LYMPHOMAS

Treatment of T-Cell lymphoma

TOMOMITSU HOTTA

Division of Hematology/Oncology, Department of Medicine, Tokai University School of Medicine, Boseidai, Isehara, Kanagawa 259-1193, Japan

Abstract

T-Cell lymphoma composes 25% of lymphoid malignancies in Japan. Peripheral T-cell lymphoma (PTCL) unspecified and adult T-cell leukemia/lymphoma (ATLL) are major subtypes of T-cell lymphoma. The Japan Clinical Oncology Group (JCOG) has conducted 7 clinical trials for aggressive non-Hodgkin's lymphoma (NHL) including T-cell lymphoma. JCOG trials revealed that patients with ATLL had an extremely poor prognosis as compared with other peripheral T-cell lymphomas. A second generation combination chemotherapy including pentostatin (JCOG9109) could not improve the prognosis of patients with aggressive ATLL with the median survival time (MST) of 7.4 months. Subsequently, JCOG developed a new alternating multi-agent chemotherapy including MCNU and carboplatin with prophylactic use of G-CSF, resulting 35% of CR rate and 31% of 2-year OS. Considering the poor prognosis of aggressive ATLL patients, allogeneic stem cell transplantation seems to be another promising approach for a cure of the disease. New active agents such as chimeric monoclonal anti-CCR antibody are under developing for PTCL and ATLL.

Incidence of T-cell lymphoma in Japan

T-cell lymphoma is a common subtype of lymphoid malignancies in Japan as compared with Western countries. The Lymphoma Study Group of Japanese Pathologists [1] reviewed 3,194 cases of lymphoid malignancies according to WHO classification [2] and demonstrated that they consisted of 69% of B-cell lymphoma, 25% of T- or NK cell lymphoma and 4% of Hodgkin lymphoma. The incidence of major subtypes of non-Hodgkin’s lymphoma (NHL) were 33.3% for diffuse large B-cell lymphoma, 8.5% for marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type, 8.5% for plasma cell myeloma, 7.5% of adult T-cell leukemia-lymphoma (ATLL), 6.7% for follicular lymphoma, 6.7% for peripheral T-cell lymphoma (PTCL) of unspecified type, 2.8% for mantle cell lymphoma, 2.6% of nasal and nasal-type NK/T-NHL, 2.4% of angioimmunoblastic T-cell lymphoma (AITL), 1.7% of T-lymphoblastic lymphoma (LBL)/T-acute lymphocytic leukemia (ALL), and 1.5% of anaplastic large cell lymphoma (ALCL). ATLL is defined as a peripheral T-cell malignancy caused by a RNA retrovirus, human T-cell leukemia virus type I (HTLV-I) which is transmitted by breast feeding and through exposure to blood and its products. Approximately 1,000,000 Japanese (mainly in Kyushu area) are seropositive for HTLV-1 and cumulative incidence of ATLL is estimated to be 2.5% among HTLV-1 carriers. ATLL occurs in adults with a median age of 55 years. Four clinical subtypes such as acute- lymphoma- chronic- and smoldering-type have been recognized. Acute type ATLL is characterized by flower cells in peripheral blood, hypercalcemia, and frequent organ involvement such as the skin, gastrointestinal tracts, lung, and central nervous system. Patients with acute- and lymphoma-types have an extremely poor prognosis; the median survival time (MST) was only 8 months.

Japanese clinical trials for advanced-stage aggressive NHL including PTCL

Most of the clinical trials for malignant lymphoma in Japan have been conducted by cooperative study groups, especially the Lymphoma Study Group of Japan Clinical Oncology Group (JCOG-LSG). JCOG is a multicenter cooperative oncology group, supported by Grants-in Aid for Cancer Research from the Ministry of Health, Labor and Welfare, Japan. JCOG has a common Data Center and consists of 13 cancer study groups including LSG. JCOG-LSG has conducted 21 multicenter trials, including eight...
randomized controlled trials for lymphoid malignancies. Table I shows the summary of JCOG-LSG trials for advanced aggressive lymphoma. The JCOG-LSG began to conduct a prospective clinical trial (JCOG8101) for B- and T-cell non-Hodgkin’s lymphoma (NHL) including adult T-cell leukemia/lymphoma (ATLL) from 1978 [3,4]. At that time, ATLL was generally classed as peripheral T-cell lymphoma. JCOG-LSG developed a CHOP-like chemotherapy, named LSG1, which consisted of vincristine (VCR), cyclophosphamide (CPM), prednisolone (PSL) and doxorubicin (ADM). The complete response (CR) was obtained in 63% of patients with B-NHL, 35% of T-NHL, and 17% of ATLL. In 1987, JCOG-LSG started a new second generation alternating multi-agent chemotherapy called LSG4 consisting of VEPA-B, M-FEPPA, VEPP-B against advanced aggressive NHL (JCOG8701) [5]. Estimated 5-year overall survival (OS) after the median follow-up of 56 months was 60% in B-NHL, 35% in T-NHL and only 12% in ATLL. The results of JCOG8701 led to the following conclusions: (1) T-cell phenotype was an important pretreatment variable for aggressive NHL, (2) LSG4 regimen was effective against B-NHL. Since the clinical diagnosis of ATLL was an independent poor prognostic factor, ATLL were excluded from aggressive NHL in subsequent Japanese trials.

JCOG9002 was a randomized phase III study to investigate survival benefit of dose-intensified multi-agent combination chemotherapy [6]. Patients were randomly assigned to either LSG9 (VEPA-B/FEPP-AB/M-FEPA, every 10 weeks; 3 courses, 28 weeks in total) or modified LSG4 (VEPA-B/FEPP-B/M-FEPA, every 14 weeks; 4 courses, 54 weeks in total). Four hundred and forty-seven patients were enrolled between 1991 and 1995. Five-year OS was 57% for LSG9 and 55% for modified LSG4. It was concluded that the increase in dose-intensity of doxorubicin in multi-agent combination chemotherapy could not improve survival of patients with aggressive NHL including ATLL.

JCOG-LSG began to explore a promising dose-intensified chemotherapy against higher risk patients with advanced aggressive lymphoma. JCOG9505 was a randomized phase II study to choose a suitable dose-intensified regimen for a subsequent phase III study to compare with CHOP [6]. Seventy patients with intermediate-high or high risk aggressive NHL according to IPI were randomly assigned to either biweekly CHOP arm or dose-intensified CHOP arm. The CR rate was 60% with biweekly CHOP and 51% with dose-escalated CHOP. Grade 4 hematological toxicities were more frequent in the dose-escalated CHOP arm. It was concluded from the results of this study that biweekly CHOP is more promising for further investigations.

Based on the results of JCOG9505, JCOG-LSG initiated a phase III study, JCOG9809 in which biweekly CHOP was compared with standard CHOP in patients with advanced aggressive NHL in 1999 [7]. The primary endpoint was progression-free survival (PFS) and planned accrual was 450. Until December 2002, 323 patients were enrolled and randomly assigned to either biweekly CHOP arm or standard CHOP arm. The first planned interim analysis for 286 patients on December 18, 2002 revealed that the PFS of biweekly CHOP arm (n = 143) was slightly inferior to that of the standard CHOP arm (n = 143). The median PFS was 34 months in the standard CHOP arm and 24 months in the biweekly CHOP arm, and 2-year PFS was 54% in the standard CHOP arm and 51% in the biweekly CHOP arm. The hazard ratio of PFS between the arms was 1.10 (95% CI, 0.76–1.57). The predictive probability of biweekly CHOP superiority was estimated as only 19%. Two-year OS was 74% in the standard CHOP arm and 75% in the biweekly arm CHOP. According to the recommendations by the Data and Safety Monitoring Committee, JCOG9809 was terminated early. It was concluded that a dose-dense strategy by interval shortening of CHOP chemotherapy was unable to prolong PFS in patients with aggressive NHL. The subset analysis showed that 3-year PFS was 28% for T-NHL (n = 33) and 53% for B-NHL (n = 248). T-cell phenotype remains an unfavorable prognostic factor in patients treated with CHOP or biweekly CHOP.

The Japanese Clinical Study Group of THP lymphomas in the Elderly (JGTL) [8] conducted a randomized phase III study of 3 CHOP-equivalent regimens, THP-adriamycin (terarubicin) -COP, dose-reduced CHOP and THP-COPE for elderly patients

Table I. Results of JCOG trials for aggressive NHL

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>No. of Pts</th>
<th>(T-NHL*)</th>
<th>%CR</th>
<th>MST (mo)</th>
<th>%OS</th>
</tr>
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<tbody>
<tr>
<td>JCOG8101 (CHOP-like)</td>
<td>III</td>
<td>190</td>
<td>(21)</td>
<td>57</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>JCOG8701 (2nd generation)</td>
<td>II</td>
<td>338</td>
<td>(42/234)</td>
<td>72</td>
<td>39</td>
<td>48</td>
</tr>
<tr>
<td>JCOG9002 (dose-intensified)</td>
<td>III</td>
<td>447</td>
<td>(74/404)</td>
<td>67</td>
<td>NA</td>
<td>56</td>
</tr>
<tr>
<td>JCOG9505 (dose-intensified CHOP, IPI-HI/H)</td>
<td>R-II</td>
<td>70</td>
<td>(10/54)</td>
<td>56</td>
<td>28</td>
<td>42</td>
</tr>
<tr>
<td>JCOG9506 (CHOP-Auto-SCT, IPI-H/H)</td>
<td>II</td>
<td>43</td>
<td>(6/33)</td>
<td>64</td>
<td>NA</td>
<td>58</td>
</tr>
<tr>
<td>JCOG9508 (CHOP, IPI-L/L)</td>
<td>II</td>
<td>213</td>
<td>(16/195)</td>
<td>74</td>
<td>NA</td>
<td>70</td>
</tr>
<tr>
<td>JCOG9809 (CHOP, Biweekly CHOP)</td>
<td>III</td>
<td>323</td>
<td>(33/290)</td>
<td>64</td>
<td>NA</td>
<td>74</td>
</tr>
</tbody>
</table>

CR, complete response; MST, median survival time; OS, overall survival, NA, nor applicable * excluding ATLL.
with aggressive NHL. Between 1990 and 1992, 501 patients were enrolled and randomly assigned into each of the 3 arms. Median age was 75 years. The Complete response (CR) in all 420 evaluable patients was 45% in THP-COP group, 44% in CHOP group and 50% in THP-COPE group, respectively. A subset analysis of response according to T/B phenotype revealed that THP adriamycin-containing regimens were more effective than dose-reduced CHOP against T-NHL. Overall survival of patients with THP-containing regimens was slightly superior to that of CHOP in T-NHL, although the difference was not statistically significant, maybe due to small sample size. We are now conducting a phase II study of THP-COP chemotherapy against PTCL unspecified at advanced-stage.

**JCOG trials for aggressive ATLL**

The main results of JCOG trials for ATLL are summarized in Table II. The first trial was a phase III, JCOG8101, which compared VEPA versus VEPA-M against advanced NHL including ATLL[3]. The CR% of VEPA-M for ATLL (37%) was higher than that of VEPA (17%) \( (P=0.09) \). However, median survival time (MST) of 54 patients treated with VEPA or VEPA-M was only 7.5 months and the estimated 4-year OS was 8%. In the subsequent phase II study (JCOG8701) of a multi-agent combination chemotherapy, the CR rate in 42 patients was 43%, which was improved from 28% of 54 patients in JCOG8101 [4]. However, the MST of these patients was 8 months and 5-year OS was 12%. The disappointing results against ATLL with conventional chemotherapies have led to explore new active agents. Pentostatin (deoxycoformycin, DCF), an inhibitor of adenosine deaminase was reported to be effective in a number of lymphoid malignancies by a multicenter phase I and II study, showing a response rate of 32% (10/31) in relapsed or refractory ATLL [9,10]. These encouraging results prompted us to conduct a phase II trial of DCF-containing chemotherapy (JCOG9101) as an initial chemotherapy for ATLL in 1991 [11]. In 60 eligible patients, there were 17 CRs (28%) and 14 PRs (25%). The MST was 7.4 months and estimated 2-year OS was 17%, identical to the results of previous studies. It was concluded that the prognosis of ATLL patients could not be improved by a DCF-containing combination chemotherapy.

In 1994, JCOG initiated a new phase II trial (JCOG9303; LSG15) of a multi-agent combination regimen consisting of VCR, CPA, DOX, PSL, MCNU, VDS, ETP, and carboplatin (CBDCA) for untreated ATLL [12]. The CR rate and 2y-OS of 93 eligible patients was 33% and 31%, respectively. Grade 4 hematologic toxicities of neutropenia and thrombocytopenia were observed in 65% and 53% of the patients, respectively. To confirm whether the LSG15 is a new standard chemotherapy for aggressive ATLL, JCOG conducted a randomized phase III study (JCOG9801), comparing the LSG15 with biweekly CHOP. Patient enrollment into this trial was completed in October 2003, and results of final analysis will be open at the end of this year.

**Allogeneic stem cell transplantation for aggressive ATLL**

Poor prognosis of patients with aggressive ATLL by conventional chemotherapy prompted us to approach to allogeneic stem cell transplantation (Allo-SCT). Fukushima et al. [13] reported a paper of retrospective study on the effect and safety of Allo-SCT for younger patients with aggressive ATLL. In this series 40 transplanted patients, median age of 44 (28–53) were reviewed. Fifteen patients were in CR, 13 in PR, 3 in SD, 9 in PD at conditioning for Allo-SCT, Grade 3/4 acute graft versus host disease (GVHD) was observed in 11 patients. Twenty one patients died of GVHD, infection (5), disease progression (3), thrombotic microangiopathy (3) and other causes (3). Three year overall survival of these 40 patients was 45.3%. These promising results suggest the possibility of graft versus ATLL effects by allo-SCT.

Okamura et al. [14] reported 16 cases of allogeneic stem cell transplantation with reduced-conditioning intensity (RIST) for patients with ATLL who were all over 50 years of age (51–67, median 57). Conditioning regimen consisted of fludarabine, busulfan and rabbit anti-thymocyte globulin. One year EFS and OS were 25% and 39%, respectively. After RIST, the HTLV-1 proviral load became undetectable in 8 patients. We are planning a phase II study of allogeneic stem cell transplantation for aggressive ATLL.

Table II. Results of JCOG trials for ATLL

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>No of Pts</th>
<th>%CR</th>
<th>MST (mo)</th>
<th>%OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>JCOG 8101 (CHOP-like)</td>
<td>III</td>
<td>54</td>
<td>28</td>
<td>7.5</td>
<td>8 (4-yr)</td>
</tr>
<tr>
<td>JCOG 8701 (2nd generation)</td>
<td>II</td>
<td>43</td>
<td>42</td>
<td>8.0</td>
<td>12 (4-yr)</td>
</tr>
<tr>
<td>JCOG 9109 (DCF-supported)</td>
<td>II</td>
<td>60</td>
<td>28</td>
<td>7.4</td>
<td>16 (2-yr)</td>
</tr>
<tr>
<td>JCOG 9303 (G-CSF-supported)</td>
<td>II</td>
<td>93</td>
<td>35</td>
<td>13</td>
<td>31 (2-yr)</td>
</tr>
<tr>
<td>JCOG 9801 (9303 vs. Bi-CHOP)</td>
<td>III</td>
<td>118</td>
<td>32</td>
<td>11</td>
<td>24 (2-yr)</td>
</tr>
</tbody>
</table>

CR, complete response; MST, median survival time; OS, overall survival, NA, nor applicable
Development of new anticancer agents for T-NHL

Cladribine is a chlorinated purine analogue resistant to adenosine deaminase (2-chlorodeoxyadenosine, 2-CDA). This agent was found to be effective against hairy cell leukemia, B-chronic lymphocytic leukemia, indolent B-NHL and cutaneous T-cell lymphoma. Japanese phase I study of cladribine, one patient with ATLL achieved PR [15]. A multicenter phase II study of cladribine as single agent showed a limited efficacy for treating relapsed or refractory ATLL (ORR 7%) [17]. CCR4 is a chemokine receptor and a kind of selective marker of Th2 phenotype of non-cytotoxic lymphocytes. CCR4 is expressed in 88% of ATLL, in 38% of PTCL unspecified, in 41% of mycosis fungoides in transformation, and in 66% ALK-negative anaplastic large cell lymphoma by immunostaining [18]. Recent studies revealed that CCR4 expression is an independent and significant prognostic factor in ATLL and PTCL [19]. Defucosylated chimeric monoclonal anti-CCR4 IgG1 antibody (KM2760) has recently been developed in Japan. Phase I/II trial to evaluate the safety and efficacy of anti-CCR4 humanized antibody will be initiated in patients with peripheral T-cell malignancies.

Acknowledgements

JCOG studies are supported by Grants—in Aid for Cancer Research from the Ministry of Health, Labor and Welfare of Japan. I would like to express sincere thanks for all the members of JCOG, in particular, Dr Tobinai for scientific advise, Dr Masanori Shimoyama, a previous chairman of the JCOG-LSG, and Dr Fukuda, Chief of JCOG Data Center for data management and analyses of JCOG trials. I am appreciative of all the members of the Japanese Clinical Study Group of THP lymphoma in the Elderly (JGTLE).

References