

Primary mediastinal large B-cell lymphoma: a retrospective analysis of rituximab and CHOP chemotherapy

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Primary mediastinal large B-cell lymphoma (PMBCL) is a recognized subtype of diffuse large B-cell lymphoma (DLBCL) with distinct clinical, pathologic, and molecular features. The therapeutic approach to PMBCL has traditionally paralleled that of DLBCL, consisting of anthracycline-based regimens with or without radiation therapy. A standard therapeutic approach for PMBCL has not been established and remains controversial. In recent years, the utilization of rituximab has expanded beyond its initially approved use for low-grade lymphoma. Several studies have demonstrated an outcome improvement with the addition of rituximab to the standard regimens in the treatment of DLBCL. Although rituximab is commonly used in the community as part of the initial treatment of PMBCL, outcome benefit has not as of yet been established. In this retrospective analysis, we report the outcomes of 10 patients with PMBCL treated in our institution and affiliated offices with rituximab and CHOP chemotherapy from 2000 to 2003. With a median follow-up of 20 months, all patients remain in complete remission. The addition of rituximab to CHOP chemotherapy for PMBCL might result in improved initial responses when compared with traditionally reported data, although the exact nature of this improvement and potential long-term outcome benefit remain to be elucidated in larger series and prospective studies.

Recognition of primary mediastinal large B-cell lymphoma (PMBCL) as a distinctive entity within the group of diffuse large B-cell lymphoma (DLBCL) in the REAL (Revised European American Lymphoma) and WHO (World Health Organization) classifications^{1,2} occurred about 15 years after it was initially described.³⁻⁵ Accumulation of data in the early 1980s led to the identification of this entity as a B-cell neoplasm of thymic origin with characteristic histologic and immunohistochemical features.⁶⁻¹⁰ Unique cytogenetic abnormalities, though not specific, have been recognized.¹¹ The most compelling data establishing distinctive features of PMBCL come from molecular profiling. Although molecular studies have confirmed an overlap of PMBCL with DLBCL, important distinctions between the two groups have also been found.¹²⁻¹⁶ In addition, subgroups of PMBCL sharing striking similarities with classic nodular sclerosis subtype Hodgkin's lymphoma (HL) were observed.^{13,15,17}

PMBCL is an uncommon neoplasm, reported at a frequency of 2.4% of all NHL (non-Hodgkin's

lymphoma) and about 5% of all aggressive lymphomas.¹⁸ It is typically seen in a young, predominantly female population, with presenting symptoms commonly related to its rapid growth in the anterosuperior mediastinum. Symptoms of chest pain, dyspnea, and cough are frequently seen at the time of presentation. Superior vena cava syndrome can be seen in about one-half of patients.¹⁹ The rapid intrathoracic growth accounts for early symptoms and presentation in a majority of patients. Contiguous tumor invasion of the chest wall, lung parenchyma, pleura, or pericardium is seen commonly, but extrathoracic organ and bone marrow involvement is unusual at the time of diagnosis.²⁰⁻²²

Despite improved knowledge about this entity, many questions regarding an optimal therapeutic approach remain unanswered. In the majority of studies, CHOP (cyclophosphamide, doxorubicin, vin-

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cristine, prednisone) or CHOP-like regimens have been utilized.²³ More recently, data illustrating improved outcomes with dose-intensified chemotherapy with MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) or VACOP-B (vincristine, doxorubicin, cyclophosphamide, etoposide, prednisone, bleomycin) over CHOP-type chemotherapy have been published.²⁴ Adjuvant radiation therapy (RT) for PMBCL has been advised by some authors, but other studies have demonstrated comparable results without RT.²⁴⁻²⁷ The use of high-dose chemotherapy with autologous stem cell transplantation (SCT) has also been investigated, but it remains controversial. Although rituximab (Rituxan) is commonly used in combination with CHOP therapy for DLBCL in the community, no studies have as of yet demonstrated benefit with its addition over CHOP therapy in PMBCL.²⁴

Materials and methods

Patients

Between January 2000 and December 2003, 16 consecutive patients with PMBCL were identified in our institution and affiliated offices. Only patients with confirmed PMBCL (according to the REAL clas-

sification) who were treated with R-CHOP (rituximab-CHOP) therapy were included in this analysis. A total of 10 patients for whom a follow-up was available met these criteria.

Staging

Staging was based on the Ann Arbor classification. All patients had a physical examination, laboratory studies, chest x-ray, bone marrow aspirate and biopsy, and computerized tomography (CT) scans of the chest, abdomen, and pelvis. Bulky disease was defined as a mass > 10 cm or that exceeding one-third of the thoracic diameter.

Treatment

All patients received a combination of rituximab and CHOP therapy (4-6 cycles). Two patients received CHOP therapy only for 2 and 3 cycles, respectively, before initiation of rituximab. Three patients received maintenance rituximab, one received 4 weekly treatments at 6 months, and the other patient underwent 4 weekly treatments at 3 and 6 months. The third patient received 4 weekly maintenance rituximab treatments at 6-month intervals. Five patients received involved-field radiation therapy (IFRT), with the median dose of 3,780 Gy (range 36-39 Gy).

Assessment/follow-up

Complete remission (CR) was defined as a complete disappearance of all measurable disease for at least 1 month; near CR, as 90% or more reduction; and partial remission (PR), as at least 50% reduction. In the event of residual masses identified on CT scan, PET scans were utilized to assess CR. Following completion of chemotherapy, all patients were restaged with CT, gallium, and/or PET scans. All patients had at least one documented PET scan upon completion of treatment. In February 2007, all patients were alive and well. Three patients had left our institution and/

or affiliated offices; in these cases, patients and/or their treating physicians were contacted, and included follow-up data were by report only. For patients with whom contact was not established, the last documented follow-up in our institution or affiliated office was taken into account.

Results

Clinical characteristics of the study patients are summarized in Table 1. The treatment specifications are summarized in Table 2. Seven patients (70%) achieved CR following completion of R-CHOP therapy, and two patients who had PR following R-CHOP therapy subsequently achieved CR after completion of RT. One of the patients had evidence of PET scan positivity after completion of RT and was referred for evaluation for autologous SCT. Repeated PET scans at regular intervals continued to demonstrate questionable PET positivity without other evidence of disease progression. The last follow-up PET scan at 22 months was negative, and the patient remained in CR (or without evidence of relapse) at the time of the last follow-up.

The median follow up was 20 months. Of note, median follow-up was calculated based on the last verifiable follow-up in our institution or affiliated office. At the last update (February 2007), all patients were alive. All patients underwent follow-up examinations by PET/CT scans at least until documentation of PET scan negativity and thereafter on a regular basis with either of the modalities.

Discussion

Our patients demonstrated basic characteristics in concordance with previously described findings in PMBCL with respect to age, sex, presenting symptoms, stage, International Prognostic Index, bone marrow involvement, serum levels of lactate dehydrogenase, and β_2 microglobulin. Previously reported studies,²³⁻²⁵ the

TABLE 1

Clinical characteristics of study patients at presentation

Median age, yr (range)	30 (22-56)
Female/male	6/4
Elevated LDH level, total (%)	9 (90%)
Stage I or II disease, total (%)	7 (70%)
Bulky disease, total (%)	6 (60%)
SVC syndrome	3 (30%)
Elevated β_2 microglobulin	0 (0%)
Bone marrow involvement	0 (0%)
B symptoms	2 (20%)
Median follow-up, months (range)	20 (13-54)

LDH = lactate dehydrogenase; SVC = superior vena cava

TABLE 2

Treatment specifications

Patient	1	2	3	4	5	6	7	8	9	10
Age	31	36	22	29	45	34	27	56	26	25
Stage	II	III	I	I	III	IB	I	I	IB	I
Bulky disease	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes
↑ LDH level	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
β ₂ microglobulin	Normal	Normal	Normal	–	–	–	Normal	–	Normal	–
B symptoms	No	No	No	No	No	Yes	No	No	Yes	No
SVC syndrome	No	Yes	No	No	Yes	No	Yes	No	No	No
ECOG PS	0	1	0	0	0	0	1	0	2	1
IPI score	1	3	1	1	3	1	1	1	2	1
Blood group	A	A	O	A	B	O	A	B	A	A
Treatment regimen	R-CHOP × 6	R-CHOP × 6	R-CHOP × 6 + MR	R-CHOP × 6	R-CHOP × 6	R-CHOP × 4 + RT	CHOP × 4 + R × 4 + MR	R-CHOP × 6	CHOP × 2 + R-CHOP × 4 + MR	R-CHOP × 6
RT	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes
CR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Follow-up (mo)	19	25	13	14	51	14	15	17	10	22

LDH = lactate dehydrogenase; SVC = superior vena cava; ECOG PS = Eastern Cooperative Oncology Group performance status; IPI = International Prognostic Index; R = rituximab; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; MR = magnetic resonance; RT = radiotherapy; CR = complete remission

majority of which are retrospective, illustrate an inconsistent therapeutic approach, largely because the studies antedated the REAL recognition of this disorder and there were only a small number of evaluable patients. Various proposed regimens have traditionally paralleled the therapeutic approach seen with DLBCL with the inclusion of anthracyclines. Early studies showed disappointing results with doxorubicin-based therapies,^{28,29} but this finding contradicts data reported by other authors.²⁴ The optimal management of PMBCL at this time remains unknown.

More recently, third-generation regimens, most notably MACOP-B and VACOP-B, have been shown to be superior to CHOP in PMBCL, despite the reported comparison in aggressive lymphomas that failed to demonstrate an advantage over CHOP.^{24,30} The most convincing data demonstrating a possible advantageous outcome with third-generation regimens come from a recently published study.²⁴ However, the need for

prospective randomized studies remains. The benefit of the addition of rituximab to CHOP chemotherapy is currently unknown; it is a distinct possibility that the addition of rituximab will provide a benefit similar to that seen in DLBCL.¹⁹ The recognition of PMBCL as a distinct entity within DLBCL will hopefully enable the determination of the optimal therapeutic regimen.

It is important to note that six of our patients received IFRT, three of whom achieved PR following R-CHOP therapy and subsequently achieved CR after RT. The addition of RT to patients who attained a CR led to a longer event-free survival in a single study.³¹ Nevertheless, studies demonstrating comparable results without the addition of RT raise some doubt of its necessity.^{24,26} High-dose chemotherapy with autologous SCT has also been investigated and at this time appears to be best reserved for patients with the highest risk of relapse.³²

Since its approval in 1997, rituximab has become a standard adjunct

in the treatment of low-grade lymphomas,³³ but because of the omnipresence of CD20 antigen in lymphoid malignancies, its utilization has expanded far beyond its initially approved indication. PMBCL is derived from B cells; however, the tumors often lack surface Ig while expressing CD79a. CD30 expression is sometimes present but contrasts with the strong expression seen in classic HL.²⁴ In particular, PMBCL shares pathologic features and molecular genetic qualities of nodular sclerosing HL.²⁴ Data showing the benefit of adding rituximab to the treatment of DLBCL stem from the landmark GELA (Groupe d'Etude des Lymphomes de l'Adulte) study that provided evidence of improved outcome in patients older than 60 years.³⁴ The magnitude of the rituximab benefit in DLBCL has only recently been demonstrated across all age groups.³⁵ The literature contains only isolated single case reports demonstrating its potential benefit in PMBCL.

All of our patients received ritux-

imab in addition to CHOP therapy. Three patients received maintenance rituximab therapy in addition to the standard dose given during initial treatment. Despite the fact that the benefit of maintenance rituximab therapy has been demonstrated in low-grade lymphomas, its use in PMBCL remains provisional. However, the use of rituximab for maintenance therapy remains speculative, and its applicability in aggressive lymphomas is entirely unknown.

Although we recognize the limitations of this retrospective study, the outcomes of this small number of relatively homogeneously treated patients may be clinically relevant. In our review, we have seen excellent responses to initial treatment with R-CHOP. All our patients have achieved CR, and with a median follow-up of 20 months, no relapses have been documented. One of the few universally accepted issues in PMBCL is the fact that achievement of CR appears to be the strongest predictor of outcome.^{25,26,31} The majority of authors report that the preponderance of adverse outcomes is seen in patients who never achieve CR. Furthermore, the highest proportion of relapses occurs early (within 6–12 months) and only rarely after 2 years.²⁴ Previously reported CR rates for CHOP or CHOP-like regimens vary across studies, ranging from 23% to 80%.²⁴

Finally, the residual mediastinal mass demonstrated by conventional imaging studies has been one of the traditionally recognized difficulties in the evaluation of response to treatment. The use of PET scanning is becoming a preferred modality for restaging lymphomas, with evidence showing its potential advantage emerging in the literature.^{26,36} This approach will likely bear significance in future studies, allowing more precise recognition of unresponsive or relapsed disease. All our patients were restaged with PET scans and were noted to be in CR following comple-

tion of treatment.

Conclusion

The addition of rituximab to CHOP in the treatment of PMBCL may be of value. Response rates in our study may eventually translate into an overall survival benefit. Recent data observed in DLBCL, with which PMBCL shares similarities despite its unique features, probably justify the use of rituximab, but its potential benefit must be confirmed by randomized prospective studies. However, since PMBCL is so uncommon, it is more likely that data regarding the value of the addition of rituximab will emerge from retrospective analyses.

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