

Department of Internal Medicine

Division of Clinical Oncology/Hematology

Keisuke Aiba, *Professor*
Fumi Mizorogi, *Professor*
Daisuke Inoue, *Associate Professor*
Hidekazu Masuoka, *Assistant Professor*
Kaichi Nishiwaki, *Assistant Professor*
Yuhichi Yahagi, *Assistant Professor*
Yoji Ogasawara, *Assistant Professor*

Tadashi Kobayashi, *Professor*
Noriko Usui, *Associate Professor*
Takaki Shimada, *Assistant Professor*
Nobuaki Dobashi, *Assistant Professor*
Shingo Yano, *Assistant Professor*
Yutaka Takei, *Assistant Professor*
Katsuki Sugiyama, *Assistant Professor*

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 solid tumors and hematological malignancies, leading to the ultimate goals of improving the natural history of malignant diseases. We have also been performing several clinical trials and basic research studies throughout 2011.

Research Activities

Leukemias

Many patients with previously untreated hematological disorders have been referred to our department. The disorders in 2011 included acute myeloid leukemia (AML), 20 cases; acute lymphoblastic leukemia (ALL), 4 cases; chronic myeloid leukemia (CML), 5 cases; and myelodysplastic syndrome (MDS), 9 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 2011 were as follows: AML/MDS-HR CS-7 study of newly diagnosed AML; refractory anemia with excess blasts II, all-case registration cohort study; APL-204 (phase III); CML-207 (phase III); AML-209-GS; and AML209-KIT. We also participated in several cooperative group studies and pilot studies: Aged Double-7 (newly diagnosed AML in the elderly: phase II), VEGA (MDS: phase II), a study of nilotinib (refractory CML: phase I/II), and a study of dasatinib (refractory CML: phase I/II).

Lymphomas

In 2011 we registered 69 patients with newly diagnosed non-Hodgkin's lymphoma and 1 patient with Hodgkin's lymphoma. We have performed clinical trials as a member of the Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG). The studies JCOG0406 (newly diagnosed mantle cell lymphoma: phase II) and JCOG0601 (newly diagnosed low risk advanced diffuse large B cell lymphoma: phase II/III) were pivotal protocol studies beginning in 2010. A randomized phase II study in patients with high-risk diffuse large B-cell lymphoma has also been started (bi-R-CHOP±CHASER vs

LEED; JCOG0908). Other cooperative studies examined biweekly rituximab, etoposide, prednisone, vincristine, hydroxydaunorubicin (R-EPOCH: relapsed and refractory B-cell lymphoma: phase II) and pirarubicin, cyclophosphamide, vincristine, and prednisolone (THP-COP: newly diagnosed T-cell lymphoma: phase II). A study of enzastaurin (non-Hodgkin's lymphoma: phase III double-blind) has been completed. Enzastaurin is a novel drug targeting protein kinase C β which has been extensively studied throughout the world, including in the United States, the European Union, and Japan.

Myeloma

We registered 13 patients with newly diagnosed multiple myeloma in 2011. A novel agent, the proteasome inhibitor bortezomib, became available in 2007, and we have used it with or without dexamethasone to treat patients who have refractory myeloma. A randomized phase II study was started in 2010 (JCOG0904) to evaluate the efficacy of bortezomib + dexamethasone versus thalidomide + dexamethasone in patients with relapsed or refractory chemoresistant multiple 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

Many patients with solid cancers have been referred to our department from related divisions or departments from both inside and outside our hospital. Several of our studies seeking improved therapeutic outcomes are in progress throughout our university hospital with related divisions or departments. The combination of fluorouracil (5-FU), epirubicin, and cyclophosphamide (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. Adriamycin and taxotere followed by taxotere and trastuzumab is a first-line chemotherapy for patients with advanced, metastatic breast cancer. Since late 2008 we have been investigating a combined-modality therapy of radiation and chemotherapy with docetaxel, cisplatin, and 24 hours' continuous infusion of 5-FU (DCF regimen) for patients with locally advanced esophageal cancer. The study has been completed, and an improved protocol was launched last year. A novel drug-development study with an orally decaying formulation of S-1 has been performed in patients with advanced gastric cancer. A multicenter cooperative randomized phase II study was started in 2011 to compare S-1 + cisplatin, S-1 + leucovorin, S-1 + leucovorin + oxaliplatin for patients with advanced and recurrent gastric cancer. Because trastuzumab is also active in patients with human epidermal growth factor receptor 2-positive gastric cancer, we treat such patients with capecitabine + cisplatin (XP) + trastuzumab. Our first-line chemotherapies for patients with advanced colorectal cancer are folinic acid,

fluorouracil, and oxaliplatin (FOLFOX) and folinic acid, 5-FU, and irinotecan (FOLFIRI). Since antibodies against vascular endothelial growth factor and against epidermal growth factor receptor became available in 2007 and 2008, respectively, combination therapies of these antibodies and FOLFOX or FOLFIRI have also been performed.

Palliative care

The mission of the palliative care team for cancer pain is to relieve patients' pain and anxiety to support the fight against cancer. Our team encourages the use of narcotics and has improved the control of cancer pain. In our 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 Hospital.

Basic research

One of our important activities is translational research on solid cancers and hematological malignancies. 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 Keio University's Department of Pharmacy. Transfer of the *MDR1* gene into hematopoietic stem cells is a method of potentially conferring chemoprotection in cancer chemotherapy. Basic research using CD34-positive cells allows us to try such a strategy. Growth and differentiation of CD34-positive cells into which the *MDR1* gene has been transferred has been investigated *in vitro* in collaboration with Keio University's Department of Pharmacy. The results have recently been published, and further research is in progress.

Publications

Inoue D, Sakuyama T, Ichiba T, Uwagawa T, Arakawa Y, Nagasaki E, Yoshizawa A, Matsu-moto T, Aiba K. Usefulness of epidural catheter with the subcutaneous reservoir for cancer pain control in homecare service (in Japanese). *Gan to Kagaku Ryoho*. 2011; **38** Suppl 1: 61-3.
Arakawa Y, Inoue D, Sakuyama T, Nagasaki E, Aiba K. Strontium-89 therapy and subarachnoid phenol block successfully eliminated intractable pain of metastasis in the patient with advanced urachal carcinoma (in Japanese). *Gan to Kagaku Ryoho*. 2011; **38** Suppl 1: 59-60.
Dobashi N, Usui N, Yano S, Yahagi Y, Takei Y, Sugiyama K, Takahara S, Ogasawara Y,

Yamaguchi Y, Saito T, Yokoyama H, Aiba K. Administration schedule of daunorubicin for elderly patients with acute myelogenous leukemia: a single-institute experience. *Jpn J Clin Oncol*. 2011; **41**: 820-4.
Yano S, Minami J, Nishiwaki K, Shimada T, Dobashi N, Yahagi Y, Takei Y, Takahara S, Ogasawara Y, Sugiyama K, Yamaguchi Y, Saito T, Kasama K, Yokoyama H, Machishima T, Katsube A, Usui N, Aiba K. Rapid progression and unusual premortal diagnosis of mucormycosis in patients with hematologic malignancies: analysis of eight patients. *Int J Hematol*. 2011; **93**: 344-50.