照射と30Gy/10回の照射法をランダム化比較し，疼痛緩和率に差を認めず(65% vs 64%)，急性期有害反応の発症は1回照射法で有意に少ないことが示された[8]。

さらに初回照射後の再照射時にも疼痛緩和として1回照射法は有効で，オランダの多施設共同研究[9]では8Gy/1回の照射後に生じた疼痛の再燃に対し再照射で66%の疼痛軽減が得られた。特に乳癌では寛解率が82～89%と良好であった。また，初回に1回照射(4～8Gy)で治療された症例において疼痛の再燃がある場合にも，4Gy/1回の再照射の有用性が報告されている[10]。

5 脊髄圧迫に対する放射線治療

脊椎への転移は，ときに腫瘍の脊柱管内，神経根への浸潤や椎体の病的骨折により脊髄圧迫症状を呈することがある。麻痺の兆候を認めた場合，速やかな治療開始が必要である。可能であれば手術の施行が望ましいが，適応がない場合は放射線治療を早急に開始する。線量・分割方法に関しては遡及的研究であるが，予後不良例には8Gy/1回を，その他の症例には30Gy/10回が推奨されるとしている[11]。照射と高用量のステロイドの併用(デキサメタゾン96mg/日)が有用との報告もみられるが，大量投与による有害事象もあるので注意が必要である[12]。

6 病的骨折に対する放射線治療

CT，MRI検査で荷重のかかる長幹骨の骨皮質に50%以上の破壊がみられた場合，または病変の長軸方向の長さが2.5cm以上に及ぶ場合に病的骨折の危険が高いとされており，外科的固定術を先行した後放射線治療を検討する。線量および分割方法は疼痛緩和目的の照射に準じる。

B-脳転移に対する放射線治療

1 乳癌の脳転移と放射線治療

脳腫瘍全国統計委員会の報告(1996年)では，乳癌は脳転移の原発巣としては肺癌に次いで多い。脳転移を有する症例は基本的に予後不良であり，無治療での予後は約1～2カ月とされる。脳転移例の治療目的は主に症状の緩和となるが，後述する予後不良因子を持たない症例では手術や定位手術的照射などの積極的な治療で予後の改善が期待できる。さらに長期予後が期待できる症例では，全脳照射後の晩期有害反応が問題となる場合もあり，脳転移における放射線治療の方法と適応は，患者の予後因子を十分把握した上で計画する必要がある。

2 脳転移症例の予後因子

RTOGでは，全脳照射に関する3つのランダム化比較試験(RCT)のデータから予後因子を検討し3群に分類した。「全身状態良好(Karnofsky performance status；KPS 70以上)」，「65歳未満」，「原発巣の制御」，「頭蓋外活動性病変なし」のすべてを満たす群(class1)では生存期間の中央値は7.1カ月，全身状態不良(KPS 70未満)の群(class 3)では2.3カ月それ以外すべての症例群(class 2)では4.2カ月であった[13]。

この予後因子を用いた分類は，手術や定位手術的照射を施行する例にも有用である。予後良好群であるclass 1では，脳転移病巣の制御を目的に定位手術的照射や手術などの積極的な治療もされるが，予後が不良なclass 2，3では，まず症状の緩和を目的に全脳照射を行う。

3 全脳照射

転移性脳腫瘍に対する基本的な治療方法であり，その目的は神経症状および頭痛・嘔気など頭蓋内圧亢進による症状の緩和である。全体的な症

状の緩和は50～85%に認め，神経学的改善は約40%に認められるが，予後の著明な改善は期待できない。

a. 照射方法

頭部固定下に左右対向2門で照射する。上方は頭蓋冠より広めの照射野をとり，頭蓋底部は前・中頭蓋窩を完全に含め眼部を遮蔽する。

b. 総線量と分割方法

全脳照射の線量・分割方法は20 Gy/5回から50 Gy/25回までの種々の放射線照射法が報告されているが，症状の改善率に差がないことからわが国では30 Gy/10回が頻用される。

c. 手術と全能照射

RCTの報告から，頭蓋外病変が制御された単発脳転移例に対して全脳照射に手術を併用する有用性が明らかとなった[14]。一方，頭蓋外活動性病変を有する場合には照射単独と比較して生存期間に差がないとする報告が多い。しかし，QOL維持の点から局所制御のもつ意味は大きく，手術可能であった症例には術後全脳照射を行うべきと考えられている。

d. 有害事象

全脳照射施行中における急性期有害事象は一過性の脳圧亢進症状があり，ステロイドやグリセオールの予防的投与を行う。

晩期有害事象としては脳萎縮，白質脳症，脳壊死，正常圧水頭症，内分泌障害などがあるが，その正確な頻度を求めることは困難である。

4 定位手術的照射

定位放射線照射は，患部の高精度固定下で病変に多方向から放射線束を集中させ，選択的に高線量を投与する放射線治療技術である。コバルト60ガンマ線を用いたガンマナイフと，直線加速器（リニアック）によるX線を用いた2つの方法があり，1回照射の場合を定位手術的照射（Stereotactic Radiosurgery；SRS）と総称する。SRSの意義は正常組織に対する影響を少なくした上で転移巣を制御することで，その効果は手術と同等とのコンセンサスが得られている[15]。さらに手術で到達できない深部の治療も可能である。

腫瘍辺縁線量で10～27 Gyを投与するが，その治療成績は局所制御率で70～90%と報告されている。先の予後因子分類に従った生存期間では，class 1で16.1カ月，class 2で10.3カ月，class 3で8.7カ月との報告がある[16]。

a. 定位手術的照射の適応

転移性脳腫瘍に対する本法の適応基準は，病変の大きさが3 cm以下であり，個数は3～4個以下，全身状態が良好（KPS 70以上），少なくとも3カ月以上の予後が見込まれることなどである。KPSが70未満の全身状態不良例でも，症状改善が期待できる場合には治療対象となり得る。

b. 全脳照射の併用

定位脳照射後の全脳照射の併用に関しても議論が多く，いくつかの後ろ向き研究で脳内制御率は全脳照射併用群に有意に良好であるが，生存期間には差がないと報告されている。併用の有用性を検討したRCTも進行中であり，QOLの評価を加えた今後のエビデンスの蓄積が待たれる。

c. 有害事象

SRSによる急性期有害反応は軽度であることが多く，病変の位置によっても異なるが，30%未満の症例で嘔気，頭痛，軽度のけいれん発作などが生じる。遅発性の反応は治療数カ月後に一部の症例に放射線脳壊死，脳浮腫を認めるが，その頻度は化学療法の併用で増加する可能性がある。

まとめ

骨転移に対する1回照射，脳転移に対する定位手術的照射の普及など，従来の照射手法に加え新たな知見が広まりつつある。新規治療がもつ可能性を過信し，生命予後の改善に関し科学的根拠に乏しい治療戦略が選択され，患者への負担を増や

さないよう熟慮が必要である。

（篠田充功・鹿間直人）

文　献

1) Hayes D：Evaluation of patients following primary therapy. Breast Diseases 2nd ed, (Harris JR), JB Lippincott, Philadelphia, p505, 1991
2) Perez JE, Machiavelli M, Leone BA, et al：Bone-only versus visceral-only metastatic pattern in breast cancer. Analysis of 150 patients. Am J Clin Oncol 13：294-298, 1990
3) van der Linden YM, Dijkstra SP, Vonk EJ, et al：Prediction of survival in patients with metastases in the spinal column：Results based on a randomized trial of radiotherapy. Cancer 103 (2)：320-328, 2005
4) Bates T：A review of local radiotherapy in the treatment of bone metastases and cord compression. Int J Radiat Oncol Biol Phys 23 (1)：217-221, 1992
5) Maher EJ：The use of palliative radiotherapy in the management of breast cancer. Eur J Cancer 28 (2-3)：706-710, 1992
6) Sze WM, Shelley MD, Held I, et al：Palliation of metastatic bone pain：single fraction versus multifraction radiotherapy—a systematic review of randomised trials. Clin Oncol (R Coll Radiol) 15 (6)：345-352, 2003
7) Wu JS, Wong RK, Lloyd NS, et al：Radiotherapy fractionation for the palliation of uncomplicated painful bone metastases—an evidence-based practice guideline. BMC Cancer 4 (1)：71, 2004
8) Hartsell WF, Scott CB, Bruner DW, et al：Randomized trial of short-versus long-course radiotherapy for palliation of painful bone metastases. J Natl Cancer Ist 97 (11)：798-804, 2005
9) van der Linden YM, Lok JJ, Steenland E, et al：Single fraction radiotherapy is efficacious：a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. Int J Radiat Oncol Biol Phys 59 (2)：528-537, 2004
10) Jeremic B, Shibamoto Y, Igrutinovic I：Single 4Gy re-irradiation for painful bone metastasis following single fraction radiotherapy. Radiother Oncol 52 (2)：123-127, 1999
11) Rades D, Stalpers LJ, Veninga T, et al：Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. J Clin Oncol 23 (15)：3366-3375, 2005
12) Loblaw DA, Laperriere NJ：Emergency treatment of malignant extradural spinal cord compression：an evidence-based guideline. J Clin Oncol 16 (4)：1613-1624, 1998
13) Gaspar L, Scott C, Rotman M, et al：Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 37 (4)：745-751, 1997
14) Patchell RA, Tibbs PA, Walsh JW, et al：A randomized trial of surgery I the treatment of single metastases to the brain. N Engl J Med 322 (8)：494-500, 1990
15) Sneed PK, Suh JH, Goetsch SJ, et al：A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. Int J Radiat Oncol Biol Phys 53 (3)：519-526, 2002
16) Sanghavi SN, Miranpuri SS, Chappell R, et al：Radiosurgery for patients with brain metastases：A multi-institutional analysis, stratified by the RTOG recursive partitioning analysis method. Int J Radiat Oncol Biol Phys 51 (2)：426-434, 2001

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 1, pp. 217–222, 2006

0360-3016/06/$–see front matter

doi:10.1016/j.ijrobp.2006.04.006

CLINICAL INVESTIGATION **Lymphoma**

A PROSPECTIVE STUDY OF REDUCED-DOSE THREE-COURSE CHOP FOLLOWED BY INVOLVED-FIELD RADIOTHERAPY FOR PATIENTS 70 YEARS OLD OR MORE WITH LOCALIZED AGGRESSIVE NON-HODGKIN'S LYMPHOMA

NAOTO SHIKAMA, M.D.,* MASAHIKO OGUCHI, M.D.,† KOICHI ISOBE, M.D.,‡ KATSUMASA NAKAMURA, M.D.,§ YOSHIO TAMAKI, M.D.,‖ MASATOSHI HASEGAWA, M.D.,¶ TAKESHI KODAIRA, M.D.,# SHIGERU SASAKI, M.D.,* AND YOSHIKAZU KAGAMI, M.D.,** ON BEHALF OF THE JAPAN RADIATION ONCOLOGY GROUP (JAROG)

*Department of Radiology, Shinshu University School of Medicine, Matsumoto, Japan; †Department of Radiation Oncology, Cancer Institute Hospital, Tokyo, Japan; ‡Department of Radiology, Chiba University Hospital, Chiba, Japan; §Department of Radiology, Kyushu University Graduate School of Medicine, Fukuoka, Japan; ‖Department of Radiology, Gunma Prefectural Cancer Center, Gunma, Japan; ¶Department of Radiation Oncology, Nara Medical University, Nara, Japan; #Department of Radiation Oncology, Aichi Cancer Center, Nagoya, Japan; **Department of Radiation Oncology, National Cancer Center, Tokyo, Japan

Purpose: We conducted a multicenter prospective study to evaluate the efficacy and safety of reduced-dose three-course CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) followed by involved-field radiotherapy for elderly patients with localized aggressive non-Hodgkin's lymphoma. The primary endpoint was compliance with the combined modality.

Methods and Materials: This study included untreated patients, ≥70 years old, with diffuse aggressive lymphoma, Stage IA or contiguous nonbulky Stage IIA. 80%-CHOP (cyclophosphamide 600 mg/m^2, doxorubicin 40 mg/m^2, vincristine 1.1 mg/m^2, and prednisolone at 80 mg/day for 5 days) was repeated every 3 weeks. After three cycles of chemotherapy, involved-field radiotherapy was performed with a radiation dose of 30–50 Gy in 15–28 fractions.

Results: Twenty-four patients with a median age of 75 years (range, 70–84 years) were enrolled. The compliance rate of the protocol study was 87.5% (95% confidence interval [CI], 67.6–97.3). Three patients received only two cycles of chemotherapy because of toxicity or second neoplasm. There were no deaths caused by severe toxicity. The 3-year progression-free and overall survival rates were 83.1% (95% CI, 75.4–90.8) and 82.9% (95% CI, 75.1–90.6), respectively.

Conclusion: Three-course 80%-CHOP followed by involved-field radiotherapy may be safe for administration to elderly patients over 70 years old. The next step is to evaluate three-course 80%-CHOP and rituximab followed by radiotherapy in elderly patients with localized disease.

Aggressive lymphoma, Chemotherapy, Elderly patients, Dose-intensity, Radiotherapy.

INTRODUCTION

Increased age at diagnosis is a poor prognostic indicator in aggressive non-Hodgkin's lymphoma (NHL) (1). Several factors may contribute to the differences in outcome between younger and elderly patients with NHL: (*1*) differences in disease biology, (*2*) poor compliance rate of treatment due to co-morbid illness or poor host organ tolerance, and (*3*) administration of less intensive chemotherapy (2). Some investigators reported that elderly patients with NHL, who had a good performance status and minimal co-morbid illness, can tolerate full-dose chemotherapy without increased toxicity (3–6). However, Tirelli *et al.* reported that 8 (11%) of 71 elderly patients over 70 years old (median, 77 years), who underwent aggressive treatment including combination chemotherapy regimens

Reprint requests to: Naoto Shikama, M.D., Department of Radiology, Shinshu University School of Medicine, 3-1-1 Asahi Matsumoto, 390-8621 Japan. Tel: (+81) 263-37-2650; Fax: (+81) 263-37-3087; E-mail: shikama@hsp.md.shinshu-u.ac.jp

This study was presented in part at the 47th Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO), Denver, Colorado, in October 2005.

This study was supported by Grants-in-Aid for Cancer Research (12-13, 16-12, 17-18) from the Ministry of Health, Labor, and Welfare of Japan.

Acknowledgments—The authors appreciate the support of Dr. K. Tobinai, Hematology Division, National Cancer Center, for helpful comments and suggestions, and Mrs. Y. Asazawa, Mrs. I. Koiwai, and Mrs. Y. Ogawa for technical assistance.

Received Dec 31, 2005, and in revised form March 25, 2006. Accepted for publication April 4, 2006.

with three or more drugs or extended field radiotherapy, died as a result of treatment-related toxicity (7). Balducci and Lyman emphasized that patients over 70 years old are at high risk for neutropenic infection (8). Lyman *et al.* conducted a nationwide survey in the United States and collected data for 4522 patients with NHL from 567 oncology practices. Their results indicated that a greater proportion of elderly patients over 60 years old received a relative dose-intensity (RDI) of less than 85% during the first five cycles of chemotherapy (9). These findings suggested that physicians may modify the dose of chemotherapy according to patient's age and other clinical factors.

The Southwest Oncology Group (SWOG) conducted a prospective randomized clinical trial to assess the effectiveness of short-course CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) followed by involved-field radiotherapy in comparison with eight-course CHOP in patients with localized NHL (10). Three-cycle CHOP followed by involved-field radiotherapy is considered the standard method of care for patients with localized aggressive disease (11, 12). On the other hand, Gomez *et al.* retrospectively analyzed the outcomes of 267 consecutive elderly patients (median age, 70 years; range, 60 to 94 years) treated with CHOP. They reported that 63% of treatment-related deaths occurred after the first cycle of chemotherapy, and infection accounted for 82% of the toxicity-related deaths (4). This suggests that careful management of elderly patients should be taken into consideration, even in cases treated with short-course chemotherapy.

We conducted a multicenter prospective study to evaluate the efficacy and safety of reduced-dose short-course CHOP followed by involved-field radiotherapy in elderly patients over 70 years old with localized disease.

METHODS AND MATERIALS

Patients

Elderly patients aged 70 years old or more with localized diffuse aggressive lymphoma were recruited from December 2000. Histologic diagnoses were made according to the REAL (revised European-American classification of lymphoid neoplasms) classification or the Working Formulation (13). The localized diseases included in the present study were Stage IA or contiguous non-bulky Stage IIA. Patients with more than two extranodal diseases were excluded from the study. Eligibility criteria for inclusion in the study were as follows: good performance status (0–2) according to the Eastern Cooperative Oncology Group; elevated serum lactate dehydrogenase less than 150% of the upper limit of the institutional normal range; no co-morbidity with other serious medical conditions, including severe ischemic heart disease and cardiomyopathy. Patients were excluded from the trial if they had a history of active cancer during the previous 5 years, positive serology for human immunodeficiency virus, or the presence of hepatitis B (HB) antigen or anti-hepatitis C virus (anti-HCV) antibody, or central nervous system, testis, stomach, or spleen involvement.

No prior chemotherapy or radiotherapy was allowed before entry into the study. All patients were required to have sufficient hematologic, renal, and hepatic functions. Minimal staging procedures included clinical examination; chest radiography; gallium scintigraphy; computed tomography of the neck, chest, abdomen, and pelvis; bone marrow biopsy; and blood studies.

This study complied fully with all provisions of the Declaration of Helsinki. All participating hospitals obtained the permission of the institutional review board, and all patients gave their written informed consent before entry into the study.

Treatment

Reduced-dose chemotherapy (80%-dose CHOP) included cyclophosphamide at 600 mg/m^2 (Day 1), doxorubicin at 40 mg/m^2 (Day 1), vincristine at 1.1 mg/m^2 (Day 1), and oral prednisolone at 80 mg/day (Days 1–5). Chemotherapy was repeated at 21-day intervals. If a patient developed Grade 4 neutropenia or febrile neutropenia, all subsequent cycles were administered with granulocyte colony-stimulating factor (G-CSF) support. If febrile neutropenia developed with infection, the dose of cyclophosphamide was decreased by 150 mg/m^2 and that of doxorubicin was decreased by 10 mg/m^2 for all subsequent cycles. Chemotherapy was discontinued in cases in which Grade 4 neutropenia persisted. If a patient developed Grade 3 or 4 thrombocytopenia, the dose of cyclophosphamide was decreased by 150 mg/m^2 and that of doxorubicin was decreased by 10 mg/m^2 for all subsequent cycles. Chemotherapy was discontinued in cases in which Grade 3 or 4 thrombocytopenia persisted.

Involved-field radiotherapy was performed after three cycles of chemotherapy. The involved-field was defined as the regional area including the primary lesion and involved nodes determined by prechemotherapy evaluations and adjacent uninvolved nodes. The radiation dose was 30–30.6 Gy given in 15–20 fractions over 3–4 weeks for patients who achieved complete remission (CR), and 40–50 Gy in 20–28 fractions over 4–6 weeks for those who did not achieve CR. Response was assessed using the standard criteria (14).

No central pathologic review was performed in this study.

Follow-up

Response to chemotherapy was evaluated after three cycles of CHOP, or after discontinuation of the planned treatment. Thereafter, clinical examination was performed every 6 months for the first 5 years, and then at the discretion of the attending physician. A neck, chest, and abdominal computed tomographic scan was performed after 6 months, and then every 6 months during the first 5 years.

Outcome measures

The primary endpoint was compliance with the combined modality therapy. Completion of the study protocol was defined as completion of three cycles of chemotherapy and planned radiation therapy. The events were defined as going off-protocol, a 5-week delay of administration of chemotherapy, disease progression or relapse, or death due to any cause. Calculation of compliance with the protocol was performed among all registered patients. The secondary endpoints included progression-free survival, overall survival, and toxicity. Progression-free survival was calculated using disease progression or death due to any cause as an event, and overall survival was calculated using death due to any cause as an event. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria grading system version 2.0. Tumor responses were classified as CR, CRu (CR unconfirmed), partial

remission, stable disease, or progressive disease according to the proposed International Workshop criteria (14).

Statistical analysis

Sample size was calculated on the basis of the primary endpoint. Based on various results obtained in previous studies with CHOP chemotherapy in this patient population, compliance with this protocol was assumed conservatively to be 90%, and the lower limit of compliance was assumed to be 70% (7, 12, 15–17). To confirm the rate of compliance with this protocol, it was calculated that 30 patients recruited over the 3 years of the study would be required to provide 80% power at the overall 5% (alpha = 0.05, 2 sides) significance level.

The progression-free survival and overall survival rate were calculated using the Kaplan-Meier method. Analyses of efficacy and safety included all patients. Statistical analyses were performed with JMP software version 5.0.1 (SAS Institute Inc., Cary, NC) by our trial office.

RESULTS

Compliance with the study protocol

The median follow-up period was 38 months (range, 2–55 months). The compliance rate with the study protocol was 87.5% (95% CI [confidence interval], 67.6–97.3). The lower limit of 95% CI was slightly below 70%, which was the threshold value defined before the study. The study protocol was not completed in 3 patients who received only two cycles of chemotherapy. The physician stopped treatment using the protocol in 1 patient, and another patient refused administration of the third round of chemotherapy. In addition, they received radiotherapy after going off-protocol. Another 1 patient developed pancreatic cancer during chemotherapy, and the protocol was stopped. In 6 patients, the administration of chemotherapy was delayed owing to hematologic toxicity, and the median interruption of chemotherapy was 2 days (range, 1–14 days). The dose of chemotherapy was reduced because of hematologic toxicity in 1 patient who was 84 years old and had Stage II disease.

Patient characteristics and response to treatment

The number of patients enrolled in the study did not increase after permission was granted for administration of rituximab (Rituxan; Roche, Basel, Switzerland) in Japan in September 2003. We stopped this protocol in February 2004. Twenty-four patients were enrolled from eight Japanese institutions between December 2000 and February 2004. The initial characteristics of all 24 patients are summarized in Table 1. The median age was 75 years (range, 70–84 years), and 4 patients (16%) were over 80 years old. Response rates after chemotherapy were 50% (12 patients) for CR, 25% (6 patients) for CRu, and 20% (5 patients) for partial remission or stable disease. Treatment response was not evaluated in 1 patient (4%) who developed pancreatic cancer during chemotherapy and died before evaluation of his response. Response rates after combined treatment were 67% (16 patients) for CR, 21% (5 patients) for CRu, and 8% (2 patients) for partial remission.

Table 1. Patient characteristics

Characteristics	No. of patients (%)
Age, years	
Median	75
Range	70–84
70–75	15 (62)
≥76	9 (38)
Gender	
Male	13 (54)
Female	11 (46)
Performance status (ECOG)	
0	18 (75)
1	6 (25)
Location	
Waldeyer's ring	11 (46)
Neck node	6 (25)
Maxillary sinus	3 (13)
Thyroid	2 (8)
Parotid gland	1 (4)
Paravertebral area	1 (4)
Stage	
I	16 (67)
II	8 (33)
Lactate dehydrogenase	
≤ULN	20 (83)
>ULN, <1.5 × ULN	4 (17)
Stage-modified International Prognostic Index*	
1	14 (59)
2	8 (33)
3	2 (8)
Tumor size	
<6 cm	19 (79)
6 cm <10 cm	4 (17)
≥10 cm	1 (4)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ULN = upper limit of the institutional normal range.

* Stage-modified International Prognostic Index; Age (≤60 vs. >60), stage (I vs. II), serum lactate dehydrogenase (normal vs. increased), performance status (0–1 vs. 2).

Progression-free and overall survival rates

The 3-year progression-free and overall survival rates were 83.1% (95% CI, 75.4–90.8) and 82.9% (95% CI, 75.1–90.6), respectively (Fig. 1). The 3-year progression-free and overall survival rates according to stage-modified International Prognostic Index score were 78.7% and 77.9% for score 1, 87.5% and 87.5% for score 2, and 100% and 100% for score 3, respectively. To date, no recurrence in the radiation field has been found. Four patients developed relapse at distant sites: lung, bone marrow, liver, kidney, heart, adrenal gland, and abdominal lymph nodes.

Toxicity

During chemotherapy, severe hematologic toxicity (Grade 3–4) occurred in 23 patients, and severe nonhematologic toxicity (Grade 3–4) occurred in 3 (diabetes mellitus in 2

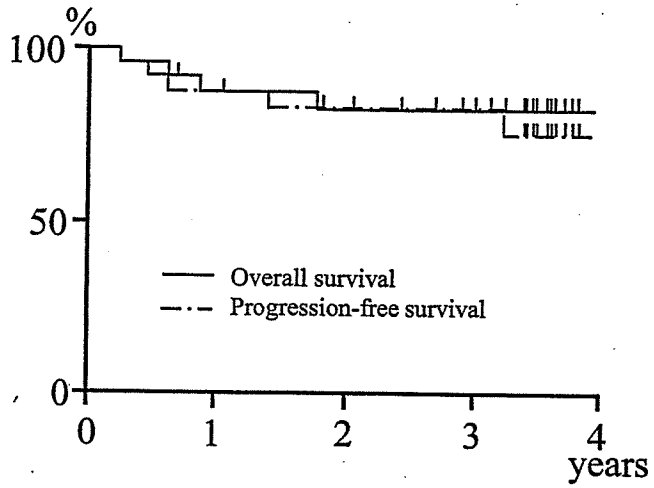

Fig. 1. Overall and progression-free survival curves of all 24 patients.

patients, pneumonia in 1) (Table 2). Only 1 patient experienced severe hematologic toxicity (Grade 4), and no patients developed symptoms of heart failure. During radiotherapy, severe hematologic toxicity (Grade 3) occurred in 1 patient, and nonhematologic severe toxicity (Grade 3) occurred in 1 (mucositis). In 2 patients, radiotherapy was interrupted for 10 and 11 days, respectively, because of radiation-induced mucositis. None of the patients died as a result of treatment-related toxicity.

DISCUSSION

Cyclophosphamide, doxorubicin, vincristine, and prednisolone is the standard regimen for treatment of patients with aggressive NHL (2, 18). Kouroukis *et al.* conducted a systematic review with regard to chemotherapy in elderly patients with advanced-stage aggressive NHL. This systematic review demonstrated that anthracycline-containing regimens, such as CHOP or CTVP (cyclophosphamide, pirarubicin, vincristine, and prednisolone), improved overall survival as compared with other regimens without anthracycline (2). Tirelli *et al.* performed a randomized trial to compare the efficacy of the CHOP regimen with that of VMP (etoposide, mitoxantrone, and prednimustine) for elderly patients over 70 years old, and showed that the overall survival rate was 30% with VMP vs. 65% with CHOP ($p = 0.004$) (18). The Dutch-Belgian Hemato-Oncology Cooperative Group conducted a randomized trial to evaluate the use of G-CSF for elderly patients over 65 years old (17). This study demonstrated that the addition of G-CSF improved the RDI of chemotherapy, but had no effect on overall survival. The rate of protocol completion of CHOP or G-CSF was approximately 70%, and patients older than 80 years completed significantly fewer treatments as compared with younger patients as a result of toxicity, refusal, or death (43% vs. 80%; $p < 0.001$). In addition, G-CSF did not prevent serious infections. Compared with this result, the rate of protocol completion in the present study was not unsatisfactory. Recently, the addition of rituximab, which is a chimeric human/murine immunoglobulin G1 monoclonal antibody that binds specifically to the B-cell-surface antigen CD20, to the full-course CHOP regimen was shown to improve treatment outcome in patients with advanced disease (19, 20). However, the role of rituximab has not been clarified in patients with localized disease. The present study was conducted before permission for use of rituximab for diffuse large B-cell lymphoma was granted in Japan, and we applied the CHOP regimen in the present study. In comparison with Western series, patients with nodal disease were less frequent in this study. However, these observations agreed well with our previous nationwide survey among Japanese radiation oncologists (15).

Recent prospective studies demonstrated the safety of the three-weekly full-dose CHOP regimen and two-weekly CHOP regimen for elderly patients older than 60 years (19, 21). However, there is controversy regarding

Table 2. Toxicity in the chemotherapy phase and radiotherapy phase

	Chemotherapy (n = 24)					Radiotherapy (n = 21)*				
	Grade					Grade				
	0	1	2	3	4	0	1	2	3	4
White blood cell	0	1	0	22	1	15	4	1	1	0
Hemoglobin	7	14	3	0	0	12	9	0	0	0
Platelet	17	6	0	1	0	19	2	0	0	0
Emesis	16	8	0	0	0	18	3	0	0	0
Mucositis	22	1	1	0	0	2	13	5	1	0
Pnuemonitis	22	0	1	1	0	20	1	0	0	0
Fever	21	1	1	1	0	—	—	—	—	—
Liver dysfunction	22	2	0	0	0	—	—	—	—	—
Renal dysfunction	24	0	0	0	0	—	—	—	—	—
Peripheral neuropathy	17	7	0	0	0	20	1	0	0	0
Diabetes mellitus	21	0	1	2	0	—	—	—	—	—

* Three patients were off-protocol.

the standard care for elderly patients over 75 years of age. Epelbaum *et al.* reported a 5-year survival rate of 80% in patients treated with ≥70% RDI of CHOP in their first cycle of chemotherapy and a 5-year survival rate of only 32% in those receiving ≤70% ($p = 0.0001$) (22). Kwak *et al.* retrospectively analyzed 115 patients treated with CHOP or other anthracycline-containing regimens, and emphasized the actual RDI of doxorubicin ≥75% as the single most important predictor of survival (23). Lee *et al.* reported that elderly patients who received doxorubicin at doses of ≥10 mg/m^2 per week had treatment outcomes that were comparable to those of young patients, and showed that in elderly patients the dose intensity of doxorubicin was a more important prognostic factor than the mean RDI of each agent (6).

The Eastern Cooperative Oncology Group conducted a randomized trial to compare low-dose (30 Gy) radiotherapy with observations in patients with localized disease achieving CR after eight-cycle CHOP (24). This study demonstrated that for patients in CR after CHOP, low-dose radiotherapy prolonged disease-free survival and provided local control, but no survival benefit was observed. Thirty-one percent of the patients in this study had bulky disease, and it was not possible to evaluate the role of radiotherapy for patients with localized disease. The Groupe d'Etude des Lymphomes de l'Adulte (GELA) conducted a prospective randomized trial to evaluate the role of consolidated radiotherapy for elderly patients over 60 years old who were treated with four-cycle CHOP (25). Bulky disease was observed in 9% of patients, and extranodal disease in 57%. The event-free survival and overall survival were not significantly different between the chemotherapy alone and the combination therapy groups. The criticism of this trial was that for patients with bulky disease four cycles of CHOP were not only effective at eliminating microscopic sites of disease (26). Therefore, we could not reach definitive conclusions regarding the role of radiotherapy for localized disease.

The clinical outcome after short-course CHOP followed by involved-field radiotherapy is excellent for patients with localized disease and no adverse factors (10). However, this combined therapy is not satisfactory for patients with poor prognostic factors, such as bulky tumors or advanced age. We should establish more effective combined therapy for patients with localized disease and poor prognostic factors. The addition of rituximab improved the treatment outcome for elderly patients with aggressive disease with CD20, but did not increase the toxicity (19, 20). A GELA study, which included Stage II–IV disease, demonstrated that rituximab was more effective for patients at low risk than for those at high risk (19). However, it has not yet been established whether the addition of rituximab produces survival benefit for patients with localized disease. A phase II study (SWOG 0014) was conducted to evaluate the efficacy and safety of four-course rituximab plus three-course CHOP followed by radiotherapy for patients with localized disease (27). The treatment outcome was excellent, and 2-year overall and progression-free survival rates were 95% and 94%, respectively. A prospective randomized trial is currently in progress to compare short-course CHOP followed by radiotherapy with this combined therapy with rituximab.

Combined modality therapy with reduced-dose CHOP and involved-field radiotherapy may be safe for administration to elderly patients aged 70 years old or more, with good performance status and minimal co-morbid illness, with Stage I or nonbulky Stage II disease. The next step is to evaluate combined therapy, including reduced-dose CHOP and radiotherapy plus rituximab for elderly patients 70 years of age or more.

REFERENCES

1. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 1993;329:987–994.
2. Kouroukis CT, Browman GP, Esmail R, Meyer RM. Chemotherapy for older patients with newly diagnosed, advanced-stage, aggressive-histology non-Hodgkin lymphoma: A systematic review. *Ann Intern Med* 2002;136:144–152.
3. Campbell C, Sawka C, Franssen E, Berinstein NL. Delivery of full dose CHOP chemotherapy to elderly patients with aggressive non-Hodgkin's lymphoma without G-CSF support. *Leuk Lymphoma* 1999;35:119–127.
4. Gomez H, Hidalgo M, Casanova L, *et al.* Risk factors for treatment-related death in elderly patients with aggressive non-Hodgkin's lymphoma: Results of a multivariate analysis. *J Clin Oncol* 1998;16:2065–2069.
5. Dixon DO, Neilan B, Jones SE, *et al.* Effect of age on therapeutic outcome in advanced diffuse histiocytic lymphoma: The Southwest Oncology Group experience. *J Clin Oncol* 1986;4: 295–305.
6. Lee KW, Kim DY, Yun T, *et al.* Doxorubicin-based chemotherapy for diffuse large B-cell lymphoma in elderly patients: Comparison of treatment outcomes between young and elderly patients and the significance of doxorubicin dosage. *Cancer* 2003;98:2651–2656.
7. Tirelli U, Zagonel V, Serraino D, *et al.* Non-Hodgkin's lymphomas in 137 patients aged 70 years or older: A retrospective European Organization for Research and Treatment of Cancer Lymphoma Group Study. *J Clin Oncol* 1988;6:1708–1713.
8. Balducci L, Lyman GH. Patients aged > or = 70 are at high risk for neutropenic infection and should receive hemopoietic growth factors when treated with moderately toxic chemotherapy. *J Clin Oncol* 2001;19:1583–1585.
9. Lyman GH, Dale DC, Friedberg J, *et al.* Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: A nationwide study. *J Clin Oncol* 2004; 22:4302–4311.
10. Miller TP, Dahlberg S, Cassady JR, *et al.* Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *N Engl J Med* 1998;339:21–26.
11. Miller TP. The limits of limited stage lymphoma. *J Clin Oncol* 2004;22:2982–2984.
12. Shenkier TN, Voss N, Fairey R, *et al.* Brief chemotherapy and involved-region irradiation for limited-stage diffuse

large-cell lymphoma: An 18-year experience from the British Columbia Cancer Agency. *J Clin Oncol* 2002; 20:197–204.
13. Harris NL, Jaffe ES, Diebold J, *et al.* The World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues. Report of the Clinical Advisory Committee meeting, Airlie House, Virginia, November, 1997. *Ann Oncol* 1999;10:1419–1432.
14. Cheson BD, Horning SJ, Coiffier B, *et al.* Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol* 1999;17:1244–1253.
15. Oguchi M, Izuno I, Takei K, *et al.* Treatment for non-Hodgkin's lymphoma (stage I, II) of the elderly: Usefulness of local and regional irradiation and reduced dose chemotherapy. *Int J Radiat Oncol Biol Phys* 1997;37:87–92.
16. Epelbaum R, Haim N, Leviov M, *et al.* Full dose CHOP chemotherapy in elderly patients with non-Hodgkin's lymphoma. *Acta Oncol* 1995;34:87–91.
17. Doorduijn JK, van der Holt B, van Imhoff GW, *et al.* CHOP compared with CHOP plus granulocyte colony-stimulating factor in elderly patients with aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 2003;21:3041–3050.
18. Tirelli U, Errante D, Van Glabbeke M, *et al.* CHOP is the standard regimen in patients > or = 70 years of age with intermediate-grade and high-grade non-Hodgkin's lymphoma: Results of a randomized study of the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Study Group. *J Clin Oncol* 1998;16:27–34.
19. Feugier P, Van Hoof A, Sebban C, *et al.* Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: A study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 2005;23: 4117–4126.
20. Pfreundschuh M, Trumper L, Ma D, *et al.* Randomized intergroup trial of first line treatment for patients ≤60 years with diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) with a CHOP-like regimen with or without the anti-CD20 antibody rituximab: Early stopping after the first interim analysis [Abstract]. *Pro Am Soc Clin Oncol* 2004;23:556.
21. Pfreundschuh M, Trumper L, Kloess M, *et al.* Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: Results of the NHL-B2 trial of the DSHNHL. *Blood* 2004; 104:634–641.
22. Epelbaum R, Haim N, Ben-Shahar M, *et al.* Dose-intensity analysis for CHOP chemotherapy in diffuse aggressive large cell lymphoma. *Isr J Med Sci* 1988;24:533–538.
23. Kwak LW, Halpern J, Olshen RA, Horning SJ. Prognostic significance of actual dose intensity in diffuse large-cell lymphoma: Results of a tree-structured survival analysis. *J Clin Oncol* 1990;8:963–977.
24. Horning SJ, Weller E, Kim K, *et al.* Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. *J Clin Oncol* 2004;22:3032–3038.
25. Fillet G, Bonnet N, Mounier N. Radiotherapy is unnecessary in elderly patients with localized aggressive non Hodgkin's lymphoma: Results of the GELA LHN 93-4 study [Abstract]. *Proc Am Soc Hematol* 2002;100:92a.
26. Fisher RI, Miller TP, O'Connor OA. Diffuse aggressive lymphoma. *Hematology* (Am Soc Hematol Educ Program) 2004; 221–236.
27. Miller TP, Unger JM, Spier CM. Effect of adding rituximab to three cycles of CHOP plus involved field radiotherapy for limited-stage aggressive diffuse B-cell lymphoma (SWOG-0014) [Abstract]. *Blood* 2004;104:48a.

Jpn J Clin Oncol 2006;36(8)499–503
doi:10.1093/jjco/hyl056

Patterns of Care Study for Postmastectomy Radiotherapy in Japan: Its Role in Monitoring the Patterns of Changes in Practice

Naoto Shikama[1,2], Michihide Mitsumori[1,3], Chikako Yamauchi[1,3], Hideki Takekawa[1,4], Kazukiyo Arakawa[1,5], Shigeru Sasaki[1,2] and Teruki Teshima[1,4]

[1]Japanese PCS Working Subgroup of Breast Cancer, [2]Department of Radiology, Shinshu University School of Medicine, Matsumoto, Nagano, [3]Department of Therapeutic Radiology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, [4]Department of Medical Engineering, Oosaka University Faculty of Medicine, Suita, Osaka and [5]Department of Radiology, Ina General Hospital, Ina, Nagano, Japan

Received March 18, 2006; accepted April 30, 2006; published online June 27, 2006

Background: Three prospective randomized clinical trials (RCT) in the 1990s demonstrated the survival benefit of postmastectomy radiotherapy (PMRT) for patients with locally advanced breast cancer. The present study was performed to evaluate whether the Patterns of Care Study (PCS) fulfills a role in monitoring the patterns of changes in clinical practices in Japan.
Methods: The first survey (JPCS-1) involved 79 Japanese facilities by two-stage cluster sampling of facilities and patients, and was carried out during 1998–2000. JPCS-1 included 1124 patients with breast cancer who were treated between 1995 and 1997. The second survey (JPCS-2) was carried out during 2001–2003, involving 827 patients who were treated between 1999 and 2001 in 76 facilities.
Results: Patients with adverse risk factors, including pathologically axillary positive nodes (≥4) and/or advanced primary disease (pT3–4) accounted for 57% of the patients who received PMRT in JPCS-1 and 72% of those in JPCS-2 ($P = 0.039$). The multiple radiotherapy target volume including the chest wall and regional lymph nodes was applied in 18% of the patients in JPCS-1 and 44% of those in JPCS-2 ($P < 0.001$). However, the dose distribution was calculated in only 42% of the patients in both surveys ($P = 0.467$).
Conclusions: The eligibility and the target volume for PMRT were influenced by the outcome of RCT, but the quality of radiotherapy did not improve sufficiently. The PCS survey is useful to monitor the changes in patterns of clinical practice and can clarify some problems with radiotherapy techniques.

Key words: breast cancer – mastectomy – patterns of care – radiotherapy

INTRODUCTION

Over the last two decades, prospective randomized clinical trials (RCT) and meta-analysis demonstrated that postmastectomy radiotherapy (PMRT) improved the loco-regional control of patients with locally advanced breast cancer, but failed to improve overall survival (1–3). Any reduction in breast cancer mortality has been offset by mortality from late adverse effects of radiotherapy, including heart disease (1). In the late 1990s, three prospective RCT demonstrated that PMRT improved not only loco-regional control but also overall survival of patients with locally advanced breast cancer (3–6). Recent meta-analysis demonstrated that PMRT with an optimal dose and optimal radiotherapy target volume was significantly associated with improved survival for up to 10 years (7). The adequate radiotherapy technique of PMRT should be established to provide the effectiveness of PMRT without increases in lethal toxicity. The recent development of three-dimensional radiotherapy planning and quality assurance of radiotherapy technique has facilitated the reduction of severe radiation-induced toxicity. In 2001, the American Society of Clinical Oncology (ASCO) proposed the clinical guidelines for PMRT to improve the level of clinical practice (8).

The Patterns of Care Study in the United States (USPCS) sponsored by the American College of Radiology has made significant contributions to improvements in the care of patients with breast cancer and with other types of cancer (9,10). The Japanese Patterns of Care Study (JPCS) Working

For reprints and all correspondence: Naoto Shikama, Department of Radiology, Shinshu University School of Medicine, Matsumoto, Japan, 3-1-1 Asahi Matsumoto, 390-8621 Japan.
E-mail: shikama@hsp.md.shinshu-u.ac.jp

Group collaborated with USPCS to evaluate each radiotherapy practice pattern and improved the research method (11–13). We conducted two national surveys to evaluate the clinical practice of radiotherapy in Japan. The first goal of this study was to evaluate whether PCS surveys fulfill the role of monitoring changes in practice patterns in Japan after three prospective randomized trials, which demonstrated the efficacy of PMRT in the late 1990s (3,5,6). In addition, the second goal of this study was to clarify whether the radiotherapy technique has been improved sufficiently to provide effectiveness of PMRT.

METHODS

We developed a data format system, which we installed on portable computers. The extramural audits of facilities were conducted by the JPCS Working Group. The audits were performed by member physicians of the working group. The audits reviewed the patients' clinical records and input the data into the portable computer on-site. The method of data collection and the JPCS data format have been reported in detail previously (14).

In 1995, according to the Japanese facility master list, a total of 556 facilities nationwide were stratified into four classifications according to the category of facility type and the number of patients, and 79 facilities were sampled at random. The first survey (JPCS-1) was carried out during 1998-2000, and collected data of 1124 patients with breast cancer treated with radiotherapy between 1995 and 1997 using two-stage cluster sampling of facilities and patients (15). In 1999, a total of 641 facilities nationwide were stratified using the same method, and 76 facilities were sampled at random. The second survey (JPCS-2) was carried out in 2001–2003, and involved 827 patients who were treated between 1999 and 2001. We could not keep the same number of facilities in the two surveys because of difficulties in gaining approval for an extramural audit from the institutional review board (14). The eligibility criteria for these surveys were as follows: (1) absence of distant metastases, (2) no bilateral lesions, (3) females, (4) no gross multiple tumors, (5) no diffuse-micro-calcification on pretreatment mammography, (6) absence of prior or concurrent malignancies, (7) absence of prior history of radiotherapy for beast cancer and (8) absence of collagen vascular disease other than rheumatoid arthritis. These eligibility criteria for the patients who received breast conservative therapy were the same as those for patients who underwent PMRT. The study office sampled the patients at random from the patient list regardless of the treatment procedures, including breast conservative therapy and PMRT.

The clinical and pathological stages were classified according to the Fifth Classification of the International Union against Cancer (UICC) (16). Academic facilities were defined as university hospitals or cancer centers and non-academic facilities were defined as other hospitals. Differences in proportion were evaluated by chi-squared test.

RESULTS

JPCS-1 included 866 patients treated with breast conservative therapy and 258 patients treated with mastectomy and PMRT. JPCS-2 included 746 patients treated with breast conservative therapy and 81 patients treated with mastectomy followed by PMRT. The patient characteristics are shown in Table 1. The proportion of patients who received PMRT among those who received postoperative radiotherapy decreased from 22.9% to 9.7% ($P < 0.001$). Among the patients who received PMRT, the proportions of those with adverse risk factors, including four or more axillary positive nodes and/or advanced primary disease (pT3-4), were 57% in JPCS-1 and 72% in JPCS-2 ($P = 0.039$).

The radiotherapy target volume included the chest wall in 31% and in 63% of the patients in JPCS-1 and in JPCS-2, respectively ($P < 0.001$). The radiotherapy target volume included the regional lymph node area, such as the supraclavicular fossa and/or internal mammary lymph nodes in 87% of the patients in JPCS-1 and in 79% of those in JPCS-2 ($P = 0.083$). The radiotherapy target volume included both chest wall and regional lymph node area in 18% of the patients in JPCS-1 and 44% of those in JPCS-2 ($P < 0.001$) (Fig. 1). The majority of the patients in JPCS-1 received irradiation of the regional lymph node area alone. In the academic facilities, the proportions of patients who received both chest wall irradiation and regional lymph node irradiation were 28% of the patients in JPCS-1 and 58% of those in JPCS-2 ($P = 0.001$). In the non-academic facilities, the proportions of patients receiving both treatments were 10% in JPCS-1 and 36% in JPCS-2 ($P < 0.001$).

The dose distribution at the iso-center plane was calculated in only 42% of the patients both in JPCS-1 and in JPCS-2 ($P = 0.467$). In the academic facilities, the dose distribution was calculated in only 46% of the patients in JPCS-1 and 52% of those in JPCS-2 ($P = 0.120$). In the non-academic facilities, the dose distribution was calculated in only 39% and in 36% of the patients in both surveys, respectively ($P = 0.894$). Among all facilities, the multiple-plane dose distribution was calculated in 4% of the patients in JPCS-1 and 15% of those in JPCS-2 ($P < 0.001$).

The immobilization cast was used in 14 and in 35% of the patients in JPCS-1 and in JPCS-2, respectively ($P < 0.001$). In the academic facilities, the immobilization cast was used in 21% of the patients in JPCS-1 and 58% of those in JPCS-2 ($P < 0.001$). In the non-academic facilities, the immobilization cast was used in 9% of the patients in JPCS-1 and 20% of those in JPCS-2 ($P = 0.018$).

No marked differences were found between the two surveys regarding the daily fraction size, total irradiation dose or photon beam energy (Table 2).

DISCUSSION

The effectiveness and the safety of breast conservative therapy have been confirmed by many randomized trials and pooled-

Table 1. Patient characteristics in two surveys

	JPCS-1 (95–97) (n = 258)	JPCS-2 (99–01) (n = 81)	P-value
Age (y)	53.6 ± 11.5	56.5 ± 10.7	0.482
Menstrual status			0.063
Pre-	86/258 (33.3)	19/81 (23.4%)	
Peri-	17/258 (6.6)	2/81 (2.5)	
Post-	106/258 (41.1)	46/81 (56.8)	
Unknown/missing	49/258 (19.0)	14/81 (17.3)	
Pathologically T stage			0.548
pTis	0/258 (0.0)	0/81 (0.0)	
pT0	1/258 (0.4)	0/81 (0.0)	
pT1	43/258 (16.7)	13/81 (16.1)	
pT2	116/258 (44.9)	33/81 (40.8)	
pT3	45/258 (17.4)	13/81 (16.0)	
pT4	27/258 (10.5)	15/81 (18.5)	
Unknown/missing	26/258 (10.1)	7/81 (8.6)	
Number of pathologically positive axillary lymph nodes			0.010
0	48/258 (18.6)	10/81 (12.3)	
1–3	51/258 (19.8)	19/81 (23.5)	
⩾4	119/258 (46.1)	49/81 (60.5)	
Unknown/missing	40/258 (15.5)	3/81 (3.7)	
Final microscopic margin			<0.001
Positive	11/258 (4.3)	17/81 (21.0)	
Close (⩽2 mm)	10/258 (3.9)	2/81 (2.5)	
Close (2–5 mm)	0/258 (0.0)	1/81 (1.2)	
Close (>5 mm)	0/258 (0.0)	0/81 (0.0)	
Negative	183/258 (70.9)	51/81 (63.0)	
Unknown/missing	54/258 (20.9)	10/81 (12.3)	
Estrogen receptor status			0.012
Not done	35/258 (13.6)	7/81 (8.6)	
Positive	61/258 (23.6)	28/81 (34.6)	
Negative	57/258 (22.1)	26/81 (32.1)	
Unknown/missing	105/258 (40.7)	20/81 (24.7)	
Progesterone receptor status			<0.001
Not done	39/258 (15.1)	7/81 (8.6)	
Positive	48/258 (18.6)	23/81 (28.4)	
Negative	50/258 (19.4)	29/81 (35.8)	
Unknown/missing	121/258 (46.9)	22/81 (27.2)	

JPCS, Japanese Patterns of Care Study.

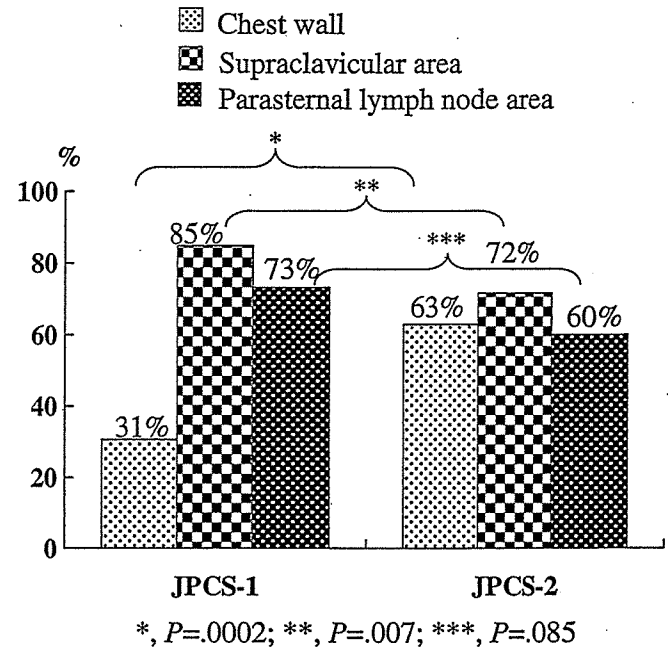

Figure 1. The radiotherapy target volume in patients who received PMRT. The majority of patients in the first survey received irradiation of the regional lymph node area alone. In the second survey, the radiotherapy target volume including the chest wall and regional lymph nodes was applied more frequently. JPCS, Japanese Patterns of Care Study

analyses (17–20). For the last two decades, breast conservative therapy has become more frequently performed in Japan. The national survey conducted by the Japanese Breast Cancer Society indicated that ~40% of patients with breast cancer received breast conservative therapy in 2000, and that nowadays more than half of the patients receive such treatment (21). However, three prospective randomized trials indicated that PMRT improved the overall survival of pre-menopausal and post-menopausal patients with locally advanced breast cancer who had pathologically four or more axillary positive nodes, and that PMRT has been used widely in the United States and in the other Western countries (2–5). Fowble reviewed a large number of reports regarding chest wall recurrence after mastectomy, and reported that 8–36% of patients with four or more pathologically positive nodes underwent treatment with mastectomy and adjuvant systemic chemotherapy (2). However, in Japan PMRT has been used infrequently in patients with adverse risk factors, because many Japanese surgeons consider that chest wall recurrence is infrequent after mastectomy and systemic therapy alone (22). However, the evidence-based guidelines for clinical practice conducted by the Japanese Breast Cancer Society recommended that PMRT should be applied in patients with pathologically four or more axillary positive nodes. These clinical guidelines may have affected the increment in a number of patients receiving PMRT in Japan. The dissemination of high-quality evidence that does not result in the progress of practical techniques would expose patients to severe adverse effects. We should monitor clinical practice to evaluate whether appropriate radiotherapy for PMRT is being performed.

PMRT has been recommended for patients with four or more pathologically proven axillary positive nodes and/or advanced primary disease (8). The clinical benefit of PMRT for patients without adverse risk factors is controversial (23,24). Smith

Table 2. Radiotherapy technique in two surveys

	JPCS-1‡ (n = 258)	JPCS-2 (n = 81)	P-value
Total radiation dose (Gy) (median, range)	49 (10–60)	49 (18–60)	0.738
Fraction size (Gy) (median ± standard deviation)	2.0 ± 0.2	2.0 ± 0.1	0.490
Beam quality of chest wall irradiation*			<0.001
Photon (≤6 MV) (%)	59/79 (74.7)	26/51 (51.0)	
Photon (>6 MV) (%)	6/79 (7.6)	2/51 (3.9)	
Electron (%)	13/79 (16.5)	23/51 (45.1)	
Mixed beam (^{60}Co and X-ray 15 MV) (%)	1/79 (1.2)	0/51 (0.0)	
Wedge filter (yes)† (%)	11/66 (16.7)	11/28 (39.3)	0.001
Boost (yes) (%)	7/258 (2.7)	5/81 (6.2)	0.141

*Calculations were performed only for patients who received chest wall irradiation.
†Calculations were performed only for patients who received chest wall irradiation using photon beam.
‡JPCS, Japanese Patterns of Care Study.

et al. (23) reported that PMRT provided clinical benefits for patients with T1-2 disease and positive axillary nodes. However, some other investigators argued that the role of PMRT had not been defined for patients with T1-2 disease and positive axillary nodes (25). Hence further studies should be performed to establish the indications for PMRT. Our surveys showed that among patients with breast cancer who received postoperative radiotherapy, the proportion of PMRT decreased from 22.9% in JPCS-1 to 9.7% in JPCS-2. This observation does not imply a decrease in the absolute number of patients who received PMRT in Japan, but rather suggests an increment in the number of patients who received breast conservative therapy. The proportions of patients with adverse risk factors, including four or more pathologically proven axillary positive nodes and/or advanced T stage, increased from 57 to 72% between the two studies. The eligibility for PMRT may be influenced by the outcome of the prospective randomized trials in the late 1990s, and PMRT came to be avoided for patients with low risk factors (3–5).

A recent meta-analysis demonstrated that PMRT with an optimal radiation dose ranging from 40 to 60 Gy in 2 Gy fractions, and an appropriate target volume, including chest wall and regional lymph node area, was associated with a statistically significant 6.4% increase in absolute survival (7). However, an inappropriate PMRT technique with an inadequate or excessive dose of radiotherapy or an inappropriate target volume failed to show clinical benefit. Our two surveys demonstrated some problems in radiotherapy techniques for PMRT. In the first survey, the majority of patients received regional lymph node irradiation alone, which was known as the hockey-stick technique. In the second survey, the radiotherapy target volume more frequently included the chest wall and regional lymph nodes. Multiple radiation fields covering anatomically complex sites require a high-quality radiotherapy technique, including three-dimensional radiation planning and quality assurance to avoid severe toxicities. The dose distribution is essential to determine the administration of wedge filter and to evaluate the irradiated lung and heart volume. In the United States, dose distribution in the iso-center plane was calculated in ~95% of patients (11). However, in our survey the dose distribution in the iso-center plane was calculated only in 40% patients, and the multiple-plane dose distribution was calculated only in 15% patients. No improvement of quality assurance was found either in the academic or in the non-academic facilities. Although the immobilization cast is an important item to reproduce the irradiation field in daily treatment, it was used in less than half of the patients in our surveys.

The main limitation of our surveys was the eligibility criteria used. The aim of our surveys was to clarify the clinical procedures applied in patients with breast cancer who received postoperative radiotherapy. The eligibility criteria for our surveys were set up to collect data for patients who received postoperative radiotherapy, including breast conservative therapy and PMRT. The population of patients who received breast conservative therapy has been increasing, and the relative size of the population receiving PMRT has decreased. We could not collect data for patients with PMRT to determine the changes in the clinical procedure sufficiently. Our surveys excluded patients with multiple gross tumors and/or diffuse microcalcification on pretreatment mammography, but the survey for PMRT should include these patients to determine the nationwide status of PMRT. In future studies, we should consider the eligibility criteria to determine the changes in the clinical procedure of PMRT.

Donabedian emphasized three components of quality of care: structure, process and outcome (15). Good processes of care help to achieve good clinical outcome for the patients, while poor processes are associated with insufficient outcome. However, we did not evaluate the correlation between poor radiotherapy technique and clinical outcome, including survival and adverse effects, because of the short follow-up time and small sample size. A survey with small sample size cannot clarify the interactions between poor processes and insufficient clinical outcome. "No difference" in the survey with small sample size does not necessarily mean the "same." Even if the poor process is not significantly associated with poor clinical outcome, this hasty interpretation does not justify by any means that a poor radiotherapy technique is acceptable. In addition, repeated analyses of the correlation between each clinical parameter and the outcome may lead to misunderstanding of the observed phenomenon because of multiplicity. A process survey including large sample size may not be efficient and economical. In contrast, a process survey using a relatively small sample size is convenient and useful to compare the observed clinical practice with the optimal radiotherapy technique that is considered appropriate according to the textbooks or previously reported evidence. However, the definition of optimized sample size for a survey is controversial.

A recent meta-analysis demonstrated that use of an inappropriate radiotherapy technique that applied excessive radiation dose and/or inappropriate target volume was associated with an increment in non-breast cancer mortality (7). In Japan, the infrastructure of radiation oncology units has been insufficient to provide safe medical service in both academic and non-academic facilities (13). The radiation oncology staff, including radiation oncologists, technologists, dosimetrists and oncology nurses, should be enriched to provide good clinical practice for the patients. An efficient monitoring system using optimized surveys combining the structure survey and process survey should be established for good clinical practice.

Acknowledgments

This study was presented in part at the 46th Annual Meeting of the American Society for Therapeutic Radiology and Oncology, Salt Lake City, UT, in October 2004.

This study was supported by a Grant-in-Aid for Cancer Research (14–6,16–12) from the Ministry of Health, Labor and Welfare of Japan. We thank all radiation oncologists who participated in this study whose efforts in providing information made these surveys possible.

References

1. Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol* 1994;12:447–53.
2. Fowble B. Postmastectomy radiation: then and now. Oncology (Williston Park) 1997;11:213–234, 239; discussion 239–240, 243.
3. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999;353:1641–8.
4. Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J Natl Cancer Inst* 2005;97:116–26.
5. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997;337:949–55.
6. Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli KS, Basco VE, Wilson KS, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997;337:956–62.
7. Gebski V, Lagleva M, Keech A, Simes J, Langlands. Survival effects of postmastectomy adjuvant radiation therapy using biologically equivalent doses: a clinical perspective. *J Natl Cancer Inst* 2006;98: 26–38.
8. Recht A, Edge SB, Solin LJ, Robinson DS, Estabrook A, Fine RE, et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001;19:1539–69.
9. Owen JB, Coia LR. The changing structure of radiation oncology: implications for the Era of Managed Care. *Semin Radiat Oncol* 1997;7:108–13.
10. Coia LR, Hanks GE. Quality Assessment in the USA: how the patterns of care study has made a difference. *Semin Radiat Oncol* 1997;7:146–56.
11. Shikama N, Nishikawa A, Mitsumori M, Hiraoka T, Yamamoto T, Teshima, T. Patterns of care study: comparison of process of post-mastectomy radiotherapy (PMRT) in Japan and the USA. *Jpn J Clin Oncol* 2003;33:518–21.
12. Shikama N, Sasaki S, Mitsumori M, Hiraoka M, Yamauchi C, Yamamoto T, et al. Patterns of care study in Japan: analysis of patients subjected to mastectomy followed by radiotherapy. *J Clin Oncol* 2003;33:456–62.
13. Teshima T, Owen JB, Hanks GE, Sato S, Tsunemoto H, Inoue T. A comparison of the structure of radiation oncology in the United States and Japan. *Int J Radiat Oncol Biol Phys* 1996;34:235–42.
14. Mitsumori M, Hiraoka M, Negoro Y, Yamauchi C, Shikama N, Sasaki S, et al. The patterns of care study for breast-conserving therapy in Japan: analysis of process survey from 1995 to 1997. *Int J Radiat Oncol Biol Phys* 2005;62:1048–54.
15. Owen JB, Sedransk J, Pajak TF. National averages for process and outcome in radiation oncology: methodology of the patterns of care study. *Semin Radiat Oncol* 1997;7:101–107.
16. Sobin L, Wittekind C. TNM Classification of Malignant Tumours. UICC International Union Against Cancer. New York: Wiley-Liss 1995.
17. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;347:1233–41.
18. Blichert-Toft M, Rose C, Andersen JA, Overgaard M, Axelsson CK, Andersen KW, et al. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. *J Natl Cancer Inst Monogr* 1992;11:19–25.
19. Veronesi U, Luini A, Galimberti V, Zurrida S. Conservation approaches for the management of stage I/II carcinoma of the breast: Milan Cancer Institute trials. *World J Surg* 1994;18:70–75.
20. Vinh-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. *J Natl Cancer Inst* 2004;96:115–21.
21. Results of questionnaires concerning breast cancer surgery in Japan: an update in 2000. *Breast Cancer* 2002;9:1.
22. Fujio K. President's Speech: Innovations and Research Progress of the Department of Breast Surgery, Cancer Institute Hospital, Tokyo, Japan. *Breast Cancer* 1998;5:326–30.
23. Smith BD, Smith GL, Haffty BG. Postmastectomy radiation and mortality in women with T1-2 node-positive breast cancer. *J Clin Oncol* 2005;23: 1409–19.
24. Truong PT, Olivotto IA, Speers CH, Wai ES, Berthelet E, Kader HA. A positive margin is not always an indication for radiotherapy after mastectomy in early breast cancer. *Int J Radiat Oncol Biol Phys* 2004;58:797–804.
25. Taghian A, Jeong JH, Mamounas E, Anderson S, Bryant J, Deutsch M, et al. Patterns of locoregional failure in patients with operable breast cancer treated by mastectomy and adjuvant chemotherapy with or without tamoxifen and without radiotherapy: results from five National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. *J Clin Oncol* 2004;22:4247–54.

Leukemia & Lymphoma, September 2006; 47(9): 1800–1805

informa
healthcare

ORIGINAL ARTICLE: CLINICAL

Treatment of primary intraocular lymphoma with radiation therapy: A multi-institutional survey in Japan

KOICHI ISOBE[1,2], YASUO EJIMA[1,3], SUNAO TOKUMARU[1,4], NAOTO SHIKAMA[1,5], GEN SUZUKI[1,6], MITSUHIRO TAKEMOTO[1,7], EMIKO TSUCHIDA[1,8], MIWAKO NOMURA[1,9], YUTA SHIBAMOTO[1,10], & NAOFUMI HAYABUCHI[1,6]

[1]*Japanese Society for Therapeutic Radiology and Oncology Lymphoma Study Group, Japan,* [2]*Department of Radiology, Chiba University Hospital, Chiba, Japan,* [3]*Division of Radiology, Kobe University Graduate School of Medicine, Kobe, Japan,* [4]*Department of Radiology, Saga Medical School, Saga, Japan,* [5]*Department of Radiology, Shinshu University, School of Medicine, Matsumoto, Japan,* [6]*Department of Radiology, Kurume University, Kurume, Japan,* [7]*Department of Radiology, Okayama University Hospital, Okayama, Japan,* [8]*Division of Radiation Oncology, Department of Molecular Genetics, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan,* [9]*Department of Radiology, Mie University Hospital, Tsu, Japan, and* [10]*Department of Radiology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan*

(Received 11 November 2005; revised 31 January 2006; accepted 13 February 2006)

Abstract

This study evaluated the clinical features and treatment outcome of 15 patients with primary intraocular lymphoma. There were nine females, with a median age of 68 years. Thirteen patients presented with bilateral lesions and median time from the onset of symptoms to diagnosis was 12 months. All but one showed the B-cell phenotype. All patients received radiation therapy (RT) with a median of 41 Gy and 10 were administered chemotherapy as well. Three patients were treated with high-dose methotrexate and nine received prophylactic cranial irradiation (PCI) with a median of 30.6 Gy. Thirteen patients obtained a complete remission. The 2-year overall and disease free survival were 74% and 58%, respectively. Although only one patient experienced local recurrence, PCI did not prevent intracranial recurrence. One patient developed a grade 3 cognitive disturbance. It was concluded that ocular RT was effective to control primary lesions. However, some modifications are indispensable to improve outcomes.

Keywords: *Primary intraocular lymphoma, PIOL, radiation therapy, chemotherapy, PCNSL*

Introduction

Primary intraocular lymphoma (PIOL), formally known as ocular reticulum cell sarcoma, is an uncommon clinical manifestation of non-Hodgkin's lymphoma, which arises in the retina or the vitreous humor [1–7]. It usually develops in patients in the fifth and sixth decade of life as a chronic, relapsing and steroid-resistant uveitis and vitritis [3,8–10]. Patients often complain of blurred vision, a painless loss of vision and floaters. According to the previous reports, it took several years from the onset of symptoms to establish a diagnosis of PIOL in some studies [8,9,11–13]. Therefore, physicians should be clinically suspicious of PIOL when uveitis is resistant to treatment with steroids. Cytological or pathological studies of a vitreous biopsy are the most common procedure to confirm a diagnosis of PIOL. However, it is sometimes difficult to make a diagnosis of PIOL, because (1) the cellular content of vitreous samples may be sparse, (2) the number of reactive cells present in the specimen and (3) lymphoma cells are fragile [2–8,11]. In such cases, immunohistochemical studies, flow cytometry and polymerase chain reaction of the rearranged immunoglobulin gene are helpful [14].

Correspondence: Koichi Isobe, MD, Department of Radiology, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba 260-8677, Japan. Tel: +81-43-226-2100. Fax: +81-43-226-2101. E-mail: isobeko@ho.chiba-u.ac.jp

ISSN 1042-8194 print/ISSN 1029-2403 online
DOI: 10.1080/10428190600632881

Intraocular lymphoma may occur independently, prior or subsequent to a primary central nervous system lymphoma (PCNSL). Primary intraocular lymphoma develops intracranial involvement in 60–85% of patients during their course [2–8,11]. On the contrary, recent estimates suggest that 15–25% of patients with PCNSL have ocular disease [3,9]. This previously rare disease has become more frequent along with the increase in the incidence of PCNSL; however, the clinical features and optimal treatment for PIOL have to be clarified.

Until now, many case series and review articles have been published in the literature, but most of these reports contained both PIOL and PCNSL or ocular involvement of systemic lymphoma, which are distinct from PIOL [1–9,11–35]. Thus, we have compiled a multi-institutional retrospective analysis to clarify the clinical features and optimal management of PIOL.

Materials and methods

A survey of patients with PIOL was carried out in May 2005. Between January 1990 and February 2005, eight of 17 institutions of the Japanese Society for Therapeutic Radiology and Oncology Lymphoma Study Group responded on a questionnaire that there were eligible patients. Eligible patients had previously untreated, histologically or cytologically proven non-Hodgkin's lymphoma demonstrating intraocular involvement. Those who had CNS involvement or systemic disease were excluded from this study. Histopathological diagnosis was based upon REAL (revised European–American classification of lymphoid neoplasms) or WHO (World Health Organization) classification [36,37]. However, cytological examination hampered the confirmation of sub-type of lymphoma in some patients. Immunohistochemical study using antibodies against CD20, CD43, CD45RO and CD79a were performed.

In principle, the staging procedures included physical examination, complete blood cell count, liver and renal function tests, ophthalmological examinations with a slit lamp, gallium scintigraphy, computed tomography (CT) of the neck, chest, abdomen and pelvis and bone marrow aspiration or biopsy. An examination of cerebrospinal fluid was undertaken to rule out disseminations. Brain magnetic resonance imaging (MRI) and/or CT was mandatory to exclude ocular involvement of PCNSL.

Since this study was a retrospective multi-institutional survey, treatment strategies were dependent upon the discretions of the treating physician. However, all patients received radiation therapy (RT) using photon beams with two lateral opposed fields. Response to the treatment was determined by ophthalmological findings and imaging studies including brain CT and/or MRI and CT scan from neck to pelvis, according to the standard criteria proposed by Cheson et al. [38]. Overall survival (OAS) and disease-free survival (DFS) were calculated using the method of Kaplan and Meier [39]. The median follow-up was 19.2 months (range 6.9–73 months). Late sequelae were graded according to the National Cancer Institute common toxicity criteria version 2.0.

Results

Patient characteristics

A survey identified 15 patients with PIOL from eight institutions. The median age was 68 years (range 38–84 years) and the male-to-female ratio was 1:1.5. Detailed patient characteristics are shown in Table I. All but two patients presented with bilateral ocular lesions. No patients showed intracranial involvement or systemic diseases as it was an exclusion criteria in this study. Eleven patients had performance status 0–1 (based on the Eastern Cooperative Oncology Group). Median time from the onset of symptoms and diagnosis of PIOL was 12 months (range 5–24 months).

Six patients were diagnosed by histopathological examination and eight cytologically. Two patients required vitrectomy for diagnosis and four patients were diagnosed by vitreal biopsy. In the remaining patient, cytological examination was highly suggestive of lymphoma with monoclonal immunoglobulin heavy chain gene rearrangement. The pathological

Table I. Patient characteristics.

Case no	Age	Sex	Duration of symptom (Mo)	Laterality	Pathology
1	77	F	21	Bilateral	DLBCL
2	67	F	7	Bilateral	DLBCL
3	68	M	20	Bilateral	DLBCL
4	73	M	8	Right	B-NHL
5	56	F	12	Bilateral	DLBCL
6	73	F	12	Left	DLBCL
7	51	F	7	Bilateral	DLBCL
8	38	M	13	Bilateral	B-NHL
9	69	F	24	Bilateral	DLBCL
10	73	F	20	Bilateral	T-NHL
11	54	M	10	Bilateral	B-NHL
12	84	F	5	Bilateral	B-NHL
13	69	M	6	Bilateral	B-NHL
14	48	F	12	Bilateral	B-NHL
15	67	M	11	Bilateral	B-NHL

F; female, M; male, Mo; months, DLBCL; diffuse large B-cell lymphoma, B-NHL; B-cell non-Hodgkin's lymphoma, further unclassified, T-NHL; T-cell non-Hodgkin's lymphoma, further unclassified.

diagnosis was based upon an institutional pathology report without central review. Histopathological diagnosis was diffuse large B-cell lymphoma (DLBCL) in seven patients and B-cell non-Hodgkin's lymphoma (NHL), further unclassified, in seven. The remaining patient demonstrated T-cell receptor gene rearrangement and, as diagnosed as T-cell NHL, further unclassified. In laboratory tests, five patients demonstrated a LDH (lactate dehydrogenase) increment and the level of sIL-2R (soluble interleukin-2 receptor) was elevated in two of 12 patients.

Treatment and outcome

The treatment characteristics are shown in Table II. Eight patients received a combination of chemotherapy and RT, while five were treated solely by RT. The remaining two experienced disease progression to the central nervous system (CNS) during chemotherapy and received salvage RT thereafter. Of the 10 patients who received chemotherapy, only three were treated with high-dose methotrexate (MTX). Four patients received doxorubicin-containing chemotherapy and the remaining three received low-dose MTX. The chemotherapy regimen was dependent upon the discretions of the treating physician. All patients received RT using photon beams with two lateral opposed fields. The total dose of RT ranged from 30–46 Gy, with a median of 41 Gy. Nine patients, including two patients with unilateral disease at presentation, received prophylactic cranial irradiation (PCI), ranging in dose from 24–32 Gy, with a median of 30.6 Gy.

Table II. Treatment and outcome.

Case no	Treatment	Relapse	Outcome	Survival (Mo)
1	Chemo → RT	Brain	DOD	6.9
2	RT → Chemo	Brain	DOD	19.7
3	RT	Brain	DOD	41.3
4	Chemo → RT		NED	25.2
5	RT → Chemo		NED	19
6	RT		NED	27.6
7	Chemo	Brain	DOD	6.9
8	Chemo → RT	Right eye	AWD	73
9	Chemo → RT		NED	39
10	RT		NED	10.8
11	Chemo → RT		NED	27.9
12	RT		NED	18
13	RT	Testis	AWD	19.2
14	Chemo	Brain	AWD	11.4
15	Chemo → RT		NED	11.2

Chemo; chemotherapy, RT; radiation therapy, Mo; months, DOD; dead of disease, NED; no evidence of disease, AWD; alive with disease.

At the time of evaluation, 13 patients achieved complete remission (CR) or CR/unconfirmed (CRu), which resulted in an 87% CR rate (95% confidence interval [CI], 67–100%). Figure 1 shows survival curves in this series. The median OAS was 41 months. The 1- and 2-year OAS were 87% (95% CI, 70–100%) and 74% (95% CI, 47–100%), respectively. The corresponding figures with respect to DFS were 67% (95% CI, 43–91%) and 58% (95% CI, 33–84%), respectively, with a median of 34 months. There were seven patients who experienced recurrences or progression. The radiological studies demonstrated brain involvement in five patients and physical examination including ophthalmological study showed local recurrence and testicular involvement in one patient each. Two of nine patients who received PCI experienced CNS recurrence, while one in four who did not receive it developed brain involvement. ($P=0.50$, Fisher's exact test) Those who received high-dose MTX did not experience CNS recurrence. At the last contact, four patients had died of their disease.

Treatment sequelae

With regard to late adverse events, a 73 year old female developed a grade 3 cognitive disturbance 27 months after RT. She received 32 Gy of PCI without chemotherapy. She also developed turbidity of the vitreous body 2 years after RT. One patient developed Grade 2 cataract and another four assessable patients who survived more than 1 year experienced no late adverse events, including retinopathy, optic neuropathy, cataract or brain injury.

Discussion

Primary intraocular lymphoma is designated as an extra-nodal non-Hodgkin's lymphoma of the eye

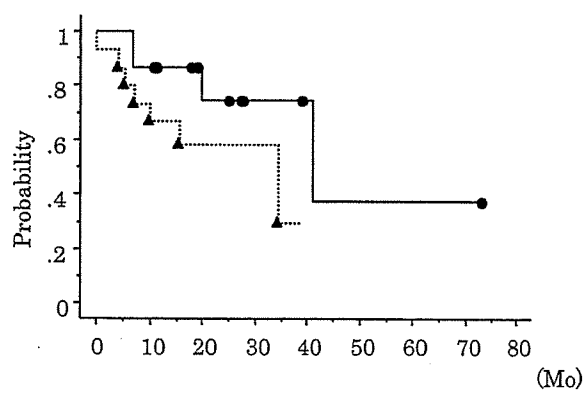

Figure 1. The curves for overall survival (solid line) and disease-free survival (dashed line).

without evidence of systemic or CNS disease. It was first described in 1951, and was originally named 'ocular reticulum cell sarcoma' [1]. Until now, many case series and review articles have been published in the literature, but most of these reports contained not only a small number of patients with PIOL, but also a large majority of PCNSL [1–28]. Thus, the findings from these reports were largely dependent upon PCNSL. Furthermore, some articles reported the ocular involvement of systemic lymphoma, which is distinct from PIOL [29–35]. These circumstances have obscured our understanding with regard to the clinical features and optimal management of PIOL. Thus, we summarize the patient characteristics in Table III. The median age of onset was 50s to 60s with some female preponderance. These findings are well in accordance with our current study.

Many researchers have concurred that the diagnostic difficulty and delay from presentation is one of the major problems in the management of PIOL [8,9,11–13]. The time from onset of ocular symptoms to diagnosis ranged from 1–48 months and many researchers argue that early diagnosis would lead to an improvement in outcome [8–10,12,13]. The diagnosis of PIOL was based upon cytological or histological examination of samples from the vitreous body, but these specimens are fragile and difficult to handle. Thus, in addition to routine cytological or histopathological examinations, some molecular studies, including polymerase chain reaction of the rearranged immunoglobulin gene, and flow cytometry would be helpful [14]. Although it was not diagnostic, Cassoux et al. [12] also recommended the measurement of the IL-10 to IL-6 ratio in the vitreous fluid. The utility of other markers such as LDH, sIL-2R and beta 2 microglobulin has not yet been evaluated.

Table III. Summary of literatures. Patient characteristics.

Ref	*n*	Age (median)	Male/ female	Time to diagnosis (median)
[1]	1	27	1/0	5
[9]	12	32–67 (58)	4/8	NR
[10]	6	46–74 (56)	4/2	1–48 (17)
[13]	4	61–70 (70)	3/1	NR
[15]	2	65–81	1/1	26–35 (30)
[16]	2	66–68	1/1	NR
[17]	1	56	1/0	48
[18]	1	37	0/1	6
[19]	1	37	0/1	8
[20]	5	62–72 (66)	1/4	NR
[21]	13	27–77 (66)	6/7	NR
[22]	1	62	1/0	NR
[23]	1	57	0/1	NR
[24]	4	46–61 (51)	2/2	NR
[25]	4	31–71 (50)	NR	NR
[27]	1	83	0/1	NR
[28]	8	NR	4/4	NR
Current	15	34–84 (68)	6/9	5–24 (12)

Ref; references, NR; not reported.

The most important issue that must be resolved has been the optimal treatment for PIOL. We summarize literatures concerning treatment, outcome and late sequelae in Table IV. Old series published in 1980s indicated that RT was first choice of treatment. Several reports discussed the optimal radiation doses and treatment portal. Some authors reported beneficial effect of RT with 35–45 Gy exclusively to the ocular lesions, given that CNS disease cannot be found [8,9]. On the other hand, other groups recommend PCI doses up to 45 Gy because the vast majority of patients eventually develop CNS diseases [15,18–22]. We observed only one local recurrence after RT with a median dose of 41 Gy in this series, which suggested that 40 Gy of RT is enough to eradicate PIOL. However, we were not able to demonstrate any decrease in CNS relapse after PCI with a median dose of 30.6 Gy. It is possible to hypothesize that higher doses are necessary to eliminate microscopic CNS disease. However, we have to be aware of the fact that higher dose RT might lead to detrimental late neurological deficits. In fact, an elderly woman developed a grade 3 cognitive disturbance after 32 Gy of PCI in this series. We did not experience CNS recurrence after high-dose MTX; thus, we advocate a strategy that combines high-dose MTX and PCI with doses of 30 Gy to control microscopic CNS disease.

In the place of RT, recent publications have recommended high-dose intravenous MTX following encouraging results in the treatment of PCNSL [3–7,12,23,25]. In fact, de Smet et al. [40] demonstrated that sustained cytotoxic MTX levels in the aqueous humor were achievable after 8.4 g/m^2 of systemic MTX administration. However, several groups have reported that ocular lesions were less responsive than those of CNS disease because vitreous MTX concentration was usually lower than that of the anterior chamber [5,25]. To overcome this problem, Fishburne et al. [41] used an intravitreal MTX injection. They reported that four patients with recurrent PIOL or PCNSL were successfully salvaged by intravitreal MTX injection without serious ocular toxic reactions. Intrathecal injection is another route for MTX administration; however, its efficacy remains to be confirmed [26].

Baumann et al. [35] treated a patient with ocular involvement from a primary breast lymphoma with high-dose cytosine arabinoside (Ara-C). They demonstrated that systemic administration of 3 g/m^2 of Ara-C also gained therapeutic levels in the anterior chamber and the vitreous humor similar to that of

Table IV. Summary of literatures. Treatment, outcome and late sequelae.

Ref	Treatment	CNS (%)	OAS (Mo)	Recommendations	Late Sequelae (%)
[1]	RT	NR	11	NR	NR
[9]	CS or RT	83	11–87	NR	NR
[11]	RT	0	24–109	NR	NR
[12]	Chemo or RT	48	NR	MTX	NR
[13]	RT + Chemo	75	14–103	Chemo	Cataract (50), Dry eye (40), Retinopathy (20), Keratopathy (20)
[15]	RT	50	9–39	RT (PCI)	Retinal atrophy (50)
[19]	RT + Chemo	0	48	Chemo + RT (PCI)	NR
[20]	Ara-C + RT	NR	6–42	Ara-C + RT (PCI)	NR
[21]	RT or Chemo	27	3–90	Ara-C + RT (PCI)	NR
[22]	Ara-C + RT	0	33	Ara-C + RT (PCI)	NR
[23]	MTX + Ara-C	0	NR	Chemo	Neurocognitive dysfunction (38)
[24]	Transplantation	0	46–84	Chemo	Cognitive dysfunction (32)
[25]	MTX	NR	8–85	MTX	No neurotoxicities
[27]	Oral Alkylator	0	8	NR	None
Current	RT + Chemo or RT	33	7–73	MTX + RT	Cognitive disturbance (10), Cataract (20)

Ref; references, CNS; central nervous system recurrence, OAS; overall survival, Mo; months, RT; radiation therapy, NR; not reported, CS: corticosteroid, Chemo; chemotherapy, MTX; methotrexate, Ara-C; cytosine arabinoside, PCI; prophylactic cranial irradiation.

high-dose MTX. Several groups have also demonstrated the efficacy of high-dose Ara-C, which suggested that it might be an alternative to high-dose MTX [20–22]. Jahnke et al. [27] showed that an oral alkylating cytostatic agent, trofosfamide, is effective with a favorable toxicity profile. They concluded that trofosfamide may offer an alternative treatment option for PIOL.

Radiation therapy rapidly improves patients' symptoms, but does cause late sequelae including cataracts, dry eye, optic neuropathy and retinopathy. Hoffman et al. [13] reported that 50% of patients developed cataracts. They also stated that 20% experienced retinopathy and 10% developed optic nerve atrophy. Other researchers have reported that half of the patients developed retinal atrophy after RT [15]. We also observed cataracts in 20% of patients. It has also been well known that detrimental neurocognitive dysfunction would develop after whole-brain irradiation. In fact, we observed a grade 3 cognitive disturbance in this series. In addition to whole-brain irradiation, chemotherapy, especially high-dose MTX, for elderly patients has also caused leukoencephalopathy. Two groups reported that about one-third of patients developed cognitive dysfunction after high-dose MTX or high-dose chemotherapy with stem cell support [23,24]. Thus, Valluri et al. [22] recommended that a combination of chemotherapy and lower dose RT may reduce radiation induced ocular morbidity.

In conclusion, the prognosis of intraocular lymphoma still remains poor, but it is impossible to establish optimal therapeutic strategies in a randomized trial due to its rarity. Systemic chemotherapy alone may not be sufficient to control PIOL and ocular RT appears still indispensable. The high incidence of CNS recurrence and the late sequelae such as cataracts, retinopathy and neurocognitive dysfunction were also problematic in the management of PIOL. From the literature review and our current experience, we recommend delivering 40 Gy of ocular RT, PCI with doses 30 Gy and high-dose MTX to control PIOL.

References

1. Cooper EL, Riker JL. Malignant lymphoma of the uveal tract. Am J Ophthalmol 1951;34:1153–1158.
2. Buettner H, Bolling JP. Intravitreal large cell lymphoma. Mayo Clin Proc 1993;68:1011–1015.
3. Buggage RR, Chan CC, Nussenblatt RB. Ocular manifestations of central nervous system lymphoma. Curr Opin Oncol 2001;13:137–142.
4. Chan CC, Buggage RR, Nussenblatt RB. Intraocular lymphoma. Curr Opin Ophthalmol 2002;13:411–418.
5. Hormigo H, DeAngelis LM. Primary ocular lymphoma: clinical features, diagnosis, and treatment. Clin Lymph 2003;4:22–29.
6. Coupland SE, Heimann H, Bechrakis NE. Primary intraocular lymphoma: a review of the clinical, histopathological and molecular biological features. Graefe's Arch Clin Exp Ophthalmol 2004;240:901–913.
7. Chan CC, Wallace DJ. Intraocular lymphoma: update on diagnosis and management. Cancer Control 2004;11: 285–295.
8. Freeman LN, Schachat AP, Knox DL, Michels RG, Green WR. Clinical features, laboratory investigations, and survival in ocular reticulum cell sarcoma. Ophthalmology 1987;94:1631–1639.
9. Peterson K, Gordon KB, Heinemann M, DeAngelis LM. The clinical spectrum of ocular lymphoma. Cancer 1993;72: 843–849.

10. Rothova A, Ooijman F, Kerkhoff F, Lelij AV, Lokhorst HM. Uveitis masquerade syndrome. Ophthalmology 2001;108: 386–399.
11. Char DH, Ljung B, Miller T, Phillips T. Primary intraocular lymphoma (ocular reticulum cell sarcoma) diagnosis and management. Ophthalmology 1988;95:625–630.
12. Cassoux N, Merle-Beral H, Leblond V, Bodaghi B, Milea D, Gerber S, et al. Ocular and central nervous system lymphoma: clinical features and diagnosis. Ocul Immunol Inflamm 2000; 8:243–250.
13. Hoffman PM, McKelvie P, Hall AJ, Stawell RJ, Santamaria JD. Intraocular lymphoma: a series of 14 patients with clinicopathological features and treatment outcomes. Eye 2003;17:513–521.
14. Baehring JM, Androudi S, Longtine JJ, Betensky RA, Sklar J, Foster CS, et al. Analysis of clonal immunoglobulin heavy chain rearrangements in ocular lymphoma. Cancer 2005;104: 591–597.
15. Margolis L, Fraser R, Lichter A, Char DH. The role of radiation therapy in the management of ocular reticulum cell sarcoma. Cancer 1980;45:688–692.
16. Simon JW, Friedman AH. Ocular reticulum cell sarcoma. Br J Ophthalmol 1980;64:793–799.
17. Lang GK, Surer JL, Green WR, Finkelstein D, Michels RG, Maumenee AE. Ocular reticulum cell sarcoma. Retina 1985; 5:79–86.
18. Scully RE, Mark EJ, McNeely BU. Case records of the Massachusetts General Hospital: bilateral uveal disorder unresponsive to corticosteroid therapy. N Engl J Med 1985; 313:436–443.
19. Trudeau M, Shepherd FA, Blackstein ME, Gospodarowicz M, Fitzpatrick P, Moffatt P. Intraocular lymphoma: report of three cases and review of the literature. Am J Clin Oncol 1988; 11:126–130.
20. Strauchen JA, Dalton J, Friedman AH. Chemotherapy in the management of intraocular lymphoma. Cancer 1989;63: 1918–1921.
21. Siegel MJ, Dalton J, Friedman AH, Strauchen J, Watson C. Ten-year experience with primary ocular 'reticulum cell sarcoma' (large cell non-Hodgkin's lymphoma). Br J Ophthalmol 1989;73:342–346.
22. Valluri S, Moorthy RS, Khan A, Rao NA. Combination treatment of intraocular lymphoma. Retina 1995;15:125–129.
23. Sandor V, Stark-Vancs V, Pearson D, Nussenblat R, Whitcup SM, Brouwers P, et al. Phase II trial of chemotherapy alone for primary CNS and intraocular lymphoma. J Clin Oncol 1998;16:3000–3006.
24. Soussain C, Suzan F, Hoang-Xuan K, Cassoux N, Levy V, Azar N, et al. Results of intensive chemotherapy followed by hematopoietic stem cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma. J Clin Oncol 2001;19:742–749.
25. Batchelor TT, Kolak G, Ciordia R, Foster CS, Henson JW. High-dose methotrexate for intraocular lymphoma. Clin Cancer Res 2003;9:711–715.
26. Mason JO, Fischer DH. Intrathecal chemotherapy for recurrent central nervous system intraocular lymphoma. Ophthalmol 2003;110:1241–1244.
27. Jahnke K, Bechrakis NE, Coupland SE, Schmittel A, Foerster MH, Fischer L, et al. Treatment of primary intraocular lymphoma with oral trofosfamide: report of two cases and review of the literatures. Graefe's Arch Clin Exp Ophthalmol 2004;242:771–776.
28. Meunier J, Lumbroso-Le Rouic L, Vincent-Salomon A, Dendale R, Asselain B, Arnaud P, et al. Ophthalmologic and intraocular non-Hodgkin's lymphoma: a large single centre study of initial characteristics, natural history, and prognostic factors. Hematol Oncol 2004;22:143–158.
29. Sullivan SF, Dallow RL. Intraocular reticulum cell sarcoma: its dramatic response to systemic chemotherapy and its angiogenic potential. Ann Ophthalmol 1977;9:401–406.
30. Solas HA, Starling J, Harper DG, Cupples HP. Update of ocular reticulum cell sarcoma. Arch Ophthalmol 1981;99: 1048–1052.
31. Michelson JB, Michelson PE, Bordin GM, Chisari FV. Ocular reticulum cell sarcoma. Arch Ophthalmol 1981;99: 1409–1411.
32. Char DH, Margolis L, Newman AB. Ocular reticulum cell sarcoma. Am J Ophthalmol 1981;91:480–483.
33. Rockwood EJ, Zakov N, Bay JW. Combined malignant lymphoma of the eye and CNS (reticulum-cell sarcoma). J Neurosurg 1984;61:369–374.
34. Leff SR, Shields JA, Augsburger JJ, Miller RV, Liberatore B. Unilateral eyelid, conjunctival, and choroidal tumours as initial presentation of diffuse large-cell lymphoma. Br J Ophthalmol 1985;69:861–864.
35. Baumann MA, Ritch PS, Hande KR, Williams GA, Topping TM, Anderson T. Treatment of intraocular lymphoma with high-dose Ara-C. Cancer 1986;57:1273–1275.
36. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JKC, Cleary ML, et al. A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood 1994;84:1361–1392.
37. Jafee ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization classifications of tumors, Pathology and genetics of tumours of haematopoietic and lymphoid tissue. Lyon: IARC Press; 2001.
38. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. J Clin Oncol 1999;17:1244–1253.
39. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.
40. de Smet MD, Stark-Vancs V, Kohler DR, Smith J, Wittes R, Nussenblatt RB. Intraocular levels of methotrexate after intravenous administration. Am J Ophthalmol 1996;121: 442–444.
41. Fishburne BC, Wilson DJ, Rosenbaum JT, Neuwelt EA. Intravitreal methotrexate as an adjunctive treatment of intraocular lymphoma. Arch Ophthalmol 1997;115:1152–1156.