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A Report of Three Patients Treated with Immunocell Therapy with Imatinib Mesylate

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Abstract. *Background: Immunocell therapy has been applied to patients with refractory cancer in clinical trials or as an unconventional cancer therapy, however the efficacy is still limited. To improve this efficacy, a combination therapy may be beneficial. Molecularly-targeted therapy acts directly on neoplasm cells to suppress their growth without causing myelosuppression. Case Report: Recently, we encountered three patients treated by immunocell therapy with imatinib mesylate (Glivec®). One patient was diagnosed as having Philadelphia chromosome (Ph) (+) acute lymphoblastic leukemia (ALL) and had a relapse-free survival of more than 24 months. The other two were diagnosed as having GIST; a partial response was observed in one which lasted more than 21 months, while the other's disease has been stabilized for more than 25 months. No side-effects were observed, other than those mentioned in the directions for the use of imatinib. Conclusion: Immunocell therapy may have a potent therapeutic effect when used in combination with molecularly-targeted therapy, which has few side-effects.*

A beneficial effect of an immunotherapy using immune cells processed *ex vivo* has been reported for some malignancies. Immunocell therapy of cancer using autologous lymphocytes activated *ex vivo* was first introduced by Rosenberg *et al.* in the late 1980s (1), and is still under development. Recently, more attention has been paid to dendritic cell-based immunotherapy, which can be another option in immunocell therapy (2). Dendritic cells (DCs) are professional antigen-presenting cells that induce cytotoxic T lymphocytes against tumor cells. DCs were induced to differentiate from peripheral blood monocytes using granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-4 (IL-4) (3). DCs pulsed with cancer antigens were used as a DC vaccine. Such modalities of immunocell therapy have been applied to patients with refractory cancer in clinical trials or as unconventional cancer therapies. We administered such immunocell therapy to a large number of patients with advanced cancer, however its therapeutic efficacy was limited (3). The response rates of this therapy were reported by previous researchers including us to be between 10 to 20% (3-7). Some investigators reported favorable efficacies of this therapy when used in combination with chemotherapy, but it was still limited (8,9). Chemotherapy has a myelosuppressive effect, leading to a failure of the immune system, so the effect of immunocell therapy may be decreased when used in combination. Recently, molecularly-targeted therapy has been developed and extensively employed in the treatment of cancer. Its agents directly inhibit receptor activation implicated in the proliferation and survival of cancer cells, resulting in tumor regression while they are not toxic to leukocytes. These agents may be used in promising combination therapies. Our preliminary clinical study on the combination of immunocell therapy and gefitinib (Iressa®) in non-small cell lung carcinoma showed a much higher response rate (11 cases exhibiting partial response out of 18 cases, unpublished observation) than that observed in a previous clinical trial of gefitinib (10).

Philadelphia (Ph) chromosome is characterized by the reciprocal t(9;22) translocation that results in a bcr-abl fusion gene encoding a chimeric 210 kD fusion protein in chronic myeloid leukemia (CML) or 190 kD fusion protein in Ph+ acute lymphoblastic leukemia (ALL) (11-14). The junction-spanning sequences of these fusion proteins could be ideal

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Key Words: Immunocell therapy, molecularly-targeted therapy, Imatinib mesylate, Ph(+)ALL, GIST.

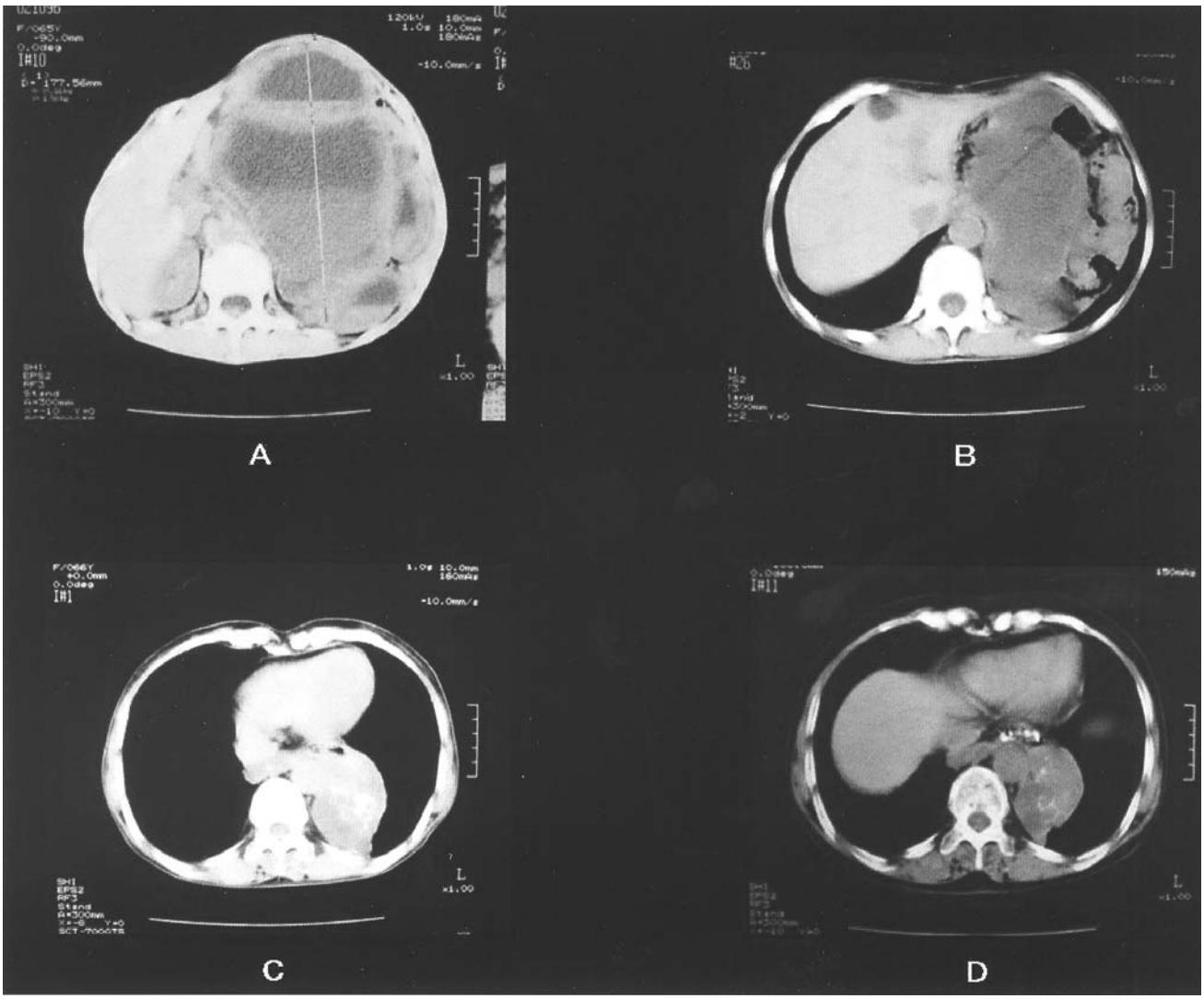

Figure 1. *After receiving the combination therapy, CT scans of Case 2 show a gradual decrease in tumor size; from 177.56x117.65 mm on 11 July 2002 (A) to 117.65x79.41 mm on 30 October 2002 (B), and further to 70.11x55.32 mm on 7 January 2003 (C), with a final decreased to 65.34x44.23 mm on 22 July 2003 (D).*

targets for immunotherapy. The coauthor Nieda has previously demonstrated that DCs pulsed with synthesized 17-mer bcr-abl fusion peptides could generate specific cytotoxic T cells, therefore these 17-mer peptides may be good candidates as antigens in DC-based immunotherapy for Ph(+) leukemia (15,16).

Imatinib mesylate (Glivec®, Novartis) is a selective inhibitor of bcr/abl tyrosine kinase, which is an abnormality causing CML or ALL (17,18). On the other hand, imatinib is also active against other tyrosine kinases, such as c-KIT or platelet -derived growth factor receptors (PDGF-Rs), whose inhibition may have potential implications in the treatment of several malignancies. In this context, imatinib has already been shown to exhibit a marked activity against ALL, CML and gastrointestinal stromal tumors (GIST) (19-22).

To date, we have encountered three patients with ALL or GIST who underwent a combination of immunocell therapy and imatinib mesylate and who have been followed-up for more than 20 months. Herein we report the good course of their disease.

Methods of Generating Activated Lymphocytes and DCs

Activated lymphocytes were generated by methods described elsewhere (3). Briefly we obtained about 22.5 ml of peripheral blood and then mononuclear cells (MNCs) were separated

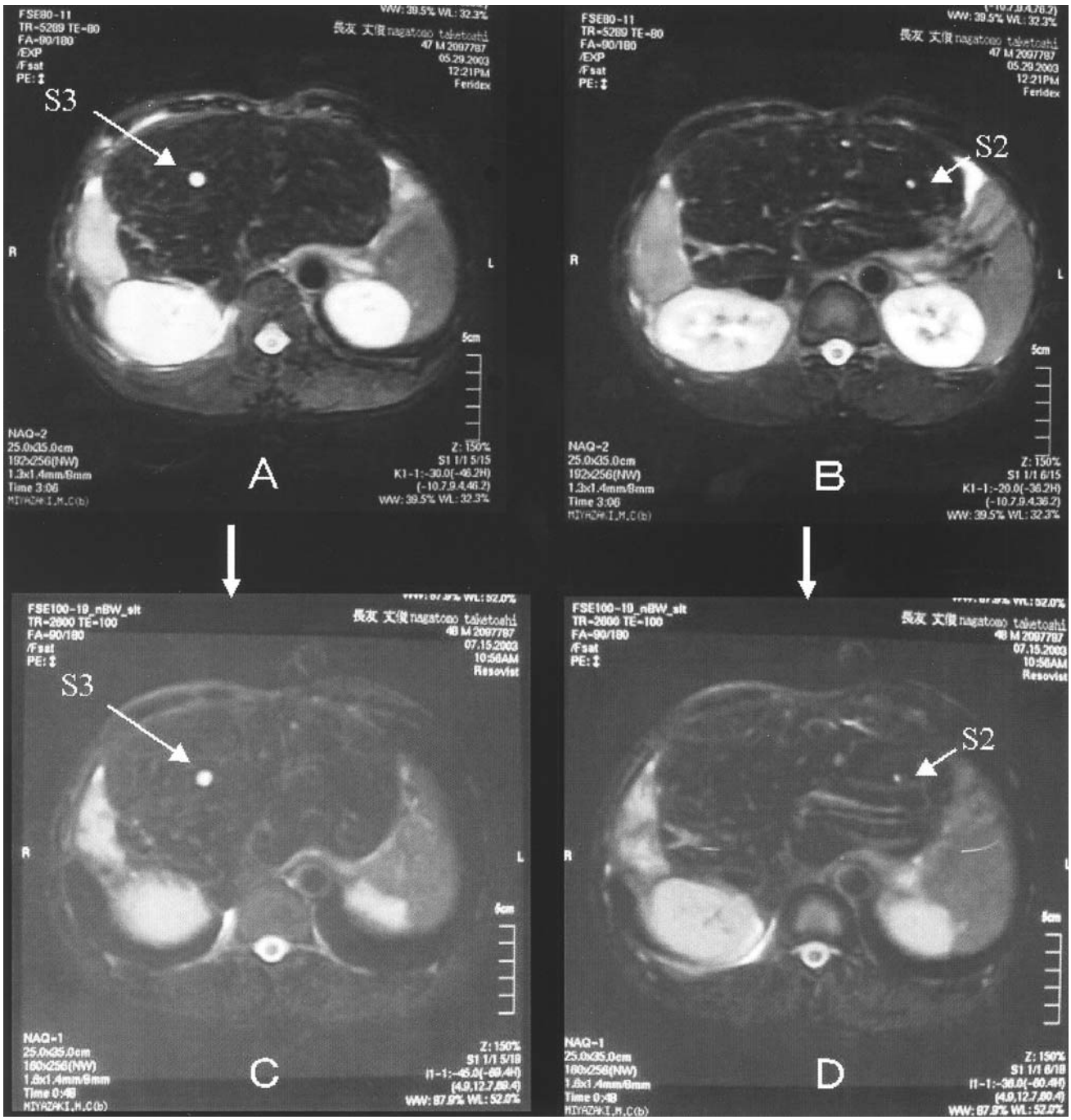

Figure 2. *In Case 3, ferridex MRI performed on 29 May 2003 showed two significant lesions, one 1.1cm lesion in the S3 area of liver (A) and one 0.6cm lesion in the S2 area (B). Ferridex MRI, performed on 15 July 2003, showed that both lesions slightly decreased in size (C, D).*

using *VACUTAINER* (Becton Dickinson NJ, USA). They were cultured for 2 weeks with 700 IU/ml recombinant interleukin-2 (Proleukin®, Chiron, Amsterdam, Netherlands) following activation with immobilized anti-CD3 monoclonal antibody (Janssen-Kyowa, Tokyo, Japan) using HyMedium 930 (Kohjin Bio, Saitama, Japan) containing 1% autologous serum. After culturing for 14 days, 3-10x10^9 cells were harvested and suspended in 100 ml of saline for intravenous injection. To generate DCs, 45 ml of peripheral blood was collected and MNCs were separated. Then, MNCs were allowed to adhere to

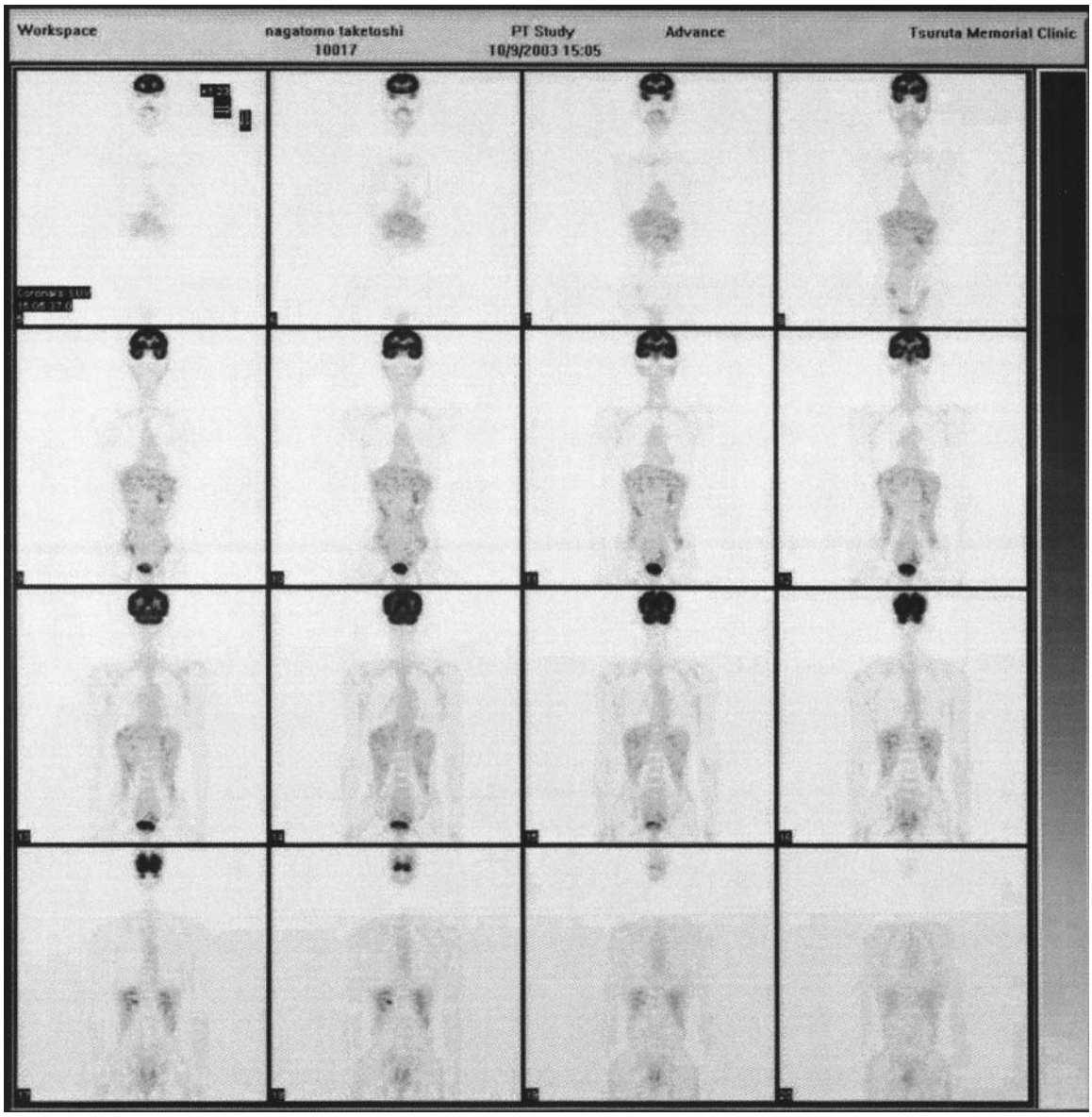

Figure 3. *In Case 3, positron emission tomography (PET), performed on 9 October 2003 showed no extraordinary accumulation.*

the plastic culture flask to obtain adherent cells. After removal of nonadherent cells, the adherent cells were cultured in the presence of 50 ng/ml GM-CSF (Primmune Corp, Osaka, Japan) and 50 ng/ml IL-4 (Primmune Corp, Osaka, Japan) for 6 days to generate immature DCs. Twenty-four hours prior to administration, DCs were cultured with the appropriate antigens for the tumors and approximately 1-5x10^6 DCs were harvested for intravenous injection.

Case No 1

In February 2002, a 77-year-old man with anemia was diagnosed as having acute lymphoblastic leukemia, which was classified as FAB L3. His medical history was unremarkable. The Ph chromosome, which had the following karyotype, 46XY; del (6), (p11p21), t (9; 22), (q34; q11), was identified in his leukemia cells. He received five courses of AdVP chemotherapy from March 2002 to May 2002. He achieved complete remission after the first course and was administered four more courses to maintain the stable condition. In the subsequent courses of the chemotherapy, he started to receive 200 mg of imatinib from 8 March 2002. Immunocell therapy using activated lymphocytes as well as DCs was initiated at Seta Clinic on 13 September 2002. DCs were pulsed with p190 minor bcr-abl fusion 17-mer peptide (ela2; EGAFHGDAEALQRPVAS). Imatinib was decreased

to 100 mg/day from 27 August 2003, and the immunocell therapy was administered every 2 weeks until May 2004. The patient has received this combination therapy for more than 20 months and he has kept in complete remission without any evidence of hematologic or genetic disorders. The observed side-effects of this therapy were edema of the face, legs and larynx, diarrhea, numbness of the fingers and lassitude.

Case No 2

In November 1999, a 66-year-old woman came to our clinic presenting with clinical features of a large abdominal tumor, which involved the diaphragm. She underwent a total gastrectomy. Pathological and immunohistological analyses of the primary lesion revealed the following; c-kit(+), CD34(+), α-SMA(partly+) and S100(-). Thus she was diagnosed as having GIST. She was diagnosed as having a mediastinal mass as well as a local recurrence in November 2001. She, however, requested to undergo a herbal remedy and some other substitute therapies that were started from 26 February 2002, but the recurrent tumor progressed markedly. When the combination of imatinib and immunocell therapy with lymphocytes activated *ex vivo* was started on 2 August 2002, a 21-cm-diameter tumor was palpable in the left hypochondriac region. After receiving the combination therapy, CT showed a gradual decrease in tumor size (Figure 1); from 177.56x117.65 mm on 11 July 2002 to 117.65x79.41 mm on 30 October 2002, and further to 70.11x55.32 mm on 7 January 2003, finally decreasing to 65.34x44.23 mm on 22 July 2003. The CA12-5 level before the treatment was 151 U/ml (normal<35 U/ml) on 2 August 2002, but was normalized to 26 U/ml by 30 October 2002. Her general condition significantly improved; for example, her appetite increased, she gained 3 kg in weight and anemia improved from Hb 8.9 to Hb 10.3 g/dl. The dose of imatinib has been maintained at 200 mg /day since 2 August 2002, while the immunocell therapy was administered 16 times every 2 to 8 weeks until 3 December 2003. She has been showing continuous improvement of the remaining tumor for 21 months, that is, up to May 2004. She had diarrhea and increase in liver enzyme levels to 58 U/ml GOT and 43 U/ml GPT during the treatment, as side-effects. In the early stages of the therapy, generalized itching with eczema of the face and limbs was observed as other side-effects. She also felt stomach discomfort immediately after receiving imatinib.

Case No 3

In February 1999, a 47-year-old man underwent total gastrectomy with a diagnosis of submucosal tumor in the cardiac part of the stomach. Pathological and immunohistological analyses of the primary lesion revealed the following findings; CD34(+), c-kit(+), desmin(-), s-100(-) and α-SMA(-), and thus the diagnosis was GIST. The patient underwent four tumor excision surgeries and microwave solidification of liver metastases, on 1 May 2000, 27 November 2000, 22 February 2002 and 9 December 2002. Imatinib mesylate at a dose of 100 to 300 mg/day was administered, which was adjusted according to his condition; *i.e.* depending on the side-effects on his digestive system. Moreover, the immunocell therapy was initiated on 23 April 2002. Sonography and Ferridex MRI performed on 29 May 2003 showed two significant lesions, one 1.1 cm lesion in the S3 area of the liver and one 0.6 cm lesion in the S2 area. Ferridex MRI performed on 15 July 2003 showed that the tumors had decreased slightly in size (Figure 2). Positron emission tomography (PET) performed on 9 October 2003 showed no extraordinary accumulation (Figure 3). Imatinib continues to be administrated at a dose of 100 mg /day. The tumor did not progress up to May 2004, that is for 25 months. He showed several symptoms of the side-effects on his digestive organs such as diarrhea.

Discussion

Bcr/abl is one of the most common and clinically relevant molecular abnormal rearrangements in acute ALL and is associated with a poor prognosis due to a high relapse rate. Preliminary data for imatinib used as a single drug for Ph(+) ALL, which is refractory or has relapsed after a standard chemotherapy or after allogenic stem-cell transplantation, have shown hematological response rates of 20%-55%, which are typically obtained within the first month of the therapy (19,20). However, the responses are usually short-lived, with most of the relapses occurring in the first 3 months of treatment. Because of this, imatinib is currently being investigated for its potential use in combination with conventional chemotherapies such as Hyper-CVAD, but the results are yet to be elucidated (22).

Ph(+) ALL patients failing to respond to an initial induction chemotherapy have a poor prognosis with few effective treatment options. There was a very interesting clinical trial involving 56 patients with relapsed or refractory Ph(+)48 ALL and 8 CML patients with lymphoid blast crisis (23). Imatinib was administered once daily at 400 mg or 600 mg. Imatinib induced complete hematological responses (CHRs) and complete marrow responses (marrow-CRs) in 29% of the ALL patients (CHR, 19%; marrow-CR, 10%), which were sustained for at least 4 weeks in 6% of them. The median estimated time to progression and the overall survival of ALL patients were 2.2 and 4.9 months, respectively. These previous observations indicated a shorter duration of response to imatinib. A poor prognosis of ALL was noted in elderly patients more than 60 years old. There have been no

adequete results on the adjuvant effect of imatinib in patients who completely responded to the induction chemotherapy. Among the elderly patients, case 1 has been saved from a recurrence for more than 24 months. This suggests the advantage of the combination therapy.

GIST are composed of KIT-positive mesenchyme-originating spindle or polygonal tumor cells in the gastrointestinal tract without immunoreactivity to desmin and S-100. According to recent studies, GIST are caused by the gain of function mutations of the c-KIT gene (90%) (24,25) or the PDGF-Rα gene (5%) (26,27). Imatinib shows a high response rate and efficacy in nonresectable and/or relapsed GIST (PR 60%) (28). Two patients presented here had a partial response or stable disease which lasted for more than 20 months.

All the 3 patients treated with the combination therapy showed some side-effects, such as grade 1 or 2 diarrhea, mild liver dysfunction, eczema and edema. It seems that these side-effects were caused by imatinib and not by the immunocell therapy(29).

The significance of the combination of immunocell therapy and molecularly-targeted therapy must be considered. To maximise the immunocell therapy itself, it may be beneficial to use a larger number of infused cells, enhance cytotoxic activity and concentrate their administration to a local area of the tumor. To this end, continued research on cell processing is required. On the other hand, combination therapy that inhibits the growth of tumor cells may be another way to make the immunocell therapy successful. Molecularly-targeted therapy without myelosuppression can be an ideal candidate for the combination when compared with toxic chemotherapies or radiotherapies. Additionally, it seems that the combination with molecularly targeted therapy produces lessside-effects than the combination with chemotherapy. Several molecularly-targeted agents, such as imatinib, gefitinib and trastumab are used in clinical practice for GIST, non-small cell lung carcinoma or breast cancer, respectively. The targeted molecules are c-kit, PDGF-Rs or epidermal growth factor receptor, implicated in the proliferation of cancer cells. PDGF-Rs are expressed on various solid tumors, such as glioma, synovial sarcoma, melanoma, aggressive fibromatosis, germ cell tumors, neuroblastoma, small cell lung carcinoma, breast carcinoma, prostate carcinoma and ovarian carcinoma (30,31), and are attractive targets for therapeutic intervention. The combination therapy may be applicable to various tumors other than leukemia or GIST.

Conclusion

To date only three patients have been treated with this combination of imatinib and immunocell therapy. All the patients had a relapse-free survival, partial response or prolonged stable disease. The duration of their treatment effects was more than 20 months from initiation of immunocell therapy. Although the number of patients reported here is too small, the potential of the combination therapy is obvious.

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