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Review

Immuno-cell Therapy of Cancer in Japan

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Abstract. *The immuno-cell therapy of cancer in Japan is in the phase of transition from therapeutic research to a more generalized option for all patients. A short history of cancer immunotherapy in Japan and its present status are summarized. In 1999, the first private clinic with a cell processing facility and specializing in immuno-cell therapy was established. Since then, the number of such clinics has increased. As a result, the number of patients who undergone the therapy has markedly increased. A summary of the clinical results of the therapy in 1401 patients treated in two leading clinics is also presented.*

Abbreviated history of cancer immunotherapy and immuno-cell therapy in Japan

In 1986, a political revolution took place in Japan. After the revolution, a wave of cultural and industrial westernization prevailed. Previously medicine in Japan was largely based on Chinese medicine. The fundamental idea of Chinese or oriental medicine is that diseases are the results of an imbalance in the whole body. Therefore, medical treatments were generally systemic and chronic, aiming at the improvement of the well-balanced internal conditions of the body. After the revolution, such traditional medicine was replaced almost completely by western medicine, which aims at exerting an immediate therapeutic effect on diseased loci. However, traditional thinking still persists among the Japanese with regard to their health and treatment of diseases, perhaps offering a favourable attitude among the general public to accept cancer immunotherapy.

Modern cancer immunotherapy started in Japan in the 1970s following its introduction in western countries. First, the use of non-specific immunopotentiators was introduced. They included stabilized bacteria and bacterial cell wall preparations. In addition, the immunopotentiating effects of β-1-3 glucan-containing fungal polysaccharides were extensively studied in Japan. Thus, some of the various glucans studied obtained government approval for medical use. In Table I, immunopotentiating agents approved by the Department of Health, Welfare and Labor and their indications are shown.

In the 1980s, due to profound progress in the field of genetic engineering, recombinant cytokines became readily available. This situation promoted the use of cytokines in the therapy of cancer; they included interferons, interleukins, tumor necrosis factor and colony stimulating factors, some of which (see Table II) have gained government approval for use in cancer therapy.

Then, in the latter half of the 1980s, immuno-cell therapy was introduced in Japan. Immuno-cell therapy is a type of cell therapy in which cells of the immune system are cultured and processed *ex vivo* and administered to patients for treatment of diseases. Immuno-cell therapy is performed using autologous cells with some exceptions. Currently, the two major fields of this therapy are autologous activated lymphocyte therapy (adoptive immunotherapy) and dendritic cell vaccination therapy, both of which include various variations.

At first, the therapeutic procedure was a direct copy of the lymphokine-activated killer (LAK) and tumor-infiltrating lymphocyte (TIL) therapies of Rosenberg *et al.* (1,2). As in western counties, these therapies were at first accepted with enthusiasm but later ended in disappointment. The therapies were accompanied with high-dose interleukin-2 (IL-2) administration. The reasons for the disappointment were the severe side-effects due to the administration of IL-2 and the limited efficacy of the therapies. However, some researchers continued to try variations of immuno-cell therapy. As a result of such trials, CD3-LAK therapy (3) is currently the predominantly used immuno-cell therapy in Japan. In this therapy, T cells that are activated and proliferated by culturing lymphocytes, mostly peripheral blood mononuclear cells, under stimulation with immobilized CD3-antibody and IL-2 are

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Table I. *Non-specific immunopotentiators with anti-cancer activity approved by the Department of Health, Labor and Welfare of Japan.*

Product	Origin	Indication
BCG	Bacillus calmette guerin (freeze-dried)	Bladder cancer (intrabladder administration)
OK432	Streptococcus biogenes (Penicillin-treated)	Stomach cancer after operation Lung cancer (with themotherapy) Gastrointestinal and lung cancers with ascites or pleural exudate Head and neck cancers after chemotherapy Thyroid cancer Lymphoangioma
PSK	Coriolus versicolor Quel	Gastrointestinal cancer after operation (with chemotherapy) Small cell lung cancer (with chemotherapy)
Schizophyllan	Schyzophylum commune	Uterine cervix cancer (with radiation therapy)
Lentinan	Lentinus edodes	Stomach cancer (inoperable or recurrent, with chemotherapy)

Table II. *Recombinant cytokines with anti-cancer activity approved by the Department of Health, Labor and Welfare of Japan.*

Product	Indication
Interleukin-2	Hemangiosarcoma
Interferon α	Kidney cancer, multiple myeloma, hairy cell leukemia, chronic myelotic leukemia, hepatitis B, hepatitis C, *etc.*
Interferon α-2a	Kidney cancer, multiple myeloma, hepatitis C
Interferon β	Glyoblastoma, astrocytoma, medulloblastoma, skin melanoma, hepatitis B, hepatitis C
Interferon β-1b	Multiple myeloma
Interferon γ-1a	Kidney cancer, severe infection associated with chronic granulosis

repeatedly administered to patients without the use of a high-dose IL-2 administration. This therapy has few undesirable severe side-effects. From the 1990s to the present, autologous activated lymphocyte therapy, including LAK, TIL, CTL and CD3-LAK therapies, has been performed as therapeutic research in many university hospitals and cancer centers. Some of these medical institutions carry out the therapy under approval of the Ministry of Health, Labor and Welfare as a "highly improved medical technology".

In the 1990s, the mechanism of antigen presentation was elucidated and tumor antigen peptides were identified. Following this progress, dendritic cell vaccination therapy was developed (4). This therapy has been studied intensively in university hospitals and cancer centers.

The first private clinic with a cell processing facility and specializing in immuno-cell therapy was established in 1999. Since then the number of such clinics has been increasing. Thus, the number of patients who are treated by immuno-cell therapy markedly increased. The therapy is now in a new stage, becoming accessible to all patients.

Results obtained in Japan on the efficacy of autologous activated lymphocyte therapy

The clinical efficacies of autologous activated lymphocyte therapy obtained in Japan are summarized in Table III. The table also contains representative reports on the original LAK therapy for comparison. There are several publications in Japanese and one publication on alogeneic activated lymphocyte therapy (22), which are not included in Table III-A.

The data shown in Table III are all from retrospective studies without control cases. Therefore, the data cannot be considered statistical evidence of efficacy, but they suggest the usefulness and limitations of the therapy. Table III-A includes reports from 13 groups. Except for one report (16), all of them dealt with the results of research carried out in university hospitals and cancer centers and the number of patients treated by one group is quite limited. The total number of patients described in the 13 reports is 260, while the average number of cases included in one report was 20.0±4.2 (mean±standard error). Patients were mostly in stage IV including those with inoperable and recurrent diseases. The efficacy of the therapy was evaluated according to the criteria of chemotherapy. Patients who completely responded (CR) or partially responded (PR) to the therapy were included in the responsive group, while those whose disease showed no change (NC) or remained progressive (PD) were included in the non-responsive group. In two of the reports (16,17), patients who remained in NC for a period of more than 6 months (prolonged NC, PNC) were included in the responsive group (numbers in

Table III. *Published results of autologous activated lymphocyte therapy carried out in Japan.*

Author (Reference)	Year of publication	Type of therapy	Organ with cancer	Number of patients	Efficacy rate (%)
(A) Reports from Japan					
Baba M *et al.* (5)	1988	LAK therapy high-dose IL-2 local administration	Lung	5	20
Komatsu T *et al.* (6)	1990	LAK therapy IL-2	Lung (primary and metastatic)	26	23
Usui A *et al.* (7)	1990	CD3-LAK therapy low-dose IL-2 plasmapheresis	Kidney	9	11
Yamaguchi Y *et al.* (8)	1991	CD3-LAK therapy Low-dose IL-2	Liver, lung (advanced)	24	20
Nakano E *et al.* (9)	1991	LAK therapy low-dose IL-2 plasmapheresis	Kidney	14	21
Aoki *et al.* (10)	1991	TIL therapy chemotherapy	Ovary (advanced) (cyclophosphamide) (cisplatin)	7	71
				10	90
Nomura K *et al.* (11)	1993	LAK therapy IL-2	Kidney	11	18
Ibayashi Y *et al.* (12)	1993	LAK therapy high-dose IL-2	Brain	9	33
Haruta I *et al.* (13)	1996	LAK therapy or CTL therapy	Liver (CTL) (Stage IV) (LAK)	18	28
				8	0
Tomita Y *et al.* (14)	1996	LAK therapy chemotherapy (cyclophosphamide)	Kidney	9	67
Toh U *et al.* (15)	2000	TIL therapy high-dose IL-2 intratumorous injection	Esophagus	11	36
Goto S *et al.* (16)	2002	CD3-LAK therapy	Various organs with inoperable or recurrent cancer	57	11(30)
Ebina T *et al.* (17)	2003	CD3-LAK therapy	Various organs with advanced cancer	42	14(76)
(B) Repots on the original LAK method					
Rosemberg SA *et al.* (1)	1986	LAK therapy high-dose IL-2	Various cancer (stage IV)	41	34
Roseberg SA *et al.* (18)	1987	LAK therapy high-dose IL-2	Various cancer (stage IV)	108	22
Steis RG *et al.* (19)	1990	LAK therapy high-dose IL-2 intraperitoneal injection	Various intraperitoneal cancer	24	29
Thompson JA *et al.* (20)	1992	LAK therapy high-dose IL-2	Kidney (stage IV)	22	41
Rosenberg SA *et al.* (21)	1993	LAK therapy with or without high-dose IL-2	Various cancer (stage IV)		
				(with IL-2) 85	28
				(without IL-2) 79	20

parentheses). PNC is considered quite beneficial to the patients when the therapy does not produce considerable side-effects (16). In these reports, the efficacy rate including the PNC is apparently higher than that not including the PNC. With some exceptions, in which the number of patients was less than 10, the response rates of systemically

Table IV. *Statistical evidence of efficacy of autologous activated lymphocyte therapy obtained in prospective randomized controlled studies.*

Author (Reference)	Year of publication	Object and therapy	Number of patients Treated	Control	Effect	Statistical significance
Fujita K et al. (23)	1995	Ovarian cancer after resection and chemotherapy (TIL therapy)	13	11	Increase in survival rate disease-free survival rate	$p<0.01$ $p<0.05$
Kimura H et al. (24)	1997	Lung cancer (stage II ~ IV) after resection and chemotherapy or radiotherapy (LAK or TIL therapy)	82	88	Increase in survival rate	$p<0.001$
Takayama T et al. (25)	2000	Liver cancer after curative resection (CD3-LAK therapy)	74	76	Increase in survival rate Increase of disease-free survival rate	$p<0.09$ $p<0.01$
Kono K et al. (26)	2002	Stomach cancer (stage IV) chemotherapy (CTL therapy) intraperitoneal injection	22	22	Increase in survival rate	$p<0.05$

administered activated lymphocytes were generally between 10 and 25%. The overall response rate of the 260 patients not including the PNC was 23.8%. On the other hand, Table III-B shows the response rates of the original LAK therapy combined with IL-2 administration described in the representative five reports (1,18-21). The overall response rate was 27.9% (78 responsive patients among 280 patients who underwent this therapy). However, high-dose IL-2 administration alone shows effectiveness (21). These results suggest that CD3-LAK therapy without IL-2 administration is not significantly different in efficacy from LAK therapy combined with toxic high-dose IL-2 administration.

In addition to the retrospective studies mentioned above, it is notable that there are other studies on prospective randomized controlled trials of autologous activated lymphocyte therapy. They are summarized in Table IV. When the therapy was performed on patients after the surgical resection of ovarian cancer (23), lung cancer (24) and liver cancer (25), it increased long-term survival rate or disease-free survival rate with statistical significance. This result shows that the therapy is effective at least when the number of the target cancer cells in the body of the patient is low. With regard to stomach cancer, it was demonstrated that the cytotoxic T lymphocyte (CTL) therapy, combined with chemotherapy, increased the survival rate of the patients in stage IV (26). These results seem to reveal that we could expect a better efficacy of immuno-cell therapy when used in combination with other therapies that bring about immediate reduction in tumor size. These therapies include standard cancer therapies such as surgical resection, radiation therapy and even chemotherapy.

Immuno-cell therapy today

At present, at least 15 large public medical institutions are carrying out autologous activated lymphocyte therapy. Seven of them have the approval from the Department of Health, Labor and Welfare as "highly advanced medical technology". Also, more than 25 large medical institutions are carrying out dendritic cell vaccination therapy. However, the number of patients who underwent these therapies in these medical institutions has been low. The reports from the above-mentioned 13 institutions covered only 260 patients over a period of 15 years. In 1999, the Seta Clinic was established in Tokyo as the first private clinic specializing in immuno-cell therapy, followed by several other clinics. Thus, the number of patients who underwent the therapy increased very rapidly. The Seta Clinic has extended to form a group with three other independent clinics. Each of them is equipped with aseptic rooms for cell culture and a common standard operation manual. The assurance of safety is carried out by self-regulation of the clinics in accordance with good manufacturer's practice guidelines applied on production of pharmaceutical materials.

Our experience in two leading clinics of the group (established in 1999 and in 2001) is summarized in Tables V and VI. In these clinics, 1401 patients with various tumors had received more than 6 infusions of autologous activated lymphocytes before the end of 1993. These patients included patients with various tumors. With a very few exceptions, they were all in stage IV. The tumor sizes of 809 of the 1401 patients were not measurable by X-ray examination. The efficacy of the therapy was evaluated by the changes in tumor size measured before and after the therapy. The evaluation

Table V. *Patients who received more than 6 infusions of autologous activated lymphocytes in Seta Clinic (1999～2003) and Shinyokohama Medical Clinic (2001～2003), Japan.*

Total number of patients	1401
Number of patients who could not be evaluated	809 (57.7 %)
Number of patients who could be evaluated	592 (42.3 %)
Immuno-cell therapy alone	284 (48.0 %)
Immuno-cell therapy in combination with chemotherapy or radiation therapy	308 (52.0 %)
Therapy on the patients who could be evaluated	
CD3-LAK[1)]	526 (88.9 %)
CTL[2)]	20 (3.4 %)
DC-CTL[3)]	8 (1.4 %)
CD+LAK[4)]	38 (6.4 %)

1) Lymphocytes were stimulated with an immobilized CD3 antibody and IL-2.
2) Lymphocytes were stimulated with autologous tumor cells and then with an immobilized CD3 antibody and IL-2.
3) Lymphocytes were stimulated with autologous dendritic cells pulsed with tumor lysate or with antigenic peptides and then with an immobilized CD3 antibody and IL-2.
4) Autologous dendritic cells, as in 3, were administered as therapeutic vaccine together with lymphocytes, as in 1.

Table VI. *Efficacy of autologous activated lymphocyte therapy (summary of results obtained in Seta Clinic (1999-2003) and in Shinyokohama Medical Clinic (2001-2003), Japan.*

(A) Basis of calculation	Efficacy rate (%)
592 patients that could be evaluated	
Including PNC in responsive patients	
Total	26
Immuno-cell therapy alone	20
Immuno cell therapy combined with chemotherapy or radiotherapy	31
Not including PNC in responsive patients	
Total	15
Immuno-cell therapy alone	9
Immuno-cell therapy combined with chemotherapy or radiotherapy	21

(B) Type of autologous activated lymphocyte therapy	Efficacy rate including PNC
CD3-LAK therapy (526 patients)	
Total	25
Immuno-cell therapy alone	21
Immuno-cell therapy in combination with chemotherapy or radiotherapy	28
(CTL therapy, DC-CTL therapy or DC+LAK therapy) (66 cases in total)	
Total	36
Immuno-cell therapy alone	14
Immuno-cell therapy in combination with chemotherapy or radiotherapy	50

was carried out according to the criteria for the evaluation of the efficacy of chemotherapy. Of the 592 patients whose tumor size could be measured, more than half received lymphocyte infusion alone without any standard therapy. Most of the patients in this group had malignancies that failed to respond to any of the standard therapies.

In the above-mentioned two clinics, four types of autologous activated lymphocyte therapy shown in Table V have been performed. Nearly 90% of the patients received CD3-LAK therapy; other patients received therapies in which specific antigenic stimulation was carried out. Because of the difference between the backgrounds of the patients studied, no conclusion can be drawn from the comparison of the efficacy rates of the two groups. However, the result suggests that there is a tendency for the therapy to be particularly effective when combined with standard therapies in the latter group. The efficacy rate obtained from the 529 patients is 15% when PNC is not included and 26% when it is included. In both cases, the group treated with a combination of immuno-cell therapy and standard therapy showed higher efficacy rates than the group treated with immuno-cell therapy alone. The overall efficacy rate of the therapy when PNC is included in the responsive patients is 31%. Although these efficacy rates were obtained in retrospective studies, some suggestions about the usefulness and limitation of the therapy seem to have been obtained because the number of the patients studied was large. The efficacy rate and the absence of harmful side-effects seem to support the view that the therapy is beneficial to patients with advanced cancer.

Conclusion

Some lines of evidence regarding the efficacy of autologous activated lymphocte therapy have been established in Japan. Also many cancer patients have been subjected to immuno-cell therapy, mainly CD3-LAK therapy in private clinics specializing in such therapy. A retrospective study on a large number of patients seems to reveal that immuno-cell therapy is beneficial to patients with advanced malignancies as well as to patients with residual cancer after standard therapies. Adequate combinations of immuno-cell therapy with standard therapies, which reduce tumor sizes, is recommendable.

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