

# Evolving Treatment Methods in the Management of Primary Breast Lymphoma (PBL)

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Since it was first described by Wiseman and Lao, primary breast lymphoma (PBL) has remained an intriguing and elusive disease [1]. The malignancy itself although rare, accounting for less than 0.5% of all breast cancers, is common enough to be the subject of several case reports and retrospective analysis. Common enough to be seen at tertiary care centers but rare enough to not have any definitive guidelines for therapy.

PBL are a relatively homogeneous group of lymphomas often with a common presentation, a painless breast mass with no distinct findings on mammography. The most common pathological variant is diffuse large B-cell lymphoma (DLBCL) with other non-Hodgkin B-cell lymphomas also seen (follicular or marginal zone lymphoma). Although unclear, the disease is believed to arise from the breast lymphatic system or mucosa-associated lymphoid tissue (MALT). T-cell lymphomas are relatively rare except in Asia although recent studies have demonstrated a possible correlation between silicone implants and anaplastic large T cell lymphomas [2].

Over the years, there has been significant controversy in the management of PBL. There are no definitive randomized trials due to the rarity and low incidence of these tumors. Prognosis and treatment is often extrapolated from other extranodal lymphomas [3]. Regardless of the treatment paradigm for these patients, it is agreed by most oncologists that combined modality therapy offers the best means of controlling disease and prolonging survival. Multiple studies have demonstrated treatment with radiation therapy and chemotherapy as favorable positive prognostic factors in patients with PBL in addition to histologic subtype, Ann Arbor stage, favorable International Prognostic Index (IPI) score and conservative surgery [4,5]. In a study by Jennings et al. [6], tumor size and node status were analyzed for outcomes and nodal status was the best single predictor of survival.

Historically, radical surgical resection was a cornerstone in the management of these patients with many women treated with mastectomy followed by adjuvant therapy. More recently, surgical resection is less common with the availability of better chemotherapy regimens and demonstrated improvement in outcomes with combined modality therapies. In a series from Ryan et al. [5], on PBL DLBCL, the median OS was 8.0 years and median progression free survival was 5.5 years. There was no benefit from mastectomy compared to biopsy or lumpectomy. A recent meta-analysis found no improvement in survival outcomes in patients undergoing mastectomy, although there was a benefit on both overall survival and recurrence rates treated with radiation (for stage I patients, node negative) or chemotherapy (for stage II patients, node positive). Overall DFS was 44.5% [6] and histologic grade predicted survival.

At our institution, the preferred treatment for most patients with PBL is a combined modality approach with chemotherapy followed by local radiation therapy. The objective of combination therapy is optimizing efficacy while minimizing treatment-related toxicity by reducing the number of chemotherapy cycles.

## Advances in Chemotherapy

Since the disease was first described in the 1970s, chemotherapeutic

options have rapidly evolved. The ability to identify tumors based on molecular phenotyping has allowed the medical oncologist to better target malignancies while avoiding unnecessary toxicity. As with other CD20 positive lymphomas, Rituximab is likely to play an important role in the management of these malignancies. Yet the means of identifying this role remains difficult. A recent phase I study from Mexico examined the role of Rituximab along with dose dense chemotherapy (CEOP-14) for PBL. Although treatment was well tolerated, response rates and overall survival were similar to previous combined modality studies not involving Rituximab [7].

There also remains the question of the ideal number of cycles needed to treat these patients. Most centers use two approaches to this issue [3], treating with a prefixed number of cycles (R-CHOP×6) regardless of the response while others use treatment response (complete and/or partial response after R-CHOP×3) to dictate the number of cycles a patient may ultimately receive. What further muddies the water is the role of imaging modalities such as positron emission tomography (PET) scans, which did not exist in the previous era and are the basis of our current regimens. At our institution, patients are typically restaged following 3 cycles of chemotherapy (R-CHOP) for stage I-II non-Hodgkin lymphomas (DLBCL) after which they receive radiation therapy to the involved regions. Additionally, patients with stage IE DLBCL of the breast are managed with a recommendation for CNS prophylaxis [3] with 4-8 doses of intrathecal methotrexate and/or cytarabine or systemic methotrexate as there is a potentially high risk for CNS disease.

## Role of Radiation Therapy

Although the primary goal of treatment remains ultimately curing the patient, the line between curing a patient and “do no harm” is thin. Radiation oncologists are often placed in the difficult position of treating patients while knowing that the patient will ultimately have an increased risk of malignancy. In addition, extrapolating from more conventional breast cancer, there is an understood increased risk of heart disease.

Intensity modulated radiation therapy (IMRT) has nearly replaced conventional photon-beam radiotherapy in treating many disease sites. The primary advantage is the ability to deliver the optimal dose of radiation to the tumor site while reducing the exposure of

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surrounding healthy tissue. At our facility, we prefer management with IMRT in order to reduce surrounding toxicity while maintaining efficacy. In addition to radiation technique, other means of reducing radiation exposure include limiting the total dose delivered as well as modifying the radiation field. The ideal dose of radiation in the management of these patients is contentious. Most studies historically used a wide array of doses ranging from 30 to 50 Gy. More recently, a phase III study examined the ideal radiation dose and showed no differences when patients were treated with a lower dose of radiation [8]. Indolent NHL (Follicular and marginal zone lymphoma) patients were randomized to receive 40-45 Gy in 20-23 fractions or 24 Gy in 12 fractions, while aggressive NHL (DLBCL, as part of combined modality therapy) were randomized to receive 40-45 Gy in 20-23 fractions or 30 Gy in 15 fractions. NCCN guidelines recommend doses of 24-30 Gy (1.8-2.0 Gy per fraction over 2-3 weeks duration) to the marginal zone lymphoma (non-stomach extranodal sites) and 30-36 Gy as consolidation after chemotherapy for DLBCL. The whole breast alone is considered in the clinical target volume (CTV). Extrapolating from this data, at our institution we typically treat patients to 30-36 Gy for PBL [3,8,10].

Over time there has been a movement to limit radiation treatment fields in order to reduce toxicity while still maintaining good outcomes. More recently, involved-field radiation therapy (IFRT) has largely replaced extended-field radiation therapy [3,9]. IFRT involves radiation to the clinically involved region in addition to the adjacent nodal regions. For patients with stage I-II PBL this results in radiation to the breast as well as involved axillary lymph nodes. The use of involved-nodal radiation therapy (INRT) or treatment only to the involved pre-chemotherapy and post-chemotherapy lymph nodes is a newer concept which has demonstrated encouraging results [9]. Multiple international trials are currently examining the role of INRT in treating lymphoma. These results will likely further modify our delineation of the treated volume.

The ideal methodology for treating PBL remains controversial. While chemotherapeutic regimens and radiation options vary by

institution, it is generally agreed that combined modality therapy offers the best rates of cure. Rather than improving outcomes in these patients, over the next years the goal will be to limit toxicity while maintaining similar efficacy. These goals will likely be met when the ideal balance between chemotherapy and radiation is reached, thereby curing the patient while limiting unnecessary side effects.

## References

1. Wiseman C, Liao KT (1972) Primary lymphoma of the breast. *Cancer* 29: 1705-1712.
2. Lazzeri D, Agostini T, Bocci G, Giannotti G, Fanelli G, et al. (2011) ALK-1-negative anaplastic large cell lymphoma associated with breast implants: a new clinical entity. *Clin Breast Cancer* 11: 283-296.
3. (2013) National Comprehensive Cancer Network (NCCN) Guidelines: Version 2.2013. Extranodal Marginal Zone B-Cell Lymphoma. 48-49, 60, 145, 251-253.
4. Jeanneret-Sozzi W, Taghian A, Epelbaum R, Poortmans P, Zwahlen D, et al. (2008) Primary breast lymphoma: patient profile, outcome and prognostic factors. A multicentre Rare Cancer Network study. *BMC Cancer* 8: 86.
5. Ryan G, Martinelli G, Kuper-Hommel M, Tsang R, Pruneri G, et al. (2008) Primary diffuse large B-cell lymphoma of the breast: prognostic factors and outcomes of a study by the International Extranodal Lymphoma Study Group. *Ann Oncol* 19: 233-241.
6. Jennings WC, Baker RS, Murray SS, Howard CA, Parker DE, et al. (2007) Primary breast lymphoma: the role of mastectomy and the importance of lymph node status. *Ann Surg* 245: 784-789.
7. Avilés A, Castañeda C, Neri N, Cleto S, Nambo MJ (2007) Rituximab and dose dense chemotherapy in primary breast lymphoma. *Haematologica* 92: 1147-1148.
8. Lowry L, Smith P, Qian W, Falk S, Benstead K, et al. (2011) Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. *Radiother Oncol* 100: 86-92.
9. Campbell BA, Voss N, Pickles T, Morris J, Gascoyne RD, et al. (2008) Involved-nodal radiation therapy as a component of combination therapy for limited-stage Hodgkin's lymphoma: a question of field size. *J Clin Oncol* 26: 5170-5174.
10. Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, et al. (1998) Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *N Engl J Med* 339: 21-26.