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Role of Radiation Therapy in the Management of Primary Mediastinal Large B-cell Lymphoma (PMLBL)

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Purpose: PMLBL is a rare disease in Japan, and its optimal management and prognosis remain to be examined. A retrospective analysis of combined modality treatment in PMLBL was performed.

Materials and Methods: Three women and four men (mean age, 36 years) were found to have PMLBL. Six patients had stage II disease, and one patient stage III disease. Each patient had a mediastinal tumor over 9 cm in diameter. The numbers of risk factors according to the international prognostic index (IPI) and modified tumor score (mTS) were 2 and 2 or 3, respectively. All patients were treated by doxorubicin-based chemotherapy. Two patients underwent tumor resection. Radiation therapy of 27.3 to 40 Gy (mean, 32 Gy) was delivered, after chemotherapy in six patients, and before chemotherapy in one.

Results: Only one stage IIE patient recurred in the bilateral kidneys and had a fatal outcome. The remaining six patients remain disease-free at follow-up ranging from seven to 126 months. Positive accumulation of gallium scintigraphy after chemotherapy was converted to negative by radiation therapy.

Conclusions: The favorable prognosis of PMLBL was confirmed in this study. Radiation therapy should preferably be delivered to all patients with PMLBL after chemotherapy.

Key words: mediastinal large B-cell lymphoma, radiation therapy, chemotherapy

INTRODUCTION

PMLBL HAS BEEN REPORTED in the western literature to constitute 4-8% of diffuse large B-cell lymphomas of all sites.[1,2] In Japan, the incidence of PMLBL appears to be much lower, because only sporadic case reports have been published.[3-6] The prognostic factors and optimal management of PMLBL remain to be studied. The role of radiation therapy is especially controversial. In our institute, PMLBL has been treated by a combined modality consisting of chemotherapy and radiation therapy. The treatment results of PMLBL in our institute were retrospectively analyzed, and controversial issues were reviewed.

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MATERIALS AND METHODS

From 1991 through 2002, seven patients with a diagnosis of PMLBL were treated by a combined modality of chemotherapy and radiation therapy at the International Medical Center of Japan. All the patients with a diagnosis of diffuse large B-cell lymphoma who were treated at the Center and presented with a predominant lesion in the anterior mediastinum were included in this study.

Pathological diagnosis

For the pathological diagnosis of PMLBL, materials were obtained through thoracotomy in four patients, needle biopsy of chest wall invasion in two, and mediastinoscopy in one. Immunohistochemistry

using CD20 was performed in all patients to confirm the B-cell origin of the tumor, and all were CD20-positive. Sclerosis of varying degrees was present in six patients, and clear cells were recognized in three (Table 1).

Patient characteristics

The patients included three women and four men with a mean age of 36 years (range, 22-50 years). Six patients presented with chest symptoms caused by the tumor. Superior vena cava syndrome was seen in two patients. In one patient, mediastinal tumor was discovered incidentally by chest X-ray at routine check-up. All patients had good performance status.

Physical examinations, differential counts of blood cells, biochemistry including LDH, chest X-ray, chest and abdominopelvic CT scans, and bilateral bone marrow biopsies were routinely performed. Gallium scintigraphy with 3 mCi of gallium citrate was obtained in five patients, and all the tumors showed avid gallium uptake.

The thoracic mediastinal ratio (TMR) of the upright chest X-ray ranged from 0.41 to 0.52, with a mean of 0.46. Maximal transverse diameter of the tumors ranged from 9 to 13 cm, with a mean of 9.6 cm, on CT. Mediastinal tumor volume was calculated on CT under mediastinal display conditions, with areas of the tumor multiplied by the slice thickness of the CT images. Only mediastinal mass and contiguous invasions were included in the calculation. Pretreatment tumor volume ranged from 135 to 670 cc, with a mean of 382 cc.

Stage and risk factors

For clinical staging, the Ann-Arbor classification was employed.[7] Direct invasion to neighboring structures as well as pleural and pericardial effusions were classified as E lesion. Discrete lung parenchymal nodule confined to a single lobe was also considered as E lesion. Pleural invasion and/or pleural effusion were seen in five patients, while pericardial invasion and/or effusion was noted in six. Cytological examinations of the effusions were not performed. Chest wall invasion was found in six patients; solitary pulmonary nodule avidly accumulating gallium was seen in one patient; and B symptom was present in two patients. Six patients were classified as stage IIE, and the remaining patient as stage III with multiple mediastinal and para-aortic lymph node involvement. The number of involved regions ranged from two to seven, with a mean of 5.4.

For prognostic groupings, the international prognostic index (IPI)[8] and modified tumor score (mTS)[9] were employed. Serum LDH was elevated in seven patients, and beta-2 microglobulin was higher than 1.6 mg/dl in one patient. According to the IPI, all patients had two risk factors. By mTS, two patients had three risk factors, and five had two risk factors.

Treatment

Mediastinal tumor resection was attempted in two patients. In one patient (#5), tumor resection with a graft replacement of the superior vena cava was performed. The operation was followed by six cycles of CHOP (cyclophosphamide, adriamycin, vincristine, predonine) and radiation therapy. In another patient (#6), repeated needle biopsies yielded only necrotic tissues, and, because of impending airway compression, chemotherapy employing CDDP, adriamycin, and etoposide was instituted initially. After attaining partial remission, tumor resection was performed and the diagnosis of PMLBL was confirmed. Radiation therapy was delivered postoperatively and six cycles of CHOP followed. In one patient (#2), emergency radiation therapy confined to the tumor with generous margins was administered without pathological diagnosis to alleviate impending airway obstruction. Needle biopsy during the radiation therapy yielded only necrotic tissues. Four months after the radiation therapy, multiple mediastinal recurrences were noted at the margins of the radiation fields, and the diagnosis of PMLBL was established. Radiation therapy to only a part of the recurrent tumors was performed to alleviate phrenic palsy, and was immediately followed by five cycles of BACOD-E (bleomycin, adriamycin, cyclophosphamide, vincristine, decadron, etoposide).[10] In the remaining four patients, doxorubicin-based chemotherapy was instituted initially, and consolidation radiation therapy ensued. Three patients underwent six cycles of CHOP, and one patient five cycles of BACOD-E (Table 2).

Radiation therapy

Radiation therapy was performed with 6 MV X-rays with anterior/posterior opposing fields and delivered to the initially involved areas with various modifications (Fig. 1). In three patients with pleural and pericardial effusions or with a solitary pulmonary nodule, entire or hemi-thorax irradiation including whole pleural cavities was performed up to 9 Gy to 12 Gy in 1 Gy daily fractionation, and in one of them the entire pericardium was further saturated up to 20 Gy after the insertion of lung field blocks. In the remaining three patients with pleural and/or pericardial invasion, thorax or pericardial irradiation was not performed, and radiation therapy was limited to the site of the initial tumor mass with margins. The dose to the tumor mass ranged from 27.3 to 40 Gy (mean, 32 Gy) with a fractional dose of 1.7 to 2 Gy. The initial site of chest wall invasion was irradiated to the same dose as the tumor mass. In two patients, anterior

Table 1. Clinicopathologic features at presentation

No. of Patients	Sex/ age	Presenting symptoms	Sclerosis	Clear cells	Clinical stage	No. of involved regions	Pleural invasion	Pericardial invasion	Chest wall invasion	Solitary pulmonary nodule	LDH	b2MG	Maximal transverse diameter	Tumor volume (cc)	No. of risk factors by IPI	No. of risk factors by mTS
#1	M/35	Chest pain Cough Hemoptysis	Yes	Yes	IIEB	7	Yes	Yes	Yes	Yes	592	1.8	9.6	314	2	3
#2	M/22	SVCS	Yes	No	IIEA	4	Yes	Yes	Yes	No	1,010	1.2	12	670	2	2
#3	M/36	Chest pain	Yes	Yes	IIEA	7	Yes	Yes	Yes	No	294	1.3	13	500	2	2
#4	M/43	Cough	No	No	IIIA	2	No	No	No	No	566	1.3	9	324	2	3
#5	F/50	Incidentally discovered	Yes	No	IIEA	6	Yes	Yes	Yes	No	345	1.1	9	135	2	2
#6	F/43	Cough	Yes	No	IIEB	6	Yes	Yes	Yes	No	579	1.0	9.8	378	2	2
#7	F/26	SVCS Dyspnoe Cough	Yes	Yes	IIEA	6	No	Yes	Yes	No	373	1.2	9	354	2	3

M: male, F: female, SVCS: superior vena cava syndrome, normal range for LDH <250, b2MG: beta-2 microglobulin, unit of b2MG: mg/dl,
IPI: international prognostic index, mTS: modified tumor score

Table 2. Treatment and results

No. of patients	Treatment	Gallium uptake after chemotherapy	Radiotherapy dose/fraction/day	Radiotherapy fields	Recurrence	Final outcome
#1	6CHOP→RT	Negative	30.6 Gy/17/22	Bilateral lung→mantle	No	45 months NED
#2	RT→RT→5BACOD-E	NP	10 Gy/5/5	Partial	No	126 months NED
#3	6CHOP→RT	Negative	30 Gy/15/19	Whole mediastinum	No	48 months NED
#4	5BACOD-E→RT	Negative	30 Gy/15/21	Localized	No	76 months NED
#5	OP→6CHOP→RT	Negative	27.3 Gy/20/29	Right lung→mantle	Bilateral kidneys	11 months DOD
#6	Chemo→OP→RT→6CHOP	NP	31.14 Gy/24/32	Left lung→whole mediastinum	No	72 months NED
#7	6CHOP→RT	Positive	40 Gy/20/30	Localized	No	7 months NED

CHOP=cyclophosphamide+adriamycin+vincristine+predonine, RT: radiation therapy, NP: not performed,
BACOD-E=bleomycin+adriamycin+cyclophosphamide+vincristine+decadron+etoposide, NED: no evidence of disease, DOD: dead of disease

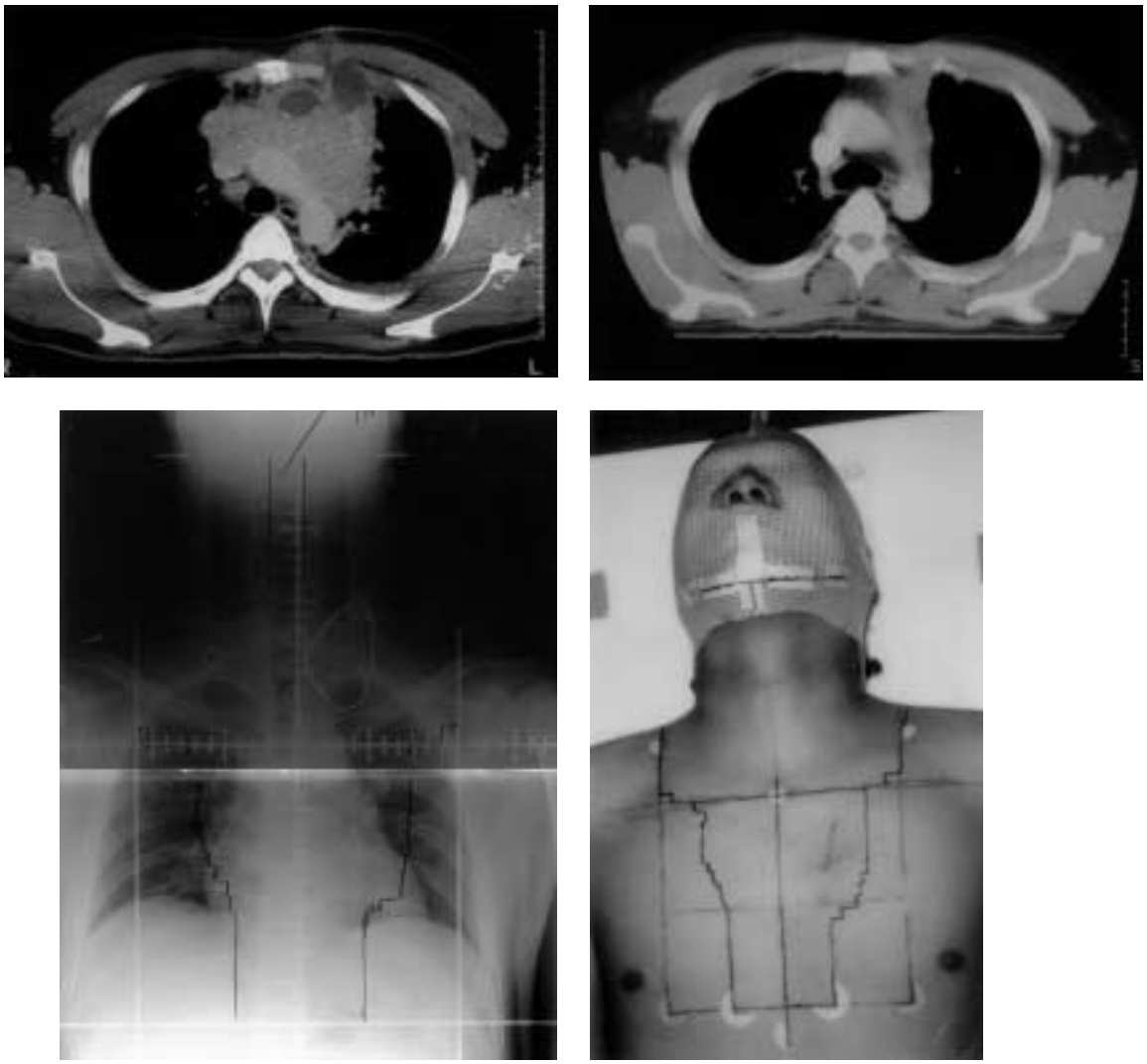

Fig. 1. a: In patient 3, PMLBL invaded the anterior chest wall. Left neck lymph node involvement was also seen with the diagnosis of stage IIE. b: After six cycles of CHOP, the mediastinal tumor decreased to 8% of the initial volume. c: Whole neck and mediastinal irradiation was delivered up to 30 Gy with conventional fractionation. In this patient, initial sites of anterior chest wall invasion could be irradiated by slightly extending X-ray fields laterally. In some cases, anterior electron irradiation is necessary to saturate the anterior chest wall. d: Biopsy scar of the anterior chest wall is included within the radiation fields.

a	**b**
c	**d**

appositional electron irradiation of an appropriate energy was employed to irradiate the chest wall in order to reduce the lung dose.

RESULTS

Recurrence, which was seen in one patient (#5), was noted in the bilateral kidneys during consolidating radiation therapy after tumor removal and six cycles of CHOP (Table 2). The recurrence was refractory to salvage ESHAP (etoposide, methylprednisolone, Ara-C, CDDP),[11] and the patient finally succumbed to disease 11 months after recurrence. The remaining six patients are alive without disease at 7-126 months' follow-up (mean, 59 months). In the current study, no prognostically significant factors could be found.

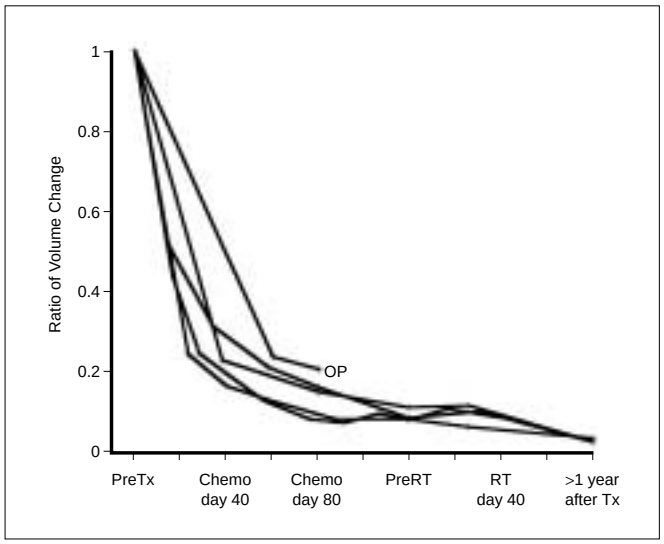

Fig. 2. Sequential volume changes of PMLBL. Tx: treatment, RT: radiation therapy, OP: operation

Sequential changes in mediastinal tumor volume are shown in Fig. 2. In the four patients who initially underwent CHOP or BACOD-E, tumor volume was reduced to less than 11% of the initial volume at the completion of chemotherapy. During consolidation radiation therapy volume changes were negligible. In the following years the tumor shrank gradually to 2% to 3% of the initial volume.

Five patients were examined by sequential gallium scintigraphy before treatment, after chemotherapy, and after consolidation radiation therapy. In all patients, the primary lesion avidly accumulated gallium. Immediately after the completion of chemotherapy, gallium uptake was seen in one patient (#7), but became negative after radiation therapy of 40 Gy. In one patient (#5) avid gallium uptake appeared in the bilateral kidneys during consolidation radiation therapy, and recurrence was diagnosed. Her mediastinum, however, showed no gallium uptake. In the other four patients, abnormal gallium uptake was not observed after consolidation radiation therapy.

DISCUSSION

PMLBL was established as a disease entity in the recently published WHO classification.[12] In western countries, especially France and Italy, studies of more than 100 PMLBL patients have been reported,[13,14] whereas only sporadic case reports have been published from Japan,[3-6] suggesting a much lower incidence of PMLBL in Japan. PMLBL is characterized its tendency to predominantly affect women in the third decade of life and by a bulky mediastinal tumor with local invasion to neighboring structures, including the superior vena cava, chest wall, and pleuropericardial cavities. While serum LDH tends to elevate, serum beta-2 microglobulin remains low.[1,2] IPI is not useful to differentiate prognostic groups, while mTS is reported to reflect prognosis better.[9,15] Pathologically, PMLBL is similar to diffuse large B-cell lymphoma in other sites, however, the presence of clear cells and sclerosis is frequently observed.[12] Specific immunohistochemical and genomic features of PMLBL are being defined, and PMLBL is now considered to be derived from thymic B-cells.[16] The patients in this study showed similar demographic and pathologic features except for a slight male predominance in the current study. The number of risk factors according to the IPI and mTS was two and two or three, respectively, with the recurrent patient having two mTS risk factors. Neither the IPI nor mTS was not useful for predicting prognosis, although the small number of patients precludes any meaningful statistical analysis.

There remain controversial issues in the pathological diagnosis of PMLBL. It is unclear whether all diffuse large B-cell lymphomas arising in the anterior mediastinum can be classified as PMLBL, and, if not, what are the criteria differentiating PMLBL from other mediastinal diffuse large B-cell lymphomas. Some investigators consider the presence of sclerosis essential

to the diagnosis of PMLBL and have demonstrated a difference in patient characteristics between PMLBL with and without sclerosis, although the prognosis was not much different.[17] In the current series, one patient was without sclerosis, and his anterior mediastinal tumor differed from other tumors in that invasion to the neighboring structures was not present. However, involvement of the right paratracheal and the abdominal lymph nodes was recognized. It is not clear whether the tumor in this patient was PMLBL. Under the present pathological criteria,[12] extraction of non-PMLBL diffuse large cell lymphoma in the mediastinum is difficult, and further refinement of the pathological and immunohistochemical criteria of PMLBL is required.

There is a general consensus that chemotherapy is a prerequisite for the cure of PMLBL, although the optimal regimen remains to be defined.[1,2] Our study confirmed that PMLBL is a highly curable disease and that CHOP and dose-intensive BACOD-E are equally effective, findings which are in accord with recent publications.[2,9,15,17] However, it remains unsettled whether radiation therapy as consolidation is indicated after chemotherapy in PMLBL. No randomized study has specifically addressed the role of radiation therapy in PMLBL. One retrospective study of PMLBL demonstrated superior survival by using radiation therapy after third-generation chemotherapy in comparison with patients treated by chemotherapy alone.[18] Additionally, it was shown that gallium positivity after chemotherapy could be converted to negativity after radiation therapy.[19,20] Most current studies employ radiation therapy in the management of PMLBL, although firm evidence for this is lacking. In the current series, one patient (#2) experienced multiple recurrences at the margins of localized mediastinal irradiation. Large parts of the recurrent tumors were treated without radiation, and secondary recurrence was not experienced for 126 months. This suggests some patients with PMLBL could be cured even without consolidation radiation therapy. Aisenberg suggested that consolidation radiation therapy would be indicated in patients with poor risk factors.[2] However, the risk factors of PMLBL have been variously reported. The presence of pleural or pericardial effusion and/or invasion,[13,14,21] positive gallium uptake,[20,21] and incomplete remission after chemotherapy[13,14,21] were shown to be poor risk factors in most studies. In the current study, four of the five patients with pleural or pericardial involvement remain disease free, and one patient with positive gallium uptake after CHOP also remains disease free. This excellent outcome might be due to the administration of consolidation radiation therapy, whose effectiveness might have obscured the influences of poor risk factors. Additionally, the definition of complete remission is especially problematic in PMLBL. Willett *et al.* demonstrated that all patients without recurrence showed volume reduction of more than 82% of the initial volume after chemotherapy,[22] even though a patient with 84% reduction recurred. In the present study, although more than 89% volume reduction was induced during chemotherapy in four patients, residual mass was seen in all. Such residual tumor masses make it difficult to diagnose complete remission immediately after chemotherapy. Because of such ambiguity in prognostic factors, it is difficult to determine the indications of consolidating radiation therapy. However, in an ECOG randomized trial of localized diffuse large B-cell lymphomas, consolidating radiation therapy after eight courses of CHOP was demonstrated to improve overall survival in comparison with patients treated by the same chemotherapy alone even in patients with a bulky lesion such as seen in PMLBL.[23] Consolidating radiation therapy should preferably be performed in all patients with PMLBL.[24]

Involved field radiation is employed in most studies for PMLBL.[9,15,17-21] The definition of involved field radiation differs among studies.[25] Involved field radiation is here assumed to be radiation to the regions defined by Kaplan and Rosenberg[26] wherein macroscopic lesions exist. For example, PMLBL confined to the anterior mediastinum would be irradiated to the whole mediastinum in the involved field radiation. Radiation to the tumor bed with a generous margin is localized radiation.

In the current study, entire or hemi-thorax irradiation was administered in three patients with pleuropericardial involvement. In contrast, only localized irradiation to the initial macroscopic tumor was performed in two patients with pleural or pericardial involvement. Recurrence in the pleuropericardial cavities was not experienced in either of them. It appears, therefore, that whole pleural or pericardial irradiation is not necessary in patients with pleural or pericardial involvement, provided that the foregoing chemotherapy could effectively reduce tumor volume to less than 20% of the initial volume.[23] Of six patients undergoing consolidating radiation therapy after chemotherapy, the whole mediastinum was irradiated in four patients, while only localized irradiation was performed in two. One of the former patients recurred in the kidneys. In consolidation radiation therapy of PMLBL, it might be possible to confine radiation fields to the localized area with generous margins. This confinement of radiation therapy has even greater significance, if one considers the increased incidence of breast cancer in young women

undergoing mantle irradiation.[27] It must be emphasized that at least the initial macroscopic tumors were included in the radiation fields in this study.

For radiation therapy of diffuse large B-cell lymphoma, 30-40 Gy in conventional fractionation is employed most often after attaining complete remission by chemotherapy.[17,24,28] The required dose is also shown to be dependent upon initial tumor volume, with a large tumor necessitating a larger dose.[28,29] In this study, the consolidation radiation dose to the initially involved areas was mostly around 30 Gy, with only one patient irradiated up to 40 Gy, even though all the patients had a large tumor greater than 9 cm. Recurrence was not observed within the radiation fields. Because of the small number of patients in this series, further study is necessary to determine whether 30 Gy is adequate for consolidation radiation therapy after chemotherapy for PMLBL.

In the current study, surgical removal of the PMLBL was attempted in two patients. Considering the excellent effects of chemotherapy and radiation therapy, surgical debulking is not required, even with the hazard of delaying prompt institution of effective therapy and the possible dissemination caused by major operative manipulations. Surgical procedures should be limited to those needed to obtain adequate material to establish the diagnosis.

In summary, CHOP followed by consolidation radiation therapy up to 30-40 Gy with localized fields seems to be the standard of management for PMLBL. Considering the excellent prognosis obtained by combined modality treatment, stem cell transplantation as a first-line therapy does not appear to be indicated. Further collection of PMLBL cases in Japan will elucidate the prognostic factors and indications of consolidating radiation therapy.

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