precursors and does not appear to activate mature eosinophils in vitro. The differentiation and proliferation of eosinophils in vitro have been shown to be supported by several cytokines, including granulocyte/macrophage-colony-stimulating factor (GM-CSF) [15], interleukin-3 [23], or interleukin-5 [5, 16]. Yamaguchi et al. [30] have also demonstrated that the eosinophilia induced by IL-2 in vivo was probably mediated by IL-5 released from IL-2-stimulated lymphocytes.

IL-2 activation of PBM in vitro or IL-2 administration in cancer patients has been shown to lead to the in vitro induction of mRNA coding for several cytokines in PBM, including IL-1β, tumor necrosis (TNFα), factor α and IL-6 [11, 14]. Further, the in vivo generation of elevated levels of several cytokines was observed in the serum of cancer patients who had received IL-2 [3, 9, 18]. In addition, the serum concentration of TNFα has been reported to correlate with clinical response to IL-2 and LAK therapy in cancer patients [13]. Since IL-5 might be responsible for the eosinophilia induced by IL-2 injection, these results suggest that cytokine production by IL-2-stimulated lymphocytes may be related to the antitumor response of cancer patients treated with IL-2, as well as this therapy.

In summary, the present results indicating that eosinophilia induced by this treatment correlated with clinical antitumor response appear to suggest not only the usefulness of this parameter to predict the efficacy of this therapy, but also the implication of IL-2 administration in the effectiveness of this treatment. Furthermore, the production of cytokines by IL-2-stimulated lymphocytes may play a role in the antitumor effect of this treatment.

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