

# Hematology

## Introduction

The Hematology Division is a part of the Division of Oncology and Hematology. Accordingly, all six staff physicians and three residents are involved in the clinical and research activities of chemotherapy for patients with both hematological and non-hematological tumors in this division. The same physicians also perform stem cell harvest by apheresis, cell processing and high dose chemotherapy with autologous stem cell transplantation. The number of patients with hematological malignancies has been increasing annually. In particular, about 130 patients with malignant lymphoma were consulted in this year.

## Routine Activities

We manage various kinds of hematological malignancies including non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, acute leukemia, chronic myeloid leukemia, myelodysplastic syndrome and others. We also manage most patients treated with aggressive chemotherapy in the 8F ward in which we have 8 laminar air flow rooms. Case conference on these patients is practiced everyday with nurses. High-dose chemotherapy with autologous hematopoietic stem cell transplantation is considered the standard treatment for relapsed non-Hodgkin's lymphoma. Therefore, the procedure of peripheral blood stem cell harvest and transplantation is increasing. Our clinical practice consists of not only the treatment of patients but also consultation concerning hematological abnormalities.

There is a weekly case conference on Tuesday afternoon in the Division of Oncology/Hematology and a monthly joint conference on malignant lymphoma with pathologists. There are also morning journal clubs on Monday, Thursday and Friday in the Division of Oncology/Hematology.

## Research Activities

The following clinical trials were conducted in this year.

### *Phase I trial*

ZD 6474

HMR1275

BAY 43-9006

SHL 749 (Zevalin)

SHT 586 (Fludarabine)

GW-572016

CHC 12103

### *Phase I/II trials*

Phase I/II study of CPT-11 and CDDP for relapsed non-Hodgkin's lymphoma

Pharmacological study of doxorubicin in 75% CHOP for elderly patients with aggressive non-Hodgkin's lymphoma

Phase I/II study of biweekly etoposide and cytarabine for relapsed diffuse large B-cell and peripheral T-cell lymphoma

### *Phase II trials*

JCOG-9801 for adult T-cell leukemia and lymphoma

Erythropoietin for anemia accompanied with non-Hodgkin's lymphoma

### *Phase III trials*

JCOG-9809, randomized study of standard CHOP and biweekly CHOP, for non-Hodgkin's lymphoma

JALSG (Japan Adult Leukemia Study Group) AML-201 for acute myeloid leukemia

JCOG-0112, randomized study of prednisolone and interferon, for relapsed multiple myeloma

JCOG-0203-MF, randomized study of rituximab-CHOP and rituximab-biweekly CHOP, for low grade non-Hodgkin's lymphoma

### *Others*

Pharmacological study of cyclophosphamide

PET study in non-Hodgkin's lymphoma

## New Developments

Although CHOP is accepted as the standard regimen for first-line chemotherapy in aggressive non-Hodgkin's lymphoma (NHL), the therapeutic outcome remains unsatisfactory and a further investigation of more effective first-line regimen is warranted. A dose-dense chemotherapy by shortening treatment intervals is one of potential strategies to improve therapeutic results of aggressive NHL. Our previous randomized phase II study (JCOG9505) comparing biweekly CHOP (Bi-CHOP) and dose-escalated CHOP with the prophylactic use of G-CSF suggested that Bi-CHOP is a more promising regimen (Ann Oncol 2002; 13: 1347), which prompted us to conduct the present

phase III study. The primary purpose of JCOG9809 was to determine whether treatment results of aggressive NHL could be improved by shortening intervals of CHOP chemotherapy. The primary endpoint was progression-free survival (PFS), and the planned accrual was 450. Between February, 1999 and December, 2002, 323 patients with advanced, aggressive NHL were randomized to standard CHOP arm (S-CHOP; CHOP x 8 every 3 weeks) and Bi-CHOP arm (CHOP x 8 every 2 weeks). Major characteristics of 304 patients enrolled until August, 2002 were as follows: median age, 57 years (range; 17-69); clinical stage, 100 patients (33%) in II, 85 (28%) in III, 118 (39%) in IV (1 ineligible for stage I); performance status by ECOG, 159 patients (52%) for 0, 120 (39%) for 1, 25 (8%) for 2; international prognostic index (IPI), 128 patients (42%) for Low, 91 (30%) for Low-Intermediate, 62 (20%) for High-Intermediate, 23 (8%) for High; Working Formulation histology, 33 patients for D, 17 for E, 39 for F, 209 (69%) for G, 5 for H, 1 for J. Major prognostic factors including IPI were well balanced between the arms. The first planned interim analysis for 286 patients on

18 December, 2002 revealed that the PFS of Bi-CHOP arm (n=143) was rather inferior to that of S-CHOP arm (n=143). The median PFS was 33.9 months in S-CHOP and 24.3 months in Bi-CHOP, and 2-year PFS was 54.4% in S-CHOP and 51.1% in Bi-CHOP. The hazard ratio of PFS between the arms was 1.10 (95% CI, 0.76-1.57). 2-year overall survival was 73.8% in S-CHOP and 74.8% in Bi-CHOP. There was 1 treatment-related death in Bi-CHOP. Toxicities of both regimens were equivalent. According to the recommendations by the JCOG Data and Safety Monitoring Committee, the study was terminated, because it was deemed highly unlikely that Bi-CHOP would be superior to S-CHOP in PFS. In conclusion, a dose-dense strategy by interval shortening of CHOP chemotherapy with the prophylactic use of G-CSF was unable to prolong PFS in patients with aggressive NHL. A new strategy for NHL including rituximab, a mouse-human chimeric anti-CD20 monoclonal antibody, is warranted.

● K. Ito ●

Number of patients admitted in this year

	Number of patients
Non-Hodgkin's lymphoma	125
Hodgkin's lymphoma	6
Acute leukemia	16
Multiple myeloma	6
Adult T-cell leukemia/lymphoma	5

Number of patients enrolled in clinical trials

	Protocol	Number of patients
Non-Hodgkin's lymphoma	SHL 749	5
	SHT 586	4
	CPT-11/CDDP	2
	75% CHOP	31
	Etoposide/cytarabine	10
	JCOG-9801	1
	Erythropoietin	6
	JCOG-9809	40
	PK of cyclophosphamide	56
	PET study	47
	JCOG 9801 (ATL98)	1
	JCOG-0203	4
	Acute myeloid leukemia	JALSG AML 201
Multiple myeloma	JCOG-0112	1