

Case studies of elderly patients with non-Hodgkin's lymphoma

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The treatment of patients with non-Hodgkin's lymphoma (NHL) is often the treatment of elderly patients, as most patients are older than 65 years at diagnosis. These elderly patients present particular therapeutic challenges, because they may be more frail and at greater risk of treatment-related toxicity, especially anthracycline-related cardiotoxicity, than younger patients. The following two case studies illustrate the challenges and therapeutic decision-making in managing elderly patients with an aggressive and an indolent form of lymphoma.

Case 1 - Elderly woman with existing cardiopathy

History

This woman was aged 79 years at presentation. She had a history of congestive cardiopathy and myocardial ischemia, and had undergone angioplasty 10 years earlier. Her recent history included a hospital admission due to abdominal pain. Initial patient "work-up" revealed the presence of a solid hypoechoic abdominal mass, of around 10 cm, on abdominal ultrasound. The patient was referred for diagnostic procedures.

Diagnosis and staging

- Clinical examination showed no systemic signs or symptoms.
- Laboratory investigations showed that complete blood count, hemoglobin, albumin, hepatorenal function, lactate dehydrogenase (LDH), beta-2 microglobulin, and serum electrophoresis were all within the normal range.
- A computed tomography (CT) scan revealed a dishomogeneous mass with rounded margins and a longest transverse diameter of 10 cm in the left flank region of the abdomen. The mass included the superior mesenteric artery, with no signs of compression.
- Diagnostic laparoscopy was performed, and a diagnosis of diffuse large B-cell lymphoma (DLBCL: CD20+, CD10-, CD5-) was made. The proliferation index, measured with MIB-1 staining, was 80%.¹
- Bone marrow biopsy showed no evidence of lymphoma.

- A 2-dimensional echocardiogram showed signs of pre-existing ischemic cardiopathy with moderate reduction of ventricular function and moderate valvular incontinence. The left ventricular ejection fraction (LVEF) was 35%.

Final diagnosis

The final diagnosis was therefore: DLBCL, stage IA, bulky, subdiaphragmatic unresectable disease, with an International Prognostic Index (IPI) of 1, due to advanced age.

Assessment for treatment

According to data from epidemiological studies, the median age of patients with DLBCL at the time of diagnosis is around 65 years, and one fifth of them are, like the reported case, within the age range of 75-80 years. Older patients with DLBCL generally show a relatively short life expectancy: overall median survival is around 12 months (range 2-23) and 15% die within 3 months of diagnosis.² However, these poor results may vary when analysis is limited to patients who are initially approached with curative intent. In such cases, median overall survival increases to 36 months, compared with 6 months for patients in this age range who are treated with only palliative intent. The main issue in elderly DLBCL patients is then to properly decide who is suitable for a full course of therapy.

The rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)-21 regimen appears to be a good option for elderly patients with aggressive lymphoma. The addition of rituximab to the standard CHOP regimen has been shown to increase its efficacy, in both young and elderly patients.³⁻⁶ In addition, although CHOP-14 was shown to be more effective than CHOP-21,^{7,8} interim analyses of comparisons of R-CHOP-21 and R-CHOP-14 have shown no significant differences in efficacy between these two regimens.^{9,10} As the R-CHOP-14 regimen is more dose intense, and may therefore be associated with more toxicities, the R-CHOP-21 regimen may be preferable in elderly patients.

As this patient had existing cardiopathy and a low LVEF, she would be at increased risk of cardiotoxicity during anthracycline treatment. However, her disease, due to the limited stage and favorable prognostic features, may be cured, with a high chance of success, if the standard approach was adopted. She would therefore probably benefit from the use of a standard regimen adapted to her concomitant disorders. Among the different strategies adaptable for this patient, there is the possibility of reducing the drug doses, using treatment regimens specifically designed for elderly patients, or using different formulations

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of the active drugs, allowing reduced toxicity. For this last strategy, the availability of the non-pegylated liposomal doxorubicin (NPLD) formulation makes it feasible to substitute conventional doxorubicin in the R-CHOP regimen, defining a different, potentially more tolerable, therapy, namely the R-COMP regimen. A prospective study in patients with lymphoma who were at risk of cardiotoxicity, and who received R-COMP therapy, showed a promising complete response rate of 76%, and only one patient developed an acute grade III cardiotoxicity.¹¹ In addition, a prospective, non-randomized study of R-COMP in elderly patients with DLBCL showed no changes in LVEF, and no cardiotoxic effects of this regimen during treatment.¹² This patient was therefore treated with R-COMP (NPLD dose of 50 mg/m²) for four cycles, followed by involved-field radiation therapy. She also received prophylactic granulocyte colony-stimulating factor and erythropoietin, and prednisone was lowered to half dose in cycles 3 and 4 in order to reduce steroid-related toxicity.

Treatment outcomes and follow-up

At the end of treatment, the patient showed no change in LVEF, which remained at 35%, and was assessed as having an unconfirmed complete response. She was diagnosed with a pulmonary embolism at the end of chemotherapy, which resolved during treatment with low-molecular-weight heparin. Her LVEF has since deteriorated to 30%. This patient remains in complete remission after 7 years.

Case 2 - Elderly man with a history of cardiovascular disease

History

This 77-year-old man was admitted to hospital due to abdominal pain and the presence of a palpable mass. The patient had a history of myocardial infarction 2 years before admission, which had been treated with coronary stenting. He had persistent arterial hypertension.

Diagnosis and staging

- The patient underwent laparoscopic biopsy, and the histologic diagnosis was grade 2 follicular lymphoma (FL).
- CT and positron emission tomography scans confirmed the presence of an abdominal mesenteric mass with pathologic adenopathies in the mediastinum and neck.
- Laboratory tests showed normal values for white blood count, hemoglobin, platelets, and erythrocyte sedimentation rate, but elevated LDH and beta-2 microglobulin.
- Bone marrow biopsy revealed several perivascular and paratrabeular lymphoid aggregates, comprising B-lymphocytes expressing CD20 and CD10.
- A 2-dimensional echocardiogram showed normal cardiac function, with an LVEF of 65%, and the patient had a normal stress electrocardiogram.

Final diagnosis

The final diagnosis was therefore: grade 2 FL, stage IVA. The patient's follicular lymphoma IPI (FLIPI) score was 4 (due to advanced age, stage, elevated LDH, and number of nodal sites).¹³ His FLIPI2 score was also 4 (due to advanced age, elevated beta-2 microglobulin, bone marrow involvement, and longest diameter of the largest involved node >6 cm).¹⁴

Assessment for treatment

As this patient was generally healthy, he could be expected to have a life expectancy of around 10-15 years if he did not have lymphoma.¹⁵ Older data indicate that, for such a patient with a poor prognosis, the 5-year overall survival rate would only be expected to be around 50%.¹³ However, these data were produced before the availability of rituximab, and the use of this chemotherapy combined with monoclonal antibody has changed outcomes for patients with FL. A more realistic 5-year overall survival rate with chemo-immunotherapy would be 70%. However, if the

patient has an indolent lymphoma and is in his eighth decade, he may experience a significant reduction in life expectancy if not properly cured of his disease.

It is not currently clear what the optimal chemotherapy is for FL. Some study data were obtained before the widespread use of rituximab, and others before the availability of the REAL classification of lymphomas,¹⁶ when FL was less strictly defined and was included among other indolent lymphomas. Based on the most recent data, a large proportion of patients are treated with R-CHOP, although rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) and fludarabine-based regimens such as rituximab, fludarabine, and mitoxantrone (R-FM) are also used. The FOLL05 study (NCT00774826) is currently underway to investigate the optimal therapy for FL, comparing R-CHOP, R-CVP, and R-FM in patients with stage II-IV newly diagnosed FL. This randomized study will provide a definite answer on which initial treatment should be proposed for patients with FL, and whether anthracyclines are also needed in this lymphoma subtype; the final results should be available by mid-2011. In addition, bendamustine plus rituximab has produced promising results in follicular lymphoma, with a better tolerability profile compared with R-CHOP.¹⁷

Treatment outcomes and follow-up

In this case, the patient received R-COMP therapy, on the assumption that he was at high risk of cardiotoxicity if conventional doxorubicin were to be used. He received six cycles of R-COMP, with 75% of the usual dose of NPLD during cycle 1, followed by two further doses of rituximab (similar to the regimen found to be effective in elderly patients with NHL).⁵ At the end of treatment the patient achieved a complete remission, and after 30 months of follow-up remains in complete remission with an excellent performance status and a conserved quality of life.

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