

## CLINICAL VIGNETTE

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# Chemotherapy for Diffuse Large B Cell Lymphoma in the Elderly: Predicting and Mitigating Toxicity

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### *Case Study*

An 81-year-old Caucasian female presented to her primary care doctor with fatigue in the spring of 2014. Her laboratories at that time demonstrated a minor normochromic, normocytic anemia. Her symptoms worsened and in late summer of 2014 she was profoundly anemic with a hemoglobin of 8.0 g/dl. She was admitted and found to have bilateral pleural effusions, retroperitoneal adenopathy, and hypodense liver lesions. She also had a right lower extremity deep venous thrombosis. Liver biopsy showed diffuse large B cell lymphoma, which was confirmed on the bone marrow biopsy.

She was treated with one cycle of standard dose rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP). She received prophylactic pegfilgastrim. At day 10, the patient developed atrial fibrillation and congestive heart failure documented on echocardiogram and radiographs. She was hospitalized and her condition was treated with diuretics, digoxin, and oxygen with improvement.

A 95-year-old Asian woman presented to her primary physician with headaches, right eye pain, and visual changes. An MRI revealed a 2.7 x 1.8 x 6 cm mass in the right intraconal orbit. There was no invasion into the central nervous system by MRI imaging. Biopsy of the mass demonstrated diffuse large B cell lymphoma, non-germinal center subtype. Her PET/CT showed involvement of multiple lymph nodes in the chest, abdomen, and pelvis.

She received therapy with etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCHR) with intrathecal methotrexate. Each cycle was followed by pegfilgastrim. She tolerated therapy well, and her PET/CT after two cycles showed resolution FDG activity. She completed four cycles without complication, and her end of treatment scan showed a complete remission (CR). She remains in CR.

### *Discussion*

Chemotherapy for the elderly person with a potentially curable condition, such as diffuse large B cell lymphoma, must consider not only the treatment goal but also the potential for side effects. Preexisting comorbidities such as cardiac disease

often predispose these patients to increased risk of arrhythmia and congestive heart failure. Specifically, in elderly patients with diffuse large B cell lymphoma treated with anthracyclines, the risk of congestive heart failure may be as high as 21%.<sup>1</sup> This incidence stands in comparison to a cohort of 1697 patients treated with a doxorubicin based therapy for non-Hodgkin lymphoma who experience a cardiac side effect rate of 3.2%.<sup>2</sup> Patients with known preexisting heart disease may have a higher incidence of cardiac events.

Several strategies to mitigate anthracycline cardiac toxicity include limiting the cumulative dose and taking into consideration preexisting cardiac disease, age, and radiation therapy to the mediastinum or left hemi thorax. Cumulative dosing recommendations in the general oncologic population demonstrate that the incidence of symptomatic congestive heart failure is 0.14% for those who received less than or equal to 400 mg/m<sup>2</sup> compared to as high as 26% for those receiving above 700 mg/m<sup>2</sup>. At an intermediate cumulative dose of 550 mg/m<sup>2</sup>, the incidence was 7%.<sup>3</sup> Most chemotherapy with curative intent for non-Hodgkin lymphoma cap the maximum cumulative dose of doxorubicin between 300 and 400 per meter squared.

Other comorbidities may contribute to cardiac toxicity. The study by Hershman, et al<sup>4</sup> suggests that in pts with preexisting heart disease, hypertension was synergistic with doxorubicin to produce worse outcomes. At 8 years, “The CHF free survival rate was 74% in doxorubicin – treated pts vs 79% in patient not treated with doxorubicin.” The only risk factor or comorbidity that was synergistic with the development of CHF was hypertension. The adjustment for a variety of comorbidities with chemo selection in the elderly suggests that this approach may balance benefit with risk.

Given that age extremes predispose patients to a higher likelihood of cardiotoxicity even when the dosing guidelines are followed, the evaluation of an elderly patient with diffuse large B cell lymphoma for chemotherapy should include careful examination of cardiac risk factors. In all age groups the chemotherapeutic regimen, (R-CHOP), is the standard of care to produce long-term improvement in survival and cure. In a large, retrospective analysis of 3479 elderly patients with DLBCL, the OS was improved in patients in patients that received at least 4 cycles of R-CHOP.<sup>5</sup> For patients over the age of 80 years, there is data to suggest favorable outcomes

with a reduced dose regimen of R-miniCHOP.<sup>6</sup> In this study patients received standard dose rituximab, doxorubicin 25mg/m<sup>2</sup>, vincristine 1mg, cyclophosphamide 400mg/m<sup>2</sup>, and prednisone 40mg/m<sup>2</sup> on days 1-5. Given the importance of anthracycline dose intensity on outcome, this may be best reserved only for patients predicted to have excess toxicity with R-CHOP.

Alternative therapies to standard doxorubicin containing regimens for diffuse large B cell lymphoma including mitoxantrone based regimens may not avoid cardiac toxicity and may lead to inferior outcomes. In a pooled meta-analysis by Bjorkhom, et al,<sup>7</sup> 9 studies comparing CNOP and CHOP were analysed. Rituxumab was not used in any of the studies. The authors found that the CR rate for CNOP was inferior to CHOP but that the OS was not significantly different. Congestive heart failure was noted in both groups. The substitution of mitoxantrone does not eliminate the risk of CHF.

Several non-anthracycline containing regimens used to treat diffuse large B cell lymphoma have been studied in high-risk patient who were not felt suitable to anthracycline based therapy. RCEOP produces approximately 50% survival rate at five years.<sup>8</sup> RGCVP produces outcomes with overall response rates of 61% with 56% of patient alive at 2 years.<sup>9</sup> An anthracycline containing regimen with doxorubicin given as a continuous infusion dose adjusted R EPOCH, produces excellent outcomes without excess cardiotoxicity.<sup>10</sup> The infusional administration of doxorubicin allows higher doses with decreased risk of cardiac toxicity. A study evaluating EPOCH in the salvage setting highlighted the ability to safely give infusional doxorubicin in patients that had previously received an anthracycline. In that cohort of patients, the median cumulative dose of doxorubicin was 510mg/m<sup>2</sup> with a range of 335-680mg/m<sup>2</sup>. Despite these doses, only 3% stopped doxorubicin, and none of the patients developed congestive heart failure.<sup>11</sup> For high-risk patients, the trial comparing R-CHOP to DA-EPOCHR is currently still in process to determine if the standard regimen of R-CHOP remain or be changed to DA-EPOCHR (NCT00118209).

### Conclusions

In summary, elderly patients with diffuse large B cell lymphoma present with a potentially curable tumor but may suffer from excess cardiac events due to therapeutic intervention. The majority of this excess of toxicity occurs as cardiac events secondary to anthracyclines and concurrent hypertension. The use of anthracyclines with lower potential cardiac toxicity may not lead to less morbidity and may compromise efficacy. Several regimens without anthracyclines may produce less cardiotoxicity than R-CHOP but possibly with inferior outcomes. DA-EPOCHR provides the ability to benefit from an anthracycline-based regimen with decreased cardiac toxicity, which makes it a favorable choice in older patients.

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