[haematologica reports]
2006;2(13):19-21

Conventional treatment of peripheral T-cell lymphoma: the Asian perspective

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Epidemiology of PTCL in Japan

Lymphoma Study Group of Japanese pathologists reviewed 3,194 cases of malignant lymphoma in Japan, according to the WHO Classification.[1] Sixty-nine percent of cases were of B-cell lymphoma, 25% were of T- or NK-cell lymphoma and 4% of Hodgkin lymphoma. Among T- or NK-cell lymphoma, human T-cell leukemia virus type-I (HTLV-I)-associated adult T-cell leukemia-lymphoma (ATL) was the most frequent subtype (7.5%), PTCL, unspecified was the second (6.7%), and the relative frequency of nasal and nasal-type NK/T-cell lymphoma (2.6%) was higher than Western countries but less than other East Asian countries including Korea and Hong Kong. The relative frequency of T- or NK-cell lymphoma in Kyushu Island (19.2%) was higher than that in other areas in Japan, mainly due to the high prevalence of ATL and HTLV-I carriers. In Japan other than Kyushu, the relative frequency of B- (78%) and T/NK-cell lymphoma (22%) was not so different from that in Western countries (87% and 13%).

Adult T-Cell leukemia-lymphoma (ATL) and clinical trials in Japan

Acute-type ATL, a prototype, has characteristic clinical features, including flower cells in peripheral blood, hypercalcemia, and frequent organ involvement including the skin, gastrointestinal tract and lung. Peripheral T-cell phenotype ($CD4^+$ in most cases), the presence of antibodies to HTLV-I in serum, and monoclonal integrations of HTLV-I provirus in tumor cells are key findings for the diagnosis of ATL. Four clinical subtypes such as acute-, lymphoma-, chronic- and smoldering-types have been recognized.[2]

The results of the consecutive clinical trials for ATL conducted by Japan Clinical Oncology Group (JCOG) are summarized in Table 1. In 1981, we initiated a multicenter clinical trial for non-Hodgkin lymphoma (NHL). In JCOG8101 using cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)-like regimens and in JCOG8701 using a 2nd generation regimen for NHL, ATL patients were enrolled.[3-5] Since 1991, we have conducted three-kinds of clinical trials specific for ATL consecutively.[6-8] In JCOG9303, a phase II study using a granulocyte colony-stimulating factor (G-CSF)-supported, dose-intensified, multiagent regimen, promising results were obtained as compared to our historical controls.[7]

Based on the encouraging results of JCOG9303, to establish a new standard for ATL, we conducted a phase III study, JCOG9801. Previously untreated patients with aggressive ATL, acute-, lymphoma- or unfavorable chronic-type, were randomized either to receive six courses of VCAP-AMP-VECP every four weeks (Arm A) or eight courses of biweekly CHOP (Arm B). Both regimens were supported with G-CSF and intrathecal prophylaxis using cytarabine, methotrexate and prednisolone. Primary endpoint was overall survival (OS). One hundred and eighteen patients (57 in Arm A, 61 in Arm B) were randomized, and the median follow-up time was 11.0 months. Seventy-two percent of the patients responded in Arm A, and the overall response rate (ORR) was 66% in Arm B. The median progression-free survival (PFS) time and PFS at one-year in Arm A were 7.0 months and 28%, respectively, whereas 5.4 months and 16% in Arm B. The median survival time and OS at 3 years in Arm A were 12.7 months and 24%, respectively, whereas 10.9 months and 13% in Arm B. Log-rank p-value for primary end point, OS, was 0.085. After adjustment of patients' character-

Table 1. Summary of JCOG Trials for ATL.

Study	%CR	MST(Mo)	%OS
JCOG 8101 (CHOP-like)	28% (15/54)	7.5	8% (4-yr)
JCOG 8701 (2nd generation)	42% (18/43)	8.0	12% (4-yr)
JCOG 9109 (DCF containing)	28% (17/60)	7.4	16% (2-yr)
JCOG 9303 (G-CSF-supported)	35% (33/93)	13	31% (2-yr)
JCOG 9801 (9303 vs Bi-CHOP)	32% (38/118)	11	24% (2-yr)

istics by Cox regression, the p-value became 0.029 because of unbalanced prognostic factors such as bulky lesion. In Arm A vs. Arm B, %grade 4 neutropenia, %grade 4 thrombocytopenia and %grade 4 infection were 98% vs. 83%, 74% vs. 17% and 7% vs. 3%, respectively. Three toxic deaths were encountered in Arm A. These results suggest that the VCAP-AMP-VECP regimen should be the new standard therapy for aggressive ATL.[8]

Recently, the results of a retrospective analysis of allogeneic stem cell transplantation (SCT) using conventional conditioning regimen for 40 patients with ATL was reported from the seven centers in Japan. The median age was 44, and the disease status at transplant was variable among patients. Although it is impossible to draw out a definite conclusion, these results suggest that allogeneic SCT provides sustained survival in a fraction of ATL patients.[9] Since the median age of ATL patients is nearly 60, conventional allogeneic SCT can be applied to a minority of patients. Therefore, reduced-intensity SCT (RIST) deserves evaluation. Recently, the results of a feasibility study of RIST for ATL patients were reported from Japan.[10] The median age was 57, and the oldest patient was 67. Although the follow-up duration is short, it was concluded that RIST is a feasible treatment for ATL and deserves further evaluation.

Chemokine receptor expression in PTCL and a possible molecular target

Ishida *et al.* analyzed the chemokine receptor expression in 102 patients with ATL. CCR4 is a kind of selective markers of Th2 phenotype. Tumor cells from most ATL cases are CCR4-positive by immunostaining. Univariate and multivariate analyses revealed that CCR4 expression is an unfavorable prognostic factor in ATL patients.[11] In addition to ATL, they analyzed CCR4 expression in various types of PTCL, and found that nearly 40% of PTCL, unspecified cases were CCR4-positive. They analyzed the expression of CCR4 and CXCR3 in 50 cases of PTLC-unspecified. CXCR3-positivity was a favorable factor, whereas CCR4-positivity was an unfavorable factor. Multivariate analysis revealed that CCR4 expression was a significantly unfavorable factor of PTCL-unspecified.[12]

Using a new technology, Kyowa Hakko, a Japanese pharmaceutical company, developed an antibody-dependent, cell-mediated cytotoxicity (ADCC)-enhanced, humanized anti-CCR4 antibody, KW-0761.[13] Pre-clinical studies of this antibody showed promising results for its clinical application to PTCL, especially to ATL.[14] Now, we will initiate a phase I study for patients with CCR4-positive PTCL in Japan.

Localized nasal NK/T-cell lymphoma and chemoradiotherapy

Nasal NK/T-cell lymphoma is a rare lymphoid neoplasm (2.6% in Japan), and its standard therapy has not been established. It is one of Epstein-Barr virus (EBV)-associated lymphoid malignancies, and lymphoma cells express P-glycoprotein associated with multi-drug resistance (MDR). Anthracycline-containing chemotherapy followed by radiotherapy (RT) has been established as the standard care for localized aggressive NHL[15]; however this strategy is not effective for localized nasal NK/T-cell lymphoma.[16] The five-year OS rates of RT alone are only 30-40%. To explore a more effective treatment for newly diagnosed localized nasal NK/T-cell lymphoma, we are conducting a multicenter phase I/II study of concurrent chemoradiotherapy consisting of 50 Gy of RT and three courses of DeVIC chemotherapy [carboplatin (CBDCA) 300 mg/m^2 d1 IV, etoposide (ETP) 100 mg/m^2 d1-3 IV, ifosfamide (IFM) 1.5 g/m^2 d1-3 IV, dexamethasone (DMS) 40 mg d1-3 IV; every 21 days]. DeVIC comprised of MDR-non-related agents and etoposide that shows both *in vitro* and *in vivo* efficacy for NK-cell neoplasms, and is effective for EBV-associated hemophagocytic syndrome. Patients with newly diagnosed, localized (IE and contiguous IIE with cervical lymph node involvement) diseases, 20-69 years of age and performance status (PS) 0-2 were eligible. The protocol requests the CT based two or three dimensional RT planning that the volume with appropriate margin (2 cm) to gross tumor, entire nasal cavities and nasopharynx should be irradiated. In the phase I portion, a standard 3+3 design was used to evaluate dose-limiting toxicities (DLTs). The doses of RT and DMS were fixed. Two dose levels of CBDCA/ETP/IFM were evaluated: Level 1 (2/3-dose DeVIC) and Level 2 (100%-dose

DeVIC). No treatment-related death occurred, and no grade 4 non-hematologic toxicities other than transient hypokalemia were observed. Grade 4 neutropenia and grade 3 mucositis due to RT were common. At Level 2, grade 4 leukopenia/anemia/thrombocytopenia and grade 3 infections were more frequent than Level 1. At Level 1, one patient developed PD before evaluation of DLT. Remaining three patients did not develop DLT. At Level 2, 4 out of 6 patients developed DLT. Thus, we selected the Level 1 for the subsequent phase II portion. Of all 10 enrolled patients, seven achieved CR, two PD, and one not evaluable. Of note, all 10 patients achieved local control. These results suggest that concurrent chemoradiotherapy using MDR-non-related agents and ETP is a promising treatment strategy for localized nasal NK/T-cell lymphoma. Feasibility and efficacy of Level 1 will be evaluated further in the phase II portion.[17]

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