

Hematology Division

Introduction

The Hematology Division is allied with the Hematopoietic Stem Cell Transplantation (HSCT) Division, and the two divisions are fully integrated. In the past, the Hematology Division had made important discoveries in a number of lymphoid malignancies including adult T-cell leukemia-lymphoma (ATL) and angioimmunoblastic T-cell lymphoma. The division is one of the leading hematology-oncology centers in the world, in number of patients treated and in its research activity, especially for lymphoid malignancies.

Routine Activities

The number of newly diagnosed cases of hematologic malignancies in our division has increased annually from 86 in 1997 to 140 in 1998, 199 in 1999, 267 in 2000, 295 in 2001, 324 in 2002, 347 in 2003, and 356 in 2004. The number of patients who visit our clinic to obtain a second opinion is also increasing. We hold a weekly case conference where a summary of each hospitalized- or out-patient is presented. An educational cytology conference is weekly held for young doctors. Newly diagnosed lymphoma cases are presented at the weekly lymphoma case conference, where oncologists, pathologists, radiologists, and radiation oncologists discuss diagnoses and treatment plans. We also participate in weekly HSCT conferences, which deal with all HSCT cases.

Our daily duties include the running of the two hematology clinics and performing bone marrow puncture or biopsy, microscopic examination, flow cytometric analysis, and molecular-genetic analysis. Four staff physicians, one or two chief residents, and one or two rotating residents share these activities.

Research Activities

In addition to immunophenotypic analysis, molecular diagnosis is routinely performed as a laboratory test using polymerase chain reaction (PCR), and fluorescence *in-situ* hybridization (FISH) for the detection of t(8;14), t(14;18), t(11;18), t(9;22), t(8;21), t(15;17), etc.

In 2004 we published eight original articles, two review articles, and two textbook chapters. Among them, the followings are unique: a phase II study of a chimeric anti-CD20 antibody (rituximab) in relapsed or refractory aggressive B-cell lymphoma, a phase II study of cladribine in indolent lymphoma, and a phase III study of multidrug

combination chemotherapy for untreated aggressive lymphoma (JCOG9002). Based on the results of the former two studies, rituximab and cladribine were approved for each disease in Japan. Two textbook chapters, which were published in the USA, dealt with ATL.

Clinical Trials

Current clinical trials include six new agent studies and three trials of chemotherapy and/or radiotherapy. Based on the encouraging results of a phase I study of ibritumomab tiuxetan, an yttrium-90-labeled murine anti-CD20 antibody, we are conducting a multicenter phase II study for relapsed or refractory indolent B-cell lymphoma. A multicenter phase II study of oral fludarabine for relapsed or refractory indolent B-cell lymphoma showed high efficacy (response rate; 60%) with acceptable toxicities. This agent is convenient in the outpatient setting.

We are enrolling patients into a phase II/III study of rituximab-containing combination chemotherapy for untreated indolent B-cell lymphoma, comparing rituximab plus CHOP (R-CHOP) versus rituximab plus biweekly CHOP (JCOG 0203). In the latter arm, augmentation of the efficacy of rituximab with the combined use of G-CSF is expected. Furthermore, we presented the results of a randomized phase II study of R-CHOP comparing concurrent and sequential administrations in untreated indolent B-cell lymphoma in the annual meeting of American Society of Clinical Oncology (ASCO).

In the treatment of ATL, we are analyzing the final results of JCOG 9801, which is the first phase III trial for ATL in the world. The results of JCOG 9801 will be presented in the next annual meeting of ASCO. In the treatment of multiple myeloma, we are conducting a phase I/II study of bortezomib, a novel proteasome inhibitor, for relapsed or refractory myeloma. The preceding US studies revealed the very promising activity of bortezomib in heavily pretreated patients with myeloma and mantle cell lymphoma.

In addition, we are preparing a phase II study of Am-80, a new synthetic retinoid for multiple myeloma, and a phase I/II study of an anti-CCR4 (CC chemokine receptor 4) humanized antibody in peripheral T-cell malignancies including ATL. Japanese investigators produced both agents, and the results of the preclinical studies are very promising.

● K. Tobinai ●

Table 1. Numbers of Newly-diagnosed Cases of Hematological Malignancies

Disease	1998	1999	2000	2001	2002	2003	2004
Acute myelocytic leukemia	12	12	18	10	8	8	9
Acute lymphocytic leukemia	6	6	3	8	3	2	1
Chronic myelocytic leukemia	6	15	9	24	11	7	5
Myelodysplastic syndrome	10	9	9	8	5	6	5
Hodgkin lymphoma	7	10	10	14	15	16	9
Non-Hodgkin lymphoma	90	133	204	215	268	291	299
Adult T-cell leukemia-lymphoma	1	3	4	5	4	5	4
Chronic lymphocytic leukemia	4	1	2	3	3	2	4
Multiple myeloma	4	7	7	8	6	9	19
Macroglobulinemia	0	3	1	1	1	1	1
Total	140	199	267	295	324	347	356

Table 2. Number of Enrolled Patients and Results of New Agent Studies

Agent	Disease	Phase	Pts(a)	Response rate(b)
CHOP + Rituximab	indolent B-NHL	II(a)	13	95%(63/66)
Rituximab	indolent B-NHL	II	3	NA
Ibritumomab tiuxetan	indolent B-NHL	II	7	NA
Oral Fludarabine	indolent B-NHL	II	10	60%(31/52)
Cladribine	indolent B-NHL	I/II	6	NA
Bortezomib	multiple myeloma	I/II	5	NA
EPOCH	malignant lymphoma	III	10	NA

(a)number of patients enrolled from our division; (b)response rate of the total enrolled patients in the multicenter study

Abbreviations: Rituximab, a chimeric anti-CD20 antibody; Ibritumomab tiuxetan, yttrium-90-labeled anti-CD20 antibody; EPOCH, erythropoietin; NA, not applicable;

NHL, non-Hodgkin lymphoma; AML, acute myelocytic leukemia; (a)randomized phase II study

Table 3. Enrolled Patients and Results of the JCOG and JALSG Studies

Disease/Protocol	Phase	Year	No. of pts(a)	%CR(b)	OS(b)
AML					
JALSG-AML 92	III	(92-95)	10	76%	38%(3-yr)
JALSG-AML 95	III	(96-97)	6	81%	40%(4-yr)
JALSG-AML 97	III	(98-01)	15	79%	NA
JALSG-AML 201	III	(02-)	11	NA	NA
JALSG-APL97	III	(98-02)	2	95%	86%(4-yr)
Therapy-related leukemia	I	(96-99)	16	75%	40%(3-yr)
ALL/Lymphoblastic lymphoma					
JCOG 9004	I	(91-94)	14	83%	31%(7-yr)
JCOG 9402	I	(94-99)	10	NA	38%(3-yr)
JALSG-ALL97	I	(98-01)	8	NA	NA
Hodgkin lymphoma					
JCOG 9305	I	(93-97)	7	79%	89%(5-yr)
JCOG 9705	I	(98-00)	6	72%	92%(2-yr)
Aggressive lymphoma					
JCOG 9002	III	(91-95)	57	70%	56%(5-yr)
JCOG 9505	II(c)	(95-98)	2	56%	42%(4-yr)
JCOG 9506	I	(95-97)	6	50%	49%(5-yr)
JCOG 9508	I	(96-99)	19	79%	69%(5-yr)
JCOG 9809	III	(99-02)	55	NA	74%(2-yr)
Indolent B-cell lymphoma					
JCOG 0203	II/III	(02-)	22	NA	NA
Adult T-cell leukemia-lymphoma					
JCOG 9109	I	(91-93)	3	28%	16%(2-yr)
JCOG 9303	I	(94-97)	6	36%	31%(2-yr)
JCOG 9801	III	(98-03)	6	NA	44%(1-yr)
Nasal NK/T-lymphoma					
JCOG 0211-DI	VI	(2003-)	3	NA	NA
Multiple myeloma					
JCOG 9301	III	(1993-98)	10	50%(d)	50%(4-yr)
JCOG 0112	III	(2002-)	9	NA	NA

(a)the number of patients enrolled from our division; (b)As the number of enrolled patients in our division is small, the %CR or OS for the entire enrolled patients in the JCOG or JALSG trials is shown here.

(c)randomized phase II study

(d)CR + PR rate. Abbreviations: JCOG, Japan Clinical Oncology Group;

JALSG, Japan Adult Leukemia Study Group; LSG, Lymphoma Study Group;

OS, overall survival; NA, not applicable; DI, data center-independent study