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Optimal Dose of Continuous Interleukin-2 (IL-2) Infusion Together with Intermittent Adriamycin Injection to the Hepatic Artery in Advanced Hepatocellular Carcinoma Patients

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Abstract: To determine the appropriate hepatic arterial infusion dose of IL-2 to obtain long-lasting direct response in hepatocellular carcinoma (HCC), we analyzed deleterious factors after various intervals of direct tumor response to immunochemotherapy using adriamycin (ADR). The direct tumor response, survival rate, and changes in peripheral NK activity of 3 groups of advanced HCC patients were compared. Seventeen patients received continuous infusion of IL-2 (0.35×10^6 JRU/day) and intermittent injections of ADR emulsion (10mg) via the hepatic artery after cannulation. Six patients received IL-2 infusion for less than 6 months because of new lesions or side effects of IL-2 (IL-2 ineffective group), and 11 for more than 6 months (IL-2 + ADR group). Seven patients received the ADR emulsion therapy alone (ADR group). In the IL-2 + ADR group, excellent direct effect on liver tumors accompanied by increase in peripheral NK activity was observed. Four patients in the IL-2 + ADR group showed complete remission (CR) and 2 partial remission (PR) of liver tumors. However, long-term observation of NK activity revealed intractable decrease after the 6th to 8th month despite an increase in IL-2 dose, and the survival rate was not higher than that in the ADR group. The ADR group did not show increase of NK levels but 2 patients showed PR. This refractory decrease in the NK activity is probably due to changes of the immunological status following continuous high-dose infusion of IL-2. The appropriate dose for IL-2 infusion, which varies with changes in NK activity after CR is obtained, should be the minimum dose which maintains high NK activity in peripheral lymphocytes, so that rebound phenomenon is not induced.

Key words: Hepatocellular carcinoma, Interleukin-2, Adriamycin, Immunochemotherapy, Hepatic arterial infusion

INTRODUCTION

Immunotherapy using IL-2 as an immunomodulator has recently been attempted in many institutions, but its effects have so far been limited, except in advanced cancers of certain organs[1-4]. Since 1988, we have used hepatic arterial continuous infusion of recombinant interleukin-2 (IL-2) targeting reduced hepatocellular carcinoma (HCC) cells after mass-reduction procedures[5,6]. The hepatic arterial infusion is thought to deliver high concentration of IL-2 to the HCC cells with few side effects. Based on our consideration that immunomodulatory effects can be obtained under a condition in which the number of target cells is reduced, this therapy is combined with intermittent adriamycin (ADR)-lipiodol emulsion injections delivered directly to the liver to obtain chemoembolization effects during the infusion therapy.

Although we previously reported excellent

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direct effects on liver tumors, accompanied by high NK activity levels in blood, with this immunochemotherapy[6], its effect on the survival rate has not been evaluated. In this study, we attempted to examine the effect of this immunochemotherapy on the survival period by comparing it with that in patients who received ADR emulsion injection alone, because it is possible that the direct effects of the present immunochemotherapy might be induced by the intermittent ADR emulsion injections. The clinical limit of continuous IL-2 infusion is indicated by changes in peripheral NK activity as an indicator of immunomodulator effect. Two case reports describing patients who entered complete remission and survived longer than 2 years are presented.

Materials and Methods

Between August, 1988 and February, 1991, we performed hepatic arterial cannulation in 24 advanced HCC patients who had received tumor-mass reduction treatments (Table 1). Eleven patients could continue to receive infusion of IL-2 and ADR for more than 6 months (IL-2 + ADR group; Table 2, top) and 6 patients were withdrawn from IL-2 infusion within 6 months (IL-2 ineffective group; Table 2, bottom), and 7 patients received infusion of ADR emulsion alone for more than 6 months (ADR group; Table 3). In 17 patients (1 at Stage III, 13 at Stage IV-A, and 3 at Stage IV-B (UICC)[7]), a cannula was attached to a subcutaneous infusion pump, Infusaid®[8] (Shiley Infusaid Inc., U.S.A.), for continuous infusion of IL-2 (S-6820, Shionogi Pharmaceutical Co., Japan) and for intermittent injection of ADR (Adriacin®, Kyowa Hakko Co, Japan) emulsion. In the remaining 7 patients (5 at Stage IV-A, and 2 at Stage IV-B), the cannula was connected to a subcutaneous port, Infuse-a-port® (Shiley Infusaid Inc., U.S.A.)[9] for injection of ADR emulsion alone. Hepatic arterial cannulation was performed either during laparotomy or with a modified Seldinger's angiography technique through the femoral artery[6]. The infusion pump or the port was placed in the subcutaneous layer of the left abdominal wall. Selection of the pump

Table 1. Backgrounds of patient group with and without IL-2 infusion

	Male / Female	Age over 60 / below 60	Stage (TNM)			Clinical stage[1]			Liver resection[2]	Perioperative ethanol injection	Cannulation
			III	IV-A	IV-B	1	2	3	≧2 : 1 ~ 2 : < 1 : (−)		Laparotomy: SAG[3]
#IL-2 infusion + ADR											
less than 6 month[4]	5/1	4/2	0	5	1	3	3	0	1 : 2 : 2 : 1	4	5 : 1
more than 6 month[5]	11/0	2/9	1	8	2	9	1	1	2 : 1 : 2 : 6	3	4 : 7
#ADR alone[6]	6/1	2/5	0	5	2	6	0	1	1 : 1 : 2 : 3	2	3 : 4

1) Clinical stage indicates the stage of liver cirrhosis, ranging from 1 to 3, according to the Liver Cancer Study Group of Japan [20]. Stage 1 is the compensative stage and Stage 3 the non-compensative stage.
2) ≧2, liver resection of 2 or more segments; 1~2, liver resection of less than 2 segments but more than 1 segment; <1, liver resection of less than one segment; (−), no liver resection.
3) Cannulation by modified Seldinger's angiography method.
4) The IL-2 ineffective group, which could not be maintained on IL-2 infusion for more than 6 months.
5) The IL-2 + ADR group, which received IL-2 infusion for more than 6 months.
6) The ADR group, which received ADR emulsion alone intermittently for more than 6 months.
There was no significant difference between these two groups in any factors shown herein by Chi-square test.

Table 2. Duration of IL-2 infusion, reasons for discontinuing of IL-2 infusion, and outcome

Patient	Duration of IL-2 infusion months	Reason for IL-2 discontinuance	Direct effect (months)[2)]	Outcome as of Oct. 1, 1993 (days after cannulation) [cause of death]
(IL-2 + ADR gruop)				
1	25	Cerebral bleeding	CR (10)	(772) [cerebral metastasis]
2	32	Radiation to bone metastasis	CR (5)	(957) [respiratory failure]
3	15	Rupture of esophageal varices	PR (11)	(455) [liver failure, respiratory failure]
4	10	Pneumonia	PD	(495) [respiratory failure]
5	8	Cerebral bleeding	PR (5)	(245) [cerebral bleeding]
6	16	Admission to another hospital, bone metastasis	NC (10)	(558) [respiratory failure] [pneumonia]
7	8	Renal failure, hemodialysis	NC (5)	(360) [respiratory failure] [liver failure]
8	10	Costal metastasis, admission to another hospital	PD	(322) [respiratory failure]
9	9	Jaundice	NC (6)	(247) [respiratory failure]
10	21	—	CR (30)	(980) alive[3)]
11	20	Liver failure	CR (18)	(735) [liver failure]
(IL-2 ineffective group)				
12	3	Ascites	—	(291) [liver failure]
13	3	Respiratory failure	—	(92) [respiratory failure]
14	1	Ascites	—	(221) [liver failure]
15	4	Liver failure	—	(130) [liver failure]
16	4	High fever	—	(123) [respiratory failure]
17	5	Pleural hemorrhage	—	(240) [rupture of esophageal varices]

1) Direct effect on liver tumors in patients with IL-2 infusion:
Complete Response (CR), no evidence of disease, with complete absence of all detectable lesions lasting more than 4 weeks; Partial Response (PR), more than 50% decrease in the total diameter of all measurable lesions, with no evidence of new ones; No Change (NC), an objective response of less than 25% in one or more existing lesions, and Progressive Disease (PD), increase of more than 25% in one or more measurable lesions or the appearance of new ones. Numbers in parenthesis indicate duration of direct effect.
2) Survival period after cannulation

or the port, that is with IL-2 infusion or not, was made by the patient and family members, without any bias of medical doctors, after being informed as to the patient's advanced status and the purpose and methods of this study. The study was performed after approval of the Human Research Review Committee of Yamanashi Medical University Hospital.

The scheduled dose of IL-2 was 0.35×10^6 JRU/day. One JRU (Japan Reference Unit) is equivalent to one BRMP (Biological Response Modifiers Program) unit. Infusion of IL-2 was started at the dose of 0.05×10^6 JRU/day during the second week after cannulation, according to clinical conditions, and the dose was then gradually increased; within 4 weeks, the dose of IL-2 was 0.35×10^6 JRU/day. Once a week, the pump reservoir (50 m*l* capacity) was filled with IL-2. The outflow rate of the pump is about 5 to 6 m*l*/day at body temperature. ADR emulsion consisting of 10mg ADR/2 m*l* of distilled water and 0.5 m*l* lipiodol was injected once a week selectively into the hepatic artery and irrigated the liver tumors through an integrated sideport in the pump or a port. The ADR injection began 2 weeks after can-

Table 3. Outcome of patients in ADR group

Patient	Direct effect (months)[1]	Survival period (days)	Cause of death[2]	Distant organ metastasis[3]
18	PR (3)	672	Liver failure	Bone
19	PD	186	Respiratory failure	Lung, Bone
20	PD	328	Liver failure	(−)
21	PR (2)	360	Liver failure	(−)
22	NC (5)	648	Liver failure	(−)[4]
23	NC (3)	299	Liver failure	(−)
24	PD	180	Respiratory failure	Lung

1) Direct effects on liver tumors in patients who received ADR injections for more than 6 months. CR, Complete Response; PR, Partial Response; NC, No Change, PD; Progressive Disease. Numbers in parentheses indicate effective periods.
2) Liver failure was induced by proliferation of intrahepatic liver tumors.
3) Presence of distant organ metastasis revealed by image diagnosis before death.
4) In the end-stage, stomach cancer was found.

nulation. After the injection of ADR emulsion, the catheter was flushed with 1,000 U heparin sulfate and 4 m*l* of saline.

The direct effect on liver tumors was evaluated as described in Table 2. The direct effect on liver tumors was assessed using computed tomography (CT) and ultrasonograpy. Complete response (CR) was defined as no visualization of tumors for more than 4 weeks on CT and US images. Changes in NK activity (mean value, 33.0 ± 11.8% in 10 healthy volunteers over 40 years old; 47.2 ± 4.3 years old) in the peripheral blood were measured as an indicator of the immunomodulator effect of the IL-2 infusion as well as of surgical stress were analyzed in the 3 groups. NK activities were measured within 2 weeks before the cannulation and at the following 6 times after the start of IL-2 infusion: within 1 week; 1 to 2 weeks; 1 to 2 months; 4 to 6 months; 8 to 9 months; and 11 to 12 months. In the case of multiple measurements of NK activities during a given interval, the highest level was used for comparison. NK activity in the peripheral blood was measured with a ^{51}Cr releasing assay, using K 562 cells as the target[4,10]. The ratio of the effector cells to target cells was 20:1. Changes in subsets of peripheral lymphocytes (CD4, CD8, CD16, CD57 and CD25 (IL-2 receptor)) were measured by the FACS technique in some patients, using monoclonal antibodies (Becton Dickinson Immunocytometry Systems), Leu3a, Leu2a, Leu11, Leu7 and IL-2 receptor, respectively.

In Patient 5, the IL-2 dose could not be increased to the scheduled dose due to jaundice and was maintained at a lower dose (0.25×10^6 JRU/day) for 8 months. In Patients 10 and 11, the dose was reduced after CR was obtained, tumors disappeared for more than 4 weeks in CT and US images, accompanied by enhanced level of NK activity in the peripheral blood, and then the dose was varied according to changes in NK activity. In Patients 1, 2, 4, and 6, the IL-2 dose was increased to 1.40, 0.50, 1.05, and 0.60×10^6 JRU/day, respectively, when NK activity response to IL-2 infusion decreased to below 20%, about 8 to 10 months after the start of infusion. Thus, the IL-2 infusion was suspended in 6 patients within 6 months, in 2 due to ascites and in 4 due to rapid development of metastatic tumors. During the interruption and after the suspension of IL-2 infusion, ADR injections

were continued until the end stage.

The cumulative survival rate of the three groups as of October 1st, 1993, were calculated by Kaplan-Meier Method and compared by generalized Wilcoxon test. All results shown are mean ± SD. Statistical significance was assessed by the Student's t-test or the paired t-test for changes in NK activity, and Chi-square test for comparisons of the clinical features of two groups.

Results

Continuity of the regional treatments:

The IL-2 infusion pumping system, which is regulated by body temperature, functioned efficiently in all patients. The longest period of continuous infusion of IL-2 was 32 months. In the IL-2 + ADR group, fever, as a side effect of IL-2, was controlled with indomethacin (25 to 50 mg) suppositories. Ascites was controlled by diuretics. Jaundice related to IL-2 infusion was seen in Patints 5 and 9. In Patient 5 IL-2 infusion was continued but the dose reduced to 0.25×10^6 JRU/day, while in Patient 9 interruption of IL-2 induced rapid appearance of lung metastasis and death. In the 11 patients in the IL-2 + ADR group, the IL-2 infusion was abandoned for the following reasons; tumor development in metastatic lesions in Patients 1, 2, 5, and 8; rupture of esophageal varices in Patient 3; pneumonia in Patient 4; hemodialysis due to renal failure in Patient 7; jaundice in Patient 9; liver failure in Patient 11; and interruption of the supply of IL-2 from the manufacturer and normalization of AFP in Patient 10. Patient 6 developed back-pain caused by bone metastasis and decided not to continue the therapy thereafter. In this patient multiple liver tumors in the both lobes and vertebral metastasis at L4 had not increased during the period of IL-2 infusion.

On the other hand, in the ADR group, an arterial biliary fistula developed in Patients 18, 19, and 23 in the 12th, 10th, and 16th month, respectively. ADR injection was suspended in Patients 18 and 23, but in Patient 19 a new catheter was placed in a collateral artery supplying the liver tumor by the modified SAG technique after interruption for one month. ADR injections were not interrupted or suspended because of side effects of the drug itself.

Direct effect of the immunochemotherapy:

CR was observed in 4 patients in the IL-2 + ADR group. Partial Response (PR), more than 50% decrease of tumor diameter, was observed in 2 patients. On the other hand, in the ADR group, PR was observed in 2 patients, but no CR case was observed. One of 2 patients with No Change (NC) survived for more than 21 months; the size of the multiple tumors in this patient did not increase for 14 months without distant organ metastasis, but then rapidly increased. The patient died due to liver failure.

Outcome and cumulative survival rate:

The cumulative survival rate of the IL-2 + ADR group was higher than that of the ADR group but this difference was not signficant (Fig. 1). The survival rate of the IL-2 ineffective group was lower than that in either of the other groups. Within one month after suspen-

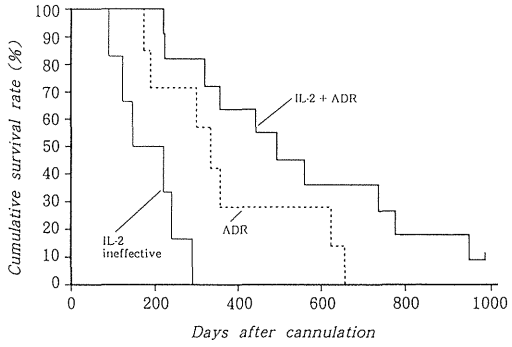

Fig. 1. The cumulative survival rates after cannulation in the IL-2 ineffective group, the IL-2 + ADR group, and the ADR group. The rate in the first group was significantly lower than that in either of the other two groups. There was no significant difference between the latter two groups in survival rate.

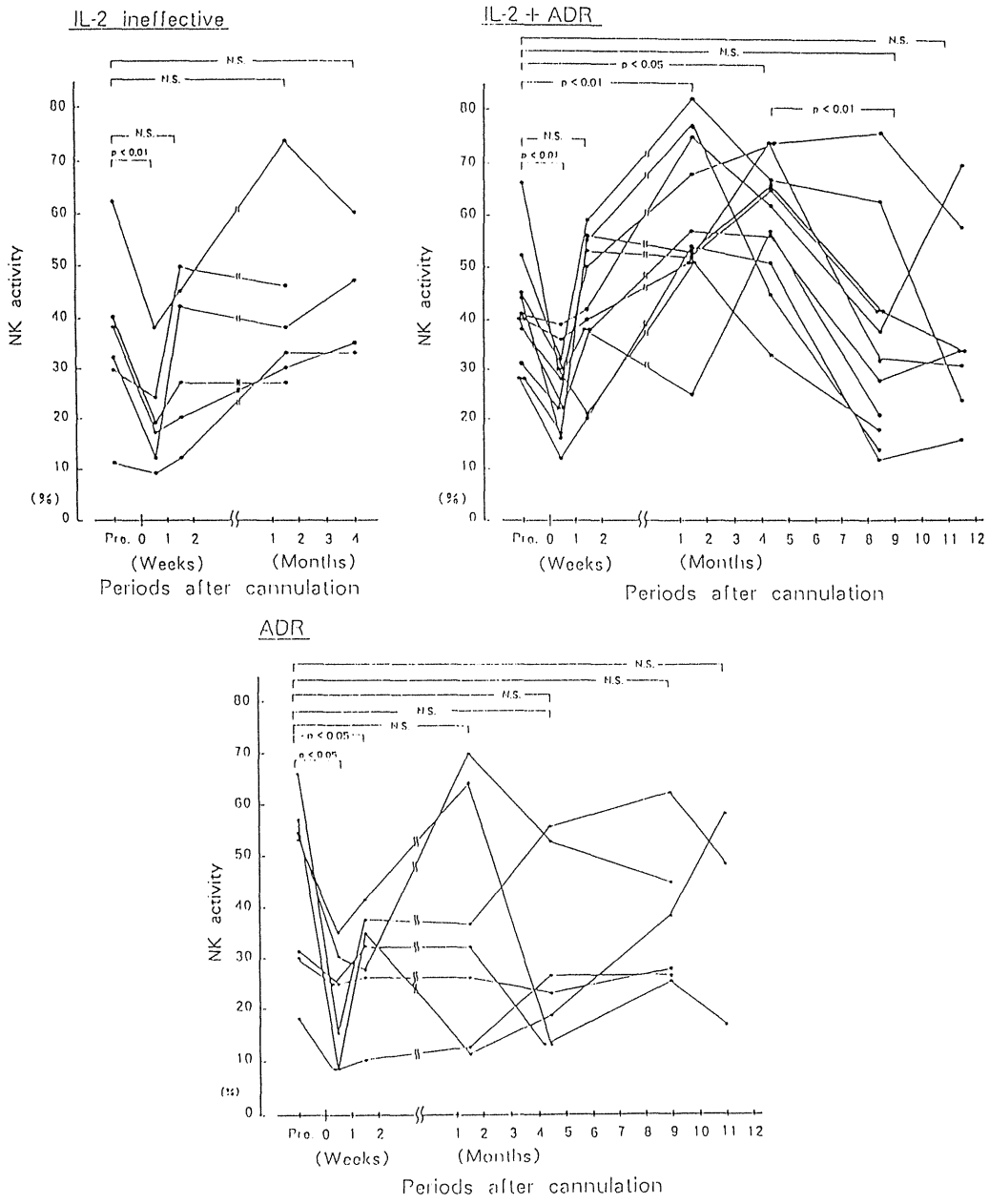

Fig. 2. Changes in peripheral NK activity before and after cannulation in the IL-2 ineffective group (above, left), the IL-2 + ADR group (above, right) and the ADR group (below). There were no significant differences among the 3 groups in the NK level before cannulation. Only in the IL-2 + ADR group was the NK level after cannulation higher than that before cannulation.

sion of the IL-2 infusion, all patients except Patients 6 and 10 had died. All had rapidly growing metastatic lesions, especially lung metastases (in Patients 3, 4, 7, and 9). In Cases 3, 4, and 7, lung metastasis had not been detected on chest X-rays at the time of suspension, but thereafter metastatic lesions appeared rapidly in the lung[11]. Patient 11, who did not have rapidly growing metastatic lesions after suspension of IL-2 infusion, died of liver failure caused by progression of liver cirrhosis. The clinical course in the one surviving patient, Patient 10, is described as one of the case reports below.

On the other hand, 5 patients in the ADR group died of liver failure caused by enlarged liver tumors. Two patients at Stage IV-B, Patients 19 and 24, died of respiratory failure caused by lung metastasis which had been detected at the beginning of ADR injection.

Changes in NK activity in the peripheral blood (Fig. 2):

The NK activity before cannulation was 41.2 ± 10.5% (n=11) in the ADR + IL-2 group, 35.5 ± 15.1% (n=6) in the IL-2 ineffective group, and 44.1 ± 16.4% (n=7) in the ADR group (no significant differences). In all 3 groups, NK activity decreased during the first week, in response to tumor-mass reduction treatments and cannulation. In the IL-2 + ADR group, within 2 weeks after start of IL-2 infusion the NK activity recovered the level before cannulation, and then increased ($P<0.01$, vs. before cannulation) within 2 months. However, the level decreased thereafter, and within 8-9 months, was significantly ($p<0.01$) decreased compared to that at 2 months. This decrease was observed even in the 4 patients whose IL-2 dose was increased. No such enhancement of NK activity was

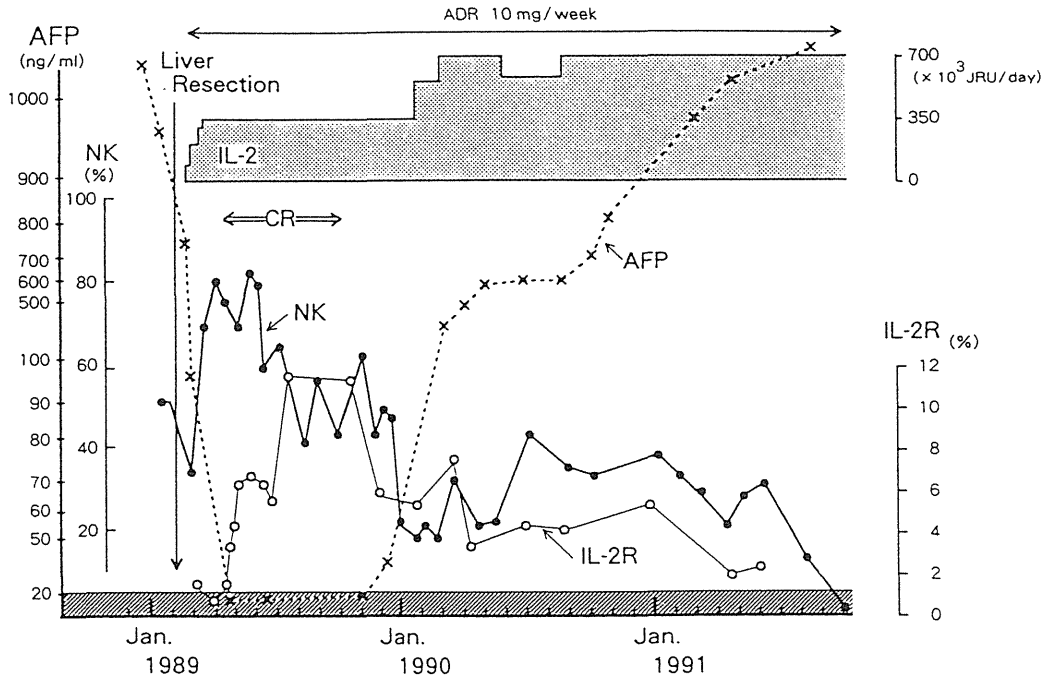

Fig. 3. Patient 2: This patient attained CR and showed refractory NK response despite an increase in the dose of IL-2 when decrease in peripheral NK activity was noted about 6 months after the start of IL-2 infusion. CR, Complete Response; IL-2R, IL-2 receptor; NK, NK activity; AFP, alpha-fetoprotein.

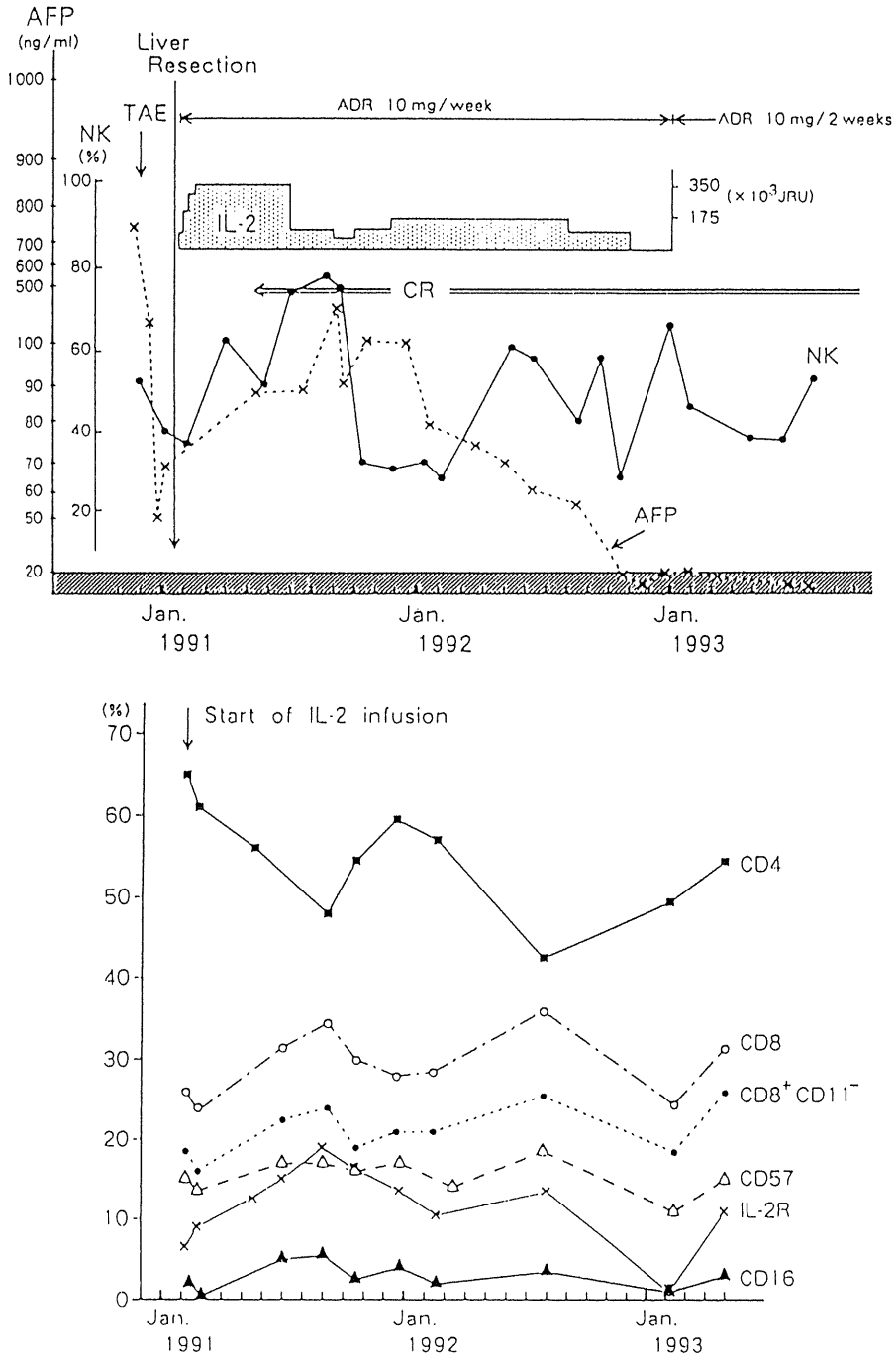

Fig. 4. Patient 10: This patient attained CR and has survived without showing intractable NK decrease during IL-2 infusion for approximately 20 months. The dose of IL-2 was reduced after CR was attained, accompanied by high NK activity. The figure below indicates changes in some subsets of lymphocytes as well as the IL-2 receptor. TAE, Transcatheter arterial embolization. Other abbreviations are the same as those in Fig. 3.

observed in either the IL-2 ineffective group or the ADR group. In the ADR group, recovery of NK activity was observed after 1-2 months but thereafter no clear tendency was observed.

Case reports

Patient 2:

This patient showed CR but NK response was refractory despite an increase in the dose of IL-2 during the decrease of peripheral NK activity, about 6 months after the start of IL-2 infusion (Fig. 3). A large tumor was present in the right lobe, one intrahepatic metastatic tumor, 2 cm in diameter, in the left lobe, and one coin lesion, 2 cm in diameter, in the right lung. After right lobectomy and perioperative ethanol injection delivered to the tumor in the left lobe, the immunotherapy was started. Within 2 months, both tumors in the remnant liver and in the lung had disappeared and the level of the NK activity was high. However, in the seventh month, a coin lesion was noted in the same region of the right lung, and AFP increased again, in conjunction with a decrease in the NK activity. This decrease was not modulated by increasing the IL-2 dose. Bone metastasis was noted in the 18th month, followed by intrahepatic metastasis despite continuous high dose infusion of IL-2. Changes in CD 25, IL-2 receptor (IL-2R), indicated non-responsiveness to IL-2. The patient died in the 34th month after cannulation.

Patient 10:

This patient showed CR and no intractable NK decrease for about 20 months during IL-2 infusion (Fig. 4). In addition to the main tumor, which was 7 cm in diameter and located in the medial segment, small multiple tumors were observed throughout the liver, and a tumor embolus in the right portal vein was recognized on lipiodol CT. After medial segmentectomy, partial resection of the lateral and anterior segments, and cholecystectomy, the patient began receiving immunochemotherapy. Postoperative CT conducted 3 months later revealed disappearance of the small tumors in the remnant liver and the tumor embolus, and no tumors were noted on subsequent CT scans. After CR was obtained with high NK activity in the fourth month, the dose of IL-2 was reduced to below the scheduled dose. The dose was then varied to maintain the high NK activity level at the reduced IL-2 dose for as long as possible. AFP (normal range, below 20 *ng*/m*l*) gradually decreased to below 20 *ng*/m*l* in the 20th month. Changes in some peripheral lymphocyte subsets are shown in the figure. These subsets apparently fluctuated concomitantly with changes in the peripheral NK activity; negatively in CD4 and positively in CD8, CD8+CD11− (cytotoxic T cell), CD16 and CD57.

Discussion

We attempted to evoke an effective immunomodulator response to IL-2 by directly administering IL-2 into the liver, in combination with intermittent ADR emulsion infusions to reduce target tumor cells to increase the efficacy of the immunotherapy. Effective direct responses to immunochemotherapy have been observed during a period of high NK activity in the peripheral blood[6], but the relationship of the effective response and the process of deterioration after the NK activity declines[6,11] to the cumulative survival rate has not been evaluated. In general, advances in imaging diagnosis have made it feasible to estimate changes in tumor size or content without operation, and we have frequently evaluated the effects of treatment by assessing the direct effect on the tumor itself.

In the present study, the cumulative survival rate of patients who received IL-2 infusion was compared with that of those who received ADR emulsion alone in order to evaluate the effect of IL-2 infusion on the survival period

and to formulate strategies for determining the optimal IL-2 dose for hepatic arterial infusion. Moreover, to clarify the side effects of IL-2 infusion[12], we compared patients who could receive the IL-2 infusion less than 6 months with those who received it for more than 6 months. The results clearly demonstrate that patients who could not continue the IL-2 infusion more than 6 months had poor outcome, even compared with those in the ADR group. Apparently, IL-2 aggravated their general condition. In the patients who could continue the infusion more than 6 months, however, an increased NK level and excellent direct effects on liver tumors were observed during certain periods, but the long-term survival rate was not significantly different from that in the traditional chemoembolization therapy (the ADR group).

Peripheral NK activity is an indicator of immunity[13] which is negatively correlated with malignant status[14]. The surgical insult of the tumor-mass reduction procedures caused NK activity to decrease significantly compared to the preoperative level. However, in patients who received subsequent IL-2 infusion for more than 6 months, within 2 months after IL-2 infusion began NK activity increased significantly compared to the preoperative level, and this elevation continued for more than 4 months. During the periods of higher NK activity, CR was observed. On the other hand, in patients who could not maintain IL-2 infusion for more than 6 months as well as in patients who had ADR emulsion alone, neither enhancement of NK activity nor CR status was observed.

The mechanisms of induction of CR and reappearance of metastatic lesions after withdrawal of high-dose IL-2 infusion are still under immunological analysis. IL-2 infusion of the hepatic artery may affect functional characteristics of organ-associated lymphoid cells and liver infiltrating lymphocytes, and the role of liver sinusoidal cells to differentiate lymphocytes as the extra-thymic center[15]. Hata *et al.*[16] suggested that CD3−CD56+CD16− NK cells, which in the normal peripheral blood represent a minor population of NK cells (CD3−CD56+)[17], constitute the majority of circulating NK cells that are elicited preferentially during therapy with IL-2 in cancer patients. It is possible that liver-associated NK cells are also involved in the disappearance or reappearance of metastatic lesions, but the details are obscure.

In our patients high NK activity began to decrease within 8 to 9 months after the immunotherapy began, despite an increase in the IL-2 dose. The prolonged high dose infusion may destroy natural tolerance, triggering hyperplasia of the lymphatic system and autoimmune reactions, or inducing the formation of anti-IL-2 antibodies[18]. It is also possible that the high IL-2 dose induces some effects on negative feed-back control which limits IL-2 activity[19]. The cause of death in most patients in the IL-2 + ADR group was respiratory failure or cerebral bleeding due to metastasis to the lung or the brain, although liver failure due to exacerbation of accompanying liver cirrhosis was also seen. However, liver failure caused by enlarged liver tumors was not the major cause of death in this group. Progression of intrahepatic tumors may have been depressed by the chemoembolization effects of ADR emulsion injection during the same period, but the clinical features in the end stage in the ADR group do not affirm this hypothesis. In the ADR group, 2 Stage IV-B patients with lung metastasis died of respiratory failure, but 5 patients died of liver failure induced by enlarged liver tumors. These differences in clinical features in the end stage may reflect the influence of IL-2 infusion.

In consideration of these experiences, in the last two patients we treated in the IL-2 + ADR group (Patients 10 and 11), we did not hesitate to decrease the dose of IL-2 after high NK activity response was obtained for 4 months, and the dose of IL-2 was varied in accordance with the NK activity level. In Patient 10, the

dose was gradually reduced after the rapid enhancement of NK activity to more than 40% and the achievement of CR. Patient 11 died of liver failure without tumor recurrence in the 18th month, and Patient 10 has remained alive for 32 months. In this patient, changes in lymphocyte subsets in the peripheral blood corresponded closely with changes in peripheral NK activity. Thus, the optimal dose of IL-2 should be determined based on the development of side effects and changes in NK activity. Further clinical and experimental studies are required to obtain longer-lasting enhancement of NK activity so that patient survival can be improved.

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