Leukemia and Lymphoma

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713643806

Immuno-chemotherapy with a combination of rituximab, methotrexate, pirarubicin and procarbazine for patients with primary CNS lymphoma - A preliminary report

To cite this Article: Yamanaka, Ryuya, Homma, Junpei, Sano, Masakazu, Tsuchiya, Naoto, Yajima, Naoki, Shinbo, Yoshikatsu, Hasegawa, Akira, Onda, Kiyoshi and Tanaka, Ryuichi, 'Immuno-chemotherapy with a combination of rituximab, methotrexate, pirarubicin and procarbazine for patients with primary CNS lymphoma - A preliminary report', Leukemia and Lymphoma, 48:5, 1019 - 1022

To link to this article: DOI: 10.1080/10428190701248009
URL: http://dx.doi.org/10.1080/10428190701248009

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article maybe used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

© Taylor and Francis 2007
LETTER TO THE EDITOR

Immuno-chemotherapy with a combination of rituximab, methotrexate, pirarubicin and procarbazine for patients with primary CNS lymphoma—A preliminary report

RYUYA YAMANAKA1,2, JUNPEI HOMMA1, MASAKAZU SANO1, NAOTO TSUCHIYA1, NAOKI YAJIMA1, YOSHIKATSU SHINBO3, AKIRA HASEGAWA4, KIYOSHI ONDA1, & RYUICHI TANAKA1

1Department of Neurosurgery, Brain Research Institute, Niigata University, Niigata, Japan, 2Research Center of Innovative Cancer Therapy, Kurume University School of Medicine, Kurume, Japan, 3Department of Neurosurgery, Itoigawa General Hospital, Itoigawa, Japan, and 4Department of Neurosurgery, Kobari Hospital, Niigata, Japan

(Received 25 October 2006; revised 23 November 2006; accepted 27 January 2007)

The optimal treatment for primary CNS lymphoma (PCNSL) has not yet been established. Several phase II studies combining chemotherapy with radiotherapy have been carried out in the last decade. Adjuvant chemotherapy may result in a mean survival rate of up to four years [1 – 3], suggesting that chemotherapy in combination with cranial irradiation at the time of initial treatment benefits patients in terms of median survival time and disease-free survival. However, the best regimens are still under discussion. Even without apparent leucoencephalopathy, the quality of life in surviving PCNSL patients is not good, and a proportion of patients suffer from mental deterioration after treatment [4]. The reason for this is not clear, but the incidence appears to be higher in patients treated with radiotherapy than in those treated without it [5,6]. The role of radiotherapy remains to be determined, and future trials that will investigate this and determine the best chemotherapeutic combination regimen are needed to achieve long-term overall survival with a minimum of late neurotoxicity.

In 1996, we initiated a study using modified ProMACE-MOPP [7] chemotherapy with radiotherapy in patients with PCNSL. We designed a treatment regimen with a combination of rituximab, moderate doses of methotrexate (MTX), pirarubicin, and procarbazine based on modified ProMACE-MOPP protocol to reduce the neurologic sequelae and early toxicities. This is a preliminary report of a pilot study.

Eleven newly diagnosed patients with PCNSL were enrolled into this study between June 2003 and June 2006. Eligibility criteria were the diagnosis of PCNSL confirmed histologically or cytologically in the cerebrospinal fluid (CSF), age 20–80 years, presence of at least one measurable lesion, adequate bone marrow function (leucocytes > 2 × 10⁹/l, thrombocytes > 100 × 10⁹/l), hepatic and renal function (bilirubin and creatinine in the normal range), and written informed consent. Isolated ocular and meningeal lymphoma manifestation were permitted; however, slit-lamp examination of the eye was not carried out in all patients. Exclusion criteria included human immunodeficiency virus type I (HIV) infection, prior treatment for PCNSL, systemic lymphoma manifestations, severe illness not related to PCNSL, and pregnancy. The staging studies required in the protocol were the following: (a) analytical (WBC count, hemoglobin, and platelet count, urea and electrolyte measurement, liver function tests, and lactate dehydrogenase levels); (b) cytology of CSF; and (c) CT or MRI of the brain, thorax, abdomen, and pelvis (performed in all patients). The trial was approved by the local ethics committee. Efficacy endpoints were response and overall survival. Safety endpoints were acute and late toxicity. Seven patients were male and four female.
The median age at the time of diagnosis was 64.9 years (range 50–77 years). The median Karnofsky performance status (KPS) for all patients was 70 (range 60–100). Six (54.5%) had multiple sites of lymphoma, and five (45.4%) had solitary tumors. Six patients were biopsied: four patients stereotactically, and two patients with open biopsy. Two patients underwent tumor resection. The diagnosis was histologically proven in patients (n = 8, diffuse large B cells and variants). Three patients had no surgical procedure, because the enhanced lesion was so small and in a deep structure such as the fourth ventricle or thalamus, and were diagnosed by cytology and elevated beta 2 microglobulin in the CSF. Lumbar puncture was performed in all patients and lymphoma cells were identified in two patients (18.1%). We fundamentally used the R-MTX protocol (rituximab 375 mg/m², MTX 1 g/m², pirarubicin 25 mg/m², procarbazine 100 mg/m², prednisone 1 mg/kg). We also used leucovorin rescue to prevent all possible side effects. These agents were administered in 21-day cycles. Radiotherapy was deferred until progression or relapse in patients over 60 years. Patients under 60 years had 20 Gy of whole brain irradiation if CR was obtained after chemotherapy. Those patients who had progressive disease (PD) during initial chemotherapy received additional whole brain irradiation or focal boosts to areas with persistent tumor. MRI scans of the brain were repeated after surgery, chemotherapy, and radiotherapy. Further scans were performed every three months during follow-up evaluations. The response rate was the CR plus partial response (PR) rate. The criteria is (a) CR, defined as disappearance of the entire tumor for a period of at least four weeks; (b) PR, defined as a reduction of 50% or more in the tumor size for at least four weeks, with no new lesions or progression of assessable disease; (c) no change (NC), defined as either a decrease of less than 50% or an increase of less than 25% in tumor size for at least four weeks; and (d) PD, defined as an increase of 25% or more in tumor size or the appearance of new lesions. The tumor size was determined by calculating the cross-sectional areas. Survival was measured from the study accrual date, which was generally when the diagnosis had been made to death or last visit. The detailed characteristics of these patients are shown in Table I. Of the 11 patients, 3 died due to PD and the remaining 8 patients are still alive. Five patients received cranial radiotherapy as planned. Six of the 11 patients (54.5%) had CR immediately after the initial three courses of chemotherapy. The response rate after chemotherapy was 90%. Three patients had a PR with chemotherapy, with all of them subsequently reaching a CR with radiotherapy. The response rate immediately after chemoradiotherapy was 100%. All patients had their performance status scored after 3 months of the treatment. Eight patients (72.7%) showed improvement, two patients showed no change in score, and one patient had a worsening of the score. The two-year actuarial probability of survival was 54% ± 40% (95% confidence intervals; CI) (Figure 1). A total of 28 cycles of R-MTX were provided. The major acute toxicity was myelosuppression, with Grade 4 leucopenia documented in 3.5%, Grade 3 anemia in 3.5%, and Grade 3 thrombocytopenia in 17.8% of cycles graded using the National Cancer Institute Common Toxicity Criteria. Six cycles required the addition of G-CSF for hematologic toxicity with good recovery. Three Grade 3 pulmonary toxicities consisted of interstitial pneumonitis. The other toxicity was hepatic (Grade 1, n = 1; Grade 2, n = 3; grade 3, n = 1), oral mucositis (Grade 1, n = 1; Grade 3, n = 1), and infection without neutropenia (Grade 3, n = 2). Deep venous thrombosis, allergic reaction after

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/gender</th>
<th>Type of lesion</th>
<th>Response to chemotherapy</th>
<th>Radiation therapy (Gy)</th>
<th>Response after radiotherapy</th>
<th>KPS (initial/after)</th>
<th>Survival (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73/M</td>
<td>Solitary</td>
<td>PR</td>
<td>WB20 + LB30</td>
<td>CR</td>
<td>60/70</td>
<td>24+</td>
</tr>
<tr>
<td>2</td>
<td>55/M</td>
<td>Multiple</td>
<td>PR</td>
<td>WB40</td>
<td>CR</td>
<td>60/90</td>
<td>10.57</td>
</tr>
<tr>
<td>3</td>
<td>70/F</td>
<td>Multiple</td>
<td>CR</td>
<td>–</td>
<td>CR</td>
<td>90/90</td>
<td>24+</td>
</tr>
<tr>
<td>4</td>
<td>63/F</td>
<td>Solitary</td>
<td>CR</td>
<td>–</td>
<td>CR</td>
<td>60/70</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>70/M</td>
<td>Solitary</td>
<td>CR</td>
<td>–</td>
<td>CR</td>
<td>70/90</td>
<td>23+</td>
</tr>
<tr>
<td>6</td>
<td>69/M</td>
<td>Multiple</td>
<td>CR</td>
<td>–</td>
<td>CR</td>
<td>70/100</td>
<td>18+</td>
</tr>
<tr>
<td>7</td>
<td>56/F</td>
<td>Solitary</td>
<td>PR</td>
<td>LB50</td>
<td>PR</td>
<td>100/100</td>
<td>14+</td>
</tr>
<tr>
<td>8</td>
<td>70/F</td>
<td>Solitary</td>
<td>CR</td>
<td>–</td>
<td>CR</td>
<td>80/100</td>
<td>13+</td>
</tr>
<tr>
<td>9</td>
<td>61/M</td>
<td>Multiple</td>
<td>PR</td>
<td>–</td>
<td>PR</td>
<td>70/90</td>
<td>11+</td>
</tr>
<tr>
<td>10</td>
<td>50/M</td>
<td>Multiple</td>
<td>CR</td>
<td>WB20</td>
<td>CR</td>
<td>80/100</td>
<td>11+</td>
</tr>
<tr>
<td>11</td>
<td>77/M</td>
<td>Multiple</td>
<td>PD</td>
<td>WB50</td>
<td>CR</td>
<td>80/60</td>
<td>14</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; PD, progressive disease; WB, whole brain; LB, local brain; KPS initial/after, Karnofsky performance status initially and after chemotherapy and/or radiotherapy.
rituximab infusion, and fever was observed in each patient. There were relatively reduced early toxicities to the even elderly patients compared to the modified ProMACE-MOPP protocol [7].

In our study with ProMACE-MOPP protocol [7], the five-year actuarial probability of survival was 56%, with a median survival of 68 months. There were eight Grade 3 or 4 respiratory toxicities causing death of the patients. The toxicities were seen when using a relatively low-dose of MTX, most of which is likely due to the combination of other agents in the regimen. To develop a more simple combination of anticancer agents, with efficient therapeutic effect and reduced side effect, we have tried the combination of immunochemotherapy with a rituximab, methotrexate, pirarubicin and procarbazine based on the modified ProMACE-MOPP protocol [7]. Procarbazine is an antineoplastic agent for the treatment of Hodgkin’s lymphoma and is often delivered in a regimen known as MOPP [7]. It is a member of a group of medicine called alkylating agents and has also the ability to cross the blood–brain barrier. Pirarubicin hydrochloride is a new kind of anthracene nucleus broad-spectrum antitumor antibiotic and has the same effect to majority of the cancers. However, under the same conditions, pirarubicin hydrochloride has fewer side effects, such as cardiac toxicity, calvities, or digestive canal reaction, and sublimes the safety of clinical medication markedly. Our collaborators reported that chemotherapy regimens containing pirarubicin were useful and safe for elderly patients with malignant systemic lymphoma [8].

Rituximab is a monoclonal antibody that targets the B-cell specific CD 20 antigen. Rituximab has reported efficacy in PCNSL [9], since most PCNSLs express CD20. As rituximab enhances the efficacy of chemotherapy when used concurrently, the present article details our experience using a combination of rituximab and MTX-based regimen for PCNSL.

HD-MTX (high dose-MTX) is widely recognized as the single most effective chemotherapeutic agent for PCNSL [1,3,10,11]. As improved survival in patients with PCNSL is being achieved, the quality of life, mental function, and performance status of surviving patients have become important. Patients treated with combined HD-MTX and radiation therapy regimens had a 25%–32% overall incidence of late toxicity after prolonged follow-up [4,5]. With a follow-up of four years or more, almost all patients over the age of 60 developed dementia [4]. The combined HD-MTX and radiation therapy regimens could produce significant cognitive problems [4,5,11,12]. Preservation of cognitive function appears better after chemotherapy alone [13], and therefore there are increasing reports [3,11,13–15] that radiotherapy can be deferred until progression or relapse in patients over 60 years. In spite of these encouraging results, at the moment, treatment with chemotherapy followed by radiotherapy is advised.

Figure 1. Kaplan–Meier plots for overall survival.
until comparable five-year survivals can be demonstrated in an unselected group of patients treated by chemotherapy alone in patients with younger than 60 years. For patients older than 60 years, reinduction chemotherapy is likely to be effective and may spare the patient the neurocognitive impairment of radiotherapy until chemoresistance develops. In conclusion, the R-MTX regimen could be delivered in doses prescribed to patients with PCNSL. Our study demonstrates that the R-MTX regimen is an effective treatment for PCNSL, although additional study should be carried out to overcome the small sample size and short follow-up period. The necessity of cranial radiotherapy remains to be defined, and further efforts must be directed at reducing the neurologic sequelae and early toxicities of such treatments. Thus, a regimen resulting in improved survival rates with a low rate of acute and late side effects for patients with PCNSL has still to be developed.

References