

# Hematology Division

## Introduction

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 hematological malignancies in our division is still increasing annually from 86 in 1997 to 140 in 1998, 199 in 1999, 267 in 2000, 295 in 2001, 324 in 2002, and 347 in 2003. 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.

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. Three staff physicians, one or two chief residents, one resident, and one or two rotating fellows share these activities.

## Research Activities

We have introduced a new World Health Organization Classification into our practices on the diagnosis of hematological malignancies. 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), including a dual-color 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 2003 we published five original articles and three review articles. Among them, the followings are unique: a multicenter phase II study of deoxycoformycin-containing combination chemotherapy for untreated ATL (JCOG9109) and a multicenter phase II study of cladribine for relapsed or refractory ATL. Although positive results were not obtained in the two studies, they will provide useful information for other investigators in the world. Among the five review articles or textbook chapters published or in press, three dealt with ATL and two with monoclonal

antibody therapy.

## Clinical Trials

Current clinical trials include seven new agent studies including two antibody studies and five trials of combination chemotherapies. We completed a phase I/II study of gemtuzumab ozogamicin, a humanized anti-CD33 chemoimmunoconjugate against acute myelocytic leukemia (AML). Of the 20 patients enrolled in the phase I portion, seven (35%) showed objective responses. In 2003, we completed a phase I study of ibritumomab tiuxetan, an yttrium-90-labeled murine anti-CD20 antibody for relapsed indolent B-cell lymphoma. This was the first clinical trial of radioimmunotherapy in Japan. Of ten patients enrolled into the cohort I (0.3 mCi/kg) or cohort II (0.4 mCi/kg), seven showed objective responses.

We are conducting a phase II/III study of a chimeric anti-CD20 monoclonal antibody (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 analyzed the results of a randomized phase II study of R-CHOP comparing concurrent and sequential administrations in untreated indolent B-cell lymphoma. The results of this unique study will be presented in the next annual meeting of American Society of Clinical Oncology (ASCO).

Between 1998 and 2002, we conducted a phase III trial comparing biweekly CHOP versus standard CHOP against advanced, aggressive lymphoma (JCOG 9809). The first planned interim analysis in December 2002 revealed that the efficacy of biweekly CHOP was rather inferior to standard CHOP. According to the recommendations by the JCOG Data and Safety Monitoring Committee, the study was terminated. In June 2003, the results of JCOG 9809 were presented in the oral session of the annual meeting of ASCO. In the treatment of ATL, we completed patient enrolment into JCOG 9801, which is the first phase III trial for ATL in the world. In the treatment of multiple myeloma, we are conducting a phase III trial to compare the efficacy of two kinds of maintenance therapy, interferon- plus prednisolone versus prednisolone alone. In addition, we are preparing 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 myeloma and mantle cell lymphoma.

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

Disease	1997	1998	1999	2000	2001	2002	2003
Acute myelocytic leukemia	5	12	12	18	10	8	8
Acute lymphocytic leukemia	2	6	6	3	8	3	2
Chronic myelocytic leukemia	4	6	15	9	24	11	7
Myelodysplastic syndrome	4	10	9	9	8	5	6
Hodgkin's lymphoma	4	7	10	10	14	15	16
Non-Hodgkin's lymphoma	62	90	133	204	215	268	291
Adult T-cell leukemia-lymphoma	2	1	3	4	5	4	5
Chronic lymphocytic leukemia	1	4	1	2	3	3	2
Multiple myeloma	2	4	7	7	8	6	9
Macroglobulinemia	2	0	3	1	1	1	1
Total	88	140	199	267	295	324	347

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)
Gemtuzumab ozogamicin	AML	I/II	15	35%(7/20)
A643 (IFN-a)	indolent B-NHL	I/II	11	17%(4/23)
KW-2307 (Navelbine)	myeloma	II	5	4%(1/23)
Oral Fludarabine	indolent B-NHL	I	3	67%(8/12)
Oral Fludarabine	indolent B-NHL	II	10	NA
Ibritumomab tiuxetan	indolent B-NHL	I	5	70%(7/10)
EPOCH	malignant lymphoma	I/II	9	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 monoclonal antibody; Gemtuzumab ozogamicin, a calicheamicin-conjugated humanized anti-CD33 monoclonal antibody; Ibritumomab tiuxetan, yttrium-90-labeled anti-CD20 monoclonal antibody; EPOCH, erythropoietin; NA, not applicable; NHL, non-Hodgkin's 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	Pts(a)	%CR(b)	OS(b)
AML					
JALSG-AML 92	III	(1992-95)	10	76%	38%(3-yr)
JALSG-AML 95	III	(1996-97)	6	75%	NA
JALSG-AML 97	III	(1998-01)	15	NA	NA
JALSG-AML 201	III	(2002-)	7	NA	NA
JALSG-APL97	III	(1998-02)	2	NA	NA
Therapy-related leukemia	I	(1996-99)	16	75%	40%(3-yr)
ALL/Lymphoblastic lymphoma					
JCOG 9004	I	(1991-94)	14	83%	31%(7-yr)
JCOG 9402	I	(1994-99)	10	NA	38%(3-yr)
JALSG-ALL97	I	(1998-01)	8	NA	NA
Hodgkin's lymphoma					
JCOG 9305	I	(1993-97)	7	79%	89%(5-yr)
JCOG 9705	I	(1998-00)	6	71%	92%(2-yr)
Aggressive lymphoma					
JCOG 9002	III	(1991-95)	57	70%	56%(5-yr)
JCOG 9505	II(c)	(1995-98)	2	56%	42%(4-yr)
JCOG 9506	I	(1995-97)	6	NA	58%(3-yr)
JCOG 9508	I	(1996-99)	19	NA	74%(4-yr)
JCOG 9809	III	(1999-02)	55	NA	74%(2-yr)
Indolent B-cell lymphoma					
JCOG 0203	IVIII	(2002-)	13	NA	NA
Adult T-cell leukemia-lymphoma					
JCOG 9109	I	(1991-93)	3	28%	16%(2-yr)
JCOG 9303	I	(1994-97)	6	36%	31%(2-yr)
JCOG 9801	III	(1998-03)	7	NA	42%(1-yr)
Nasal NK/T-lymphoma					
JCOG 0211-DI	VI	(2003- )	1	NA	NA
Multiple myeloma					
JCOG 9301	III	(1993-98)	10	50%(d)	50%(4-yr)
JCOG 0112	III	(2002-)	6	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; OS, overall survival; NA, not applicable; DI, data center-independent study