

## Department of Internal Medicine

### Division of Clinical Oncology/Hematology

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### General Summary

The immediate goals of our clinical and basic research are to investigate basic and clinical aspects of malignant diseases and to try to improve outcomes for patients with hematological malignancies and solid tumors, leading to the ultimate goal of improving the natural history of malignant diseases. We have also been performing several clinical trials and basic research studies throughout 2007.

#### *Leukemias*

Many patients with previously untreated hematological disorder have been referred to our department. The disorders include acute myeloid leukemia (AML), 16 cases; acute promyelocytic leukemia (APL), 2 cases; acute lymphoblastic leukemia (ALL), 7 cases, including 3 cases of Philadelphia chromosome — positive ALL; chronic myeloid leukemia (CML), 5 cases; and myelodysplastic syndrome (MDS), 10 cases. We have performed clinical trials as a member of the Japan Adult Leukemia Study Group (JALSG), which is a distinguished leukemia research group established more than 20 years ago in Japan for AML, ALL, and CML. The JALSG protocol studies performed in 2007 were as follows: AML/MDS-HR CS-7 study (newly diagnosed AML, refractory anemia with excess blasts II, all case registration: cohort study), AML-201 VLA4 study (prognosis evaluation study), AML-206 DNR assigned group (relapse and refractory AML: phase I), APL-204 (phase III), APL-205R (relapsed and refractory APL: phase II), and ALL-202 (phase III). We also performed several cooperative group studies and pilot studies: Aged Double-7 (newly diagnosed aged AML: phase II), V EGA (MDS: phase II), nilotinib (refractory CML: phase I/II), and dasatinib study (refractory CML: phase I/II).

#### *Lymphomas*

In 2007 we registered patients with newly diagnosed non-Hodgkin's lymphoma (NHL), 65 cases, or Hodgkin's lymphoma (HL), 5 cases. We have performed clinical trials as a member of the Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG-LSG). The studies JCOG0211-DI (newly diagnosed natural killer/T lymphoma: phase I/II) and JCOG0203-MF (newly diagnosed follicular lymphoma: phase III) were pivotal protocol studies in 2007. Other cooperative studies examined

biweekly rituximab, etoposide, prednisone, vincristine, hydroxydaunorubicin (R-EPOCH; relapsed and refractory B cell lymphoma: phase II), pirarubicin, cyclophosphamide, vincristine, and prednisolone (THP-COP; newly diagnosed T-cell lymphoma: phase II), and enzastaurin (NHL: phase III, double blind). Enzastaurin is a novel drug targeting protein kinase  $C\beta$  that has been extensively studied throughout the world, including the United States, the European Union, and Japan.

### *Myeloma*

We completed our original pilot study evaluating a combination of thalidomide and dexamethasone in 2007. A novel agent, the proteasome inhibitor bortezomib, became available in 2007, and we have used it to treat patients who have refractory myeloma.

### *Hematopoietic stem cell transplantation*

To investigate and establish safer and more effective hematopoietic stem cell transplantation (HSCT), we have performed serial clinical studies examining umbilical cord blood transplantation with a bone marrow-nonablative procedure, a bone marrow — nonablative procedure using antithymic globulin, and mechanisms of graft-versus-host disease in HSCT.

### *Solid tumors*

Several of our studies are in progress throughout our university hospital with related divisions or departments, seeking improved therapeutic outcomes. Fluorouracil (5-FU), 500 mg/m<sup>2</sup>; epirubicin, 100 mg/m<sup>2</sup>; and cyclophosphamide, 500 mg/m<sup>2</sup> (FEC100) with or without taxotere therapy is an adjuvant therapy for patients with breast cancer treated with curative surgery. FEC100 followed by taxotere is a preoperative combination chemotherapy for patients with locally advanced breast cancer. AT — followed by taxotere and herceptin is a first-line chemotherapy for patients with advanced metastatic breast cancer. The standard treatment for operable, locally advanced esophageal cancer has been altered, resulting in the use of chemoradiation therapy rather than surgical resection. We, therefore, have been investigating a combined modality therapy of radiation and chemotherapy with low-dose cisplatin and 24 hours' continuous infusion of 5-FU for such patients since 2002. The results will be reported next year. For patients with advanced gastric cancer, a combination chemotherapy of S-1 and cisplatin has been performed. Our first-line chemotherapies for patients with advanced colorectal cancer are folinic acid, 5-FU, and irinotecan (FOL-FIRI) and folinic acid, fluorouracil, and oxaliplatin (FOLFOX).

### *Palliative care*

The mission of the Palliative Care Team for Cancer Pain Purposes is to relieve patients' pain and anxiety to support the fight against cancer. Our team encourages the use of narcotics and improved the control of cancer pain.

In our new division, we aim to attain individual goals by sharing our thoughts and to contribute to the further growth of palliative care at The Jikei University School of Medicine.

*Basic research*

One of our important activities is translational research on hematological malignancies and solid cancers. The structural differences between M protein produced by myeloma cells and that from monoclonal gammopathy of undetermined significance have been examined, and the function of ATP-binding cassette transporters in cancer chemotherapy has also been studied in collaboration with the Kyoritsu University of Pharmacy (Keio University Department of Pharmacy).

**Publications**

**Saito T, Usui N, Asai O, Dobashi N, Yano S, Osawa H, Takei Y, Takahara S, Ogasawara Y, Otsubo H, Yamaguchi Y, Minami J, Hoshi Y, Kataoka M, Aiba K.** Elevated serum levels of human matrix metalloproteinase-9 (MMP-9) during the induction of peripheral blood stem cell mobilization by granulocyte colony-stimulating factor (G-CSF). *J Infect Chemother* 2007; **13**: 426-8.

**Mitsuhashi J, Tsukahara S, Suzuki R, Oh-hara Y, Nishi S, Hosoyama H, Katayama K, Noguchi K, Minowa S, Shibata H, Ito Y, Hatake K, Aiba K, Takahashi S, Sugimoto Y.** Retroviral integration site analysis and the fate of transduced clones in an MDR1 gene therapy protocol targeting metastatic breast cancer. *Hum Gene Ther* 2007; **18**: 895-906.

**Takahashi N, Nimura H, Aoki H, Koyama T, Mitsumori N, Aiba K, Kashiwagi H, Yanaga K.** Successful preoperative chemotherapy with S-1 plus low-dose cisplatin for advanced gastric cancer with synchronous liver metastases: report of 2 cases. *Chemotherapy* 2007; **53**: 378-82.

**Takahashi S, Aiba K, Ito Y, Hatake K, Nakane M, Kobayashi T, Minowa S, Shibata H, Mitsuhashi J, Tsukahara S, Ishikawa E, Suzuki R, Tsuruo T, Sugimoto Y.** Pilot study of MDR1 gene transfer into hematopoietic stem cells and chemoprotection in metastatic breast cancer patients. *Cancer Sci* 2007; **98**: 1609-16.

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**Yano S, Asai O, Dobashi N, Osawa H, Takei Y, Takahara S, Otsubo H, Ogasawara Y, Yamaguchi**

**Y, Saito T, Minami J, Hoshi Y, Usui N.** Long-term follow-up of autologous stem cell transplantation for patients with aggressive non-Hodgkin lymphoma who had bone marrow involvement at initial diagnosis in the pre-rituximab era. *Clin Lymphoma Myeloma* 2007; **7**: 361-3.

**Kaito K, Otsubo H, Takahara S, Hyouki M, Abe M, Abe I, Usui N.** Carcinoembryonic antigen-producing multiple myeloma detected by a transcription-reverse transcription concerted reaction system. *Int J Hematol* 2007; **85**: 128-31.

**Suzuki H, Arakawa Y, Ito M, Saito S, Takeda N, Yamada H, Horiguchi-Yamada J.** MLF1-interacting protein is mainly localized in nucleolus through N-terminal bipartite nuclear localization signal. *Anticancer Res* 2007; **27**: 1423-30.

**Yamada H, Sekikawa T, Iwase S, Arakawa Y, Suzuki H, Agawa M, Akiyama M, Takeda N, Horiguchi-Yamada J.** Segregation of megakaryocytic or erythroid cells from a megakaryocytic leukemia cell line (JAS-R) by adhesion during culture. *Leuk Res* 2007; **31**: 1537-43.

**Reviews and Books**

**Inoue D, Hayashi K, Kobayashi T, Yoshizawa T, Mouri J, Sakuyama T, Keisuke Aiba.** Usefulness of oxycodone for pain control in patients with Ewing's sarcoma. *Eur J Pain* 2007; (SupplA).

**Inoue D, Mori S, Arakawa Y, Sakuyama T, Kobayashi T, Aiba K.** A case of recurrent breast cancer suggesting chemotherapy affected the pain control with oxycodone. *Eur J Pain* 2007 Dec. 5 (SupplA).