Management Strategies for Elderly Patients with Diffuse Large B-Cell Lymphoma

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Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most commonly occurring form of lymphoma and most commonly presents in the sixth decade. Given the dramatic rise of the incidence of lymphoma since the late 1990s in patients who present over the age of 65, and the expected increase in the prevalence of DLBCL with the ageing population, defining appropriately tailored modern therapy for elderly DLBCL patients is an increasingly important clinical concern. Moreover, age has been one of the most important adverse prognostic features, with numerous studies associating older age with inferior outcomes. Although it has been well established that B-cell diversity decreases with age, and that the loss of diversity can be associated with clonal expansion of B-cells, it remains unknown how this or other factors contribute to the pathogenesis and poor prognosis in elderly patients with DLBCL. Furthermore, elderly patients often have more co-morbid illnesses, worse performance status, less haematologic reserve and altered pharmacokinetics related to decreased metabolism and clearance of drugs. We examine the impact of these factors on therapeutic decision-making in patients with DLBCL and explore treatment alternatives for elderly individuals. Future research is needed not only to address treatment strategies but also to define the biologic heterogeneity between younger and older patients with DLBCL, so that more rational therapeutic approaches can be investigated.

Keywords

Diffuse large B-cell lymphoma, non-Hodgkin lymphoma, elderly, treatment, cancer, lymphoma, age, therapy

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Diffuse large B-cell lymphoma (DLBCL) is the most commonly occurring form of non-Hodgkin lymphoma (NHL), accounting for approximately one-third of adult lymphomas. There was an unprecedented rise in NHL incidence (3–4 % per year) from the 1970s to the mid-1990s, comparable only to the rise in skin cancers.[1] It is estimated that there will be 70,140 new NHL cases in 2012, making NHL the seventh most common cancer.[2] DLBCL most commonly presents in the sixth decade, but there is some racial variation in the age of onset, with white Americans presenting at a mean age of 64 compared with a mean age of 54 for black patients.[3] Although there appears to be a stabilisation in the incidence of lymphoma since the late 1990s in young patients, this does not appear to be true for elderly patients, the majority of whom present over the age of 65.[4,5] The median age of the world's population is increasing, with the proportion of the US population aged ≥65 years projected to increase from 12.4 % in 2000 to 19.6 % in 2030.[6] It is expected that the prevalence of NHL will increase with the ageing population, and it is well recognised that this patient population would benefit from the most appropriate modern therapy.

Although heterogeneous, DLBCL has an aggressive natural history, with a median survival of one year in untreated patients.[7] In the majority of studies conducted before 2000, older patients were systematically considered to be poor candidates for standard therapy and were treated with less intensive regimens.[8,9] The dilemma when managing elderly patients is that, with aggressive treatment, DLBCL is curable in the majority of patients; however, providing adequate therapy to this patient population can be complicated by co-morbid conditions, decreased drug metabolism and worse performance status when compared with younger patients. Herein, we examine emerging trends in the clinical management and biology of DLBCL in the elderly patient population, and explore findings from recent meetings and publications that will aid in further defining our management of this disease.

Age, Clinical or Biologic Predictor

Age has been one of the most important adverse prognostic features in NHL. Numerous studies have associated older age with inferior outcomes.[10–13] Age, stratified at >60 years, is a component of the international prognostic index (IPI), developed in the 1990s as a clinical tool to predict outcome for patients with DLBCL.[14] In addition to age, clinical features that were predictive of overall survival (OS) and relapse-free survival were derived from a pooled analysis of more than 2,000 patients with aggressive lymphoma (mainly DLBCL) treated with an anthracycline-containing chemotherapy regimen. These factors include advanced disease stage, elevated serum lactate

dehydrogenase, poorer performance status and a number of extranodal disease sites ≥2. Patients are scored based on the presence of these clinical features and can then be risk-stratified into one of four discrete prognostic groups, with five-year predicted survival rates of 73, 51, 43 and 26 %, respectively. A more recent analysis of more than 1,000 patients treated with chemoimmunotherapy suggests that the IPI maintains its relevance in the rituximab era and remains a valid prognostic tool.[15] An alternative index, the Elderly IPI (E-IPI), with an age cut-off of 70 years rather than 60, has been reported to provide better discrimination of outcome for patients >60 years with DLBCL treated with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP).[16] These findings were recently validated when the conventional IPI and the E-IPI were compared in the RICOVER-60 data set. Both the IPI and E-IPI provided prognostic discrimination for OS; however, the E-IPI outperformed the conventional IPI.[17]

Although age is a relevant clinical predictor of outcome, is it a reflection of a patient's overall clinical status or is it related to an intrinsic biological feature of the tumour? Over the past decade, there have been significant efforts to define biologically relevant subgroups of DLBCL. Gene-expression profiling (GEP) from DNA microarrays has delineated expression patterns that reflect differences in cell of origin, proliferation rate and host immune response to the tumour.[18] DLBCL can now be subdivided using GEP into at least three molecular subtypes: activated B-cell-like (ABC), germinal center B-cell-like (GCB) and primary mediastinal large B-cell lymphoma. The ABC and GCB signatures are biologic determinants of prognosis in patients treated with chemoimmunotherapy, independent of IPI, with the GCB subtype having a significantly better five-year survival rate than ABC DLBCL (OS 60 versus 35 %, $p<0.001$).[19]

Whether there is a relationship between ageing and the distribution of these two gene expression profiles has not been clearly defined. Rosenwald et al. reported a trend towards a higher proportion of ABC subtypes in patients over the age of 60 years.[20] A retrospective analysis studied this further. GEP was performed on 131 *de novo* DLBCL patients >50 years of age (median 68 years, range 50–91) and reported a significant increase in ABC subtypes in proportion to increasing age.[21] To strengthen these results, a similar analysis was done on data accessed from the Lenz study.[22] The investigators found a similar increase in the proportion of ABC subtypes associated with age (average increase of 13.7 % in ABC for every 10 years after the age of 50, versus 7.5 % in the Lenz series).[21] In contrast to adults, children with DLBCL have excellent prognosis. Oschlies et al. found a striking predominance of GCB subtypes in 63 cases of paediatric DLBCL, which may explain their better outcomes and again suggests a relationship between DLBCL subtype distribution and age.[23]

To counter these claims, a retrospective analysis of very elderly patients (>80 years) reported that clinical and biologic characteristics of older patients with lymphoma at presentation are similar to those of younger ones, but there were significant differences in disease management.[9] No specific chromosomal or genetic abnormalities have been described in elderly patients; however, the majority of studies have been focused on defining the level of heterogeneity between different subtypes, not heterogeneity between age groups. Further speculation on the pathogenesis of poor prognosis in elderly patients with DLBCL includes the finding that B-cell diversity decreases dramatically with age, and this loss of diversity is characterised by clonal expansion of B-cells *in vivo*.[24] A well recognised predisposing risk factor for the occurrence of NHL is immunosuppression.[25] Host factors that have been implicated in this increased risk include a high prevalence of the Epstein–Barr virus (EBV) and defects in immune regulation with resultant cytokine production. EBV-related DLBCL is almost exclusively reported in the elderly, including in very old patients, and portends a poor prognosis with a median survival of two years.[26] Further study into the relationship between age and tumour biology is warranted.

Assessing Therapeutic Options

One of the challenges faced with this particular patient population are the age-related factors that must be considered when discussing treatment options with patients. It is well-known that with increasing age, the likelihood of co-morbid disease also increases. For example, in one survey, 61 % of the patients aged 70 years or older had at least one co-morbid condition, compared with 20 % of patients younger than 60 years.[27] Of particular importance is the prevalence of heart disease, which may hinder therapeutic options such as anthracyclines. Co-morbid conditions also frequently result in polypharmacy. Elderly patients may have alterations in drug absorption, distribution, metabolism and clearance, which change the pharmacodynamics of therapeutic agents, and attention to the appropriate dosing of drugs is imperative.[28] Haematopoietic reserve is also different from younger patients and myelotoxicity can be increased with standard regimens.[29]

Determining performance status, though subjective, carries prognostic implications. Assessing the degree of functional dependence and frailty in elderly patients is also important. Age and performance status are currently the most frequently used criteria to select patients for standard chemotherapy, but the final decision is generally left to the clinical judgement of the treating physician.[30] There is a large body of geriatric literature that tries to address this problem of subjectivity by designing specific comprehensive geriatric assessment scores as more effective and objective tools than clinical decision-making, but the use of such assessments has not been shown to affect OS. Because validated predictors of treatment-related toxicity in older patients have not gained widespread use, assessing the tolerability of systemic therapy in elderly patients remains complex. When possible, clinicians should use systematic approaches and objective data to make decisions about decreasing dosage or withholding potentially curative therapy in older individuals with DLBCL.[31,32]

Treatment and Outcomes in the Elderly

Developed in the 1970s, the anthracycline-based CHOP chemotherapy regimen was found to be better tolerated than, and to have similar OS to, more intensive regimens, leading CHOP to become the standard therapy for DLBCL.[33,34] Several attempts to decrease the chemotherapy doses in the standard CHOP regimen or substitute less toxic drugs in the combination for elderly patients decreased toxicity but did not improve survival.[12,35,36] An important development in the treatment of aggressive B-cell lymphomas occurred when rituximab (R) demonstrated activity in Phase II studies,[37,38] leading to the development of Phase III trials across the world comparing R-CHOP with standard CHOP. One of the earliest reports of survival benefit from the addition of R to CHOP was from the Groupe d'Étude des Lymphomes de l'Adulte, demonstrating that patients over the age of 60 years with DLBCL treated with R-CHOP had superior outcomes compared with patients treated with CHOP when both regimens were given every 21 days.[39] This study did not include patients over 80 years of age but did show a similar benefit for patients aged 60–70, 71–75 and 76–80

years.[40] The benefits of R-CHOP in older patients was confirmed by a US Intergroup trial, which randomised patients to R-CHOP-21 or CHOP-21, with a second randomisation of responders to maintenance R or observation.[41,42] The three-year failure-free survival rate was 53 % for R-CHOP patients and 46 % for CHOP patients (p=0.04) and no benefit was seen with maintenance R in the R-CHOP arm. Based on these and other data, R-CHOP has been well established as the standard induction regimen in DLBCL.

Given the improvement in outcomes with the addition of R, the German High Grade Non-Hodgkin Lymphoma Study Group explored a dose-intense regimen incorporating R based on previous data demonstrating improved outcomes in older patients treated with CHOP given every 14 days (CHOP-14).[43] The RICOVER-60 trial randomised elderly (61–80 years) patients to receive six or eight cycles of CHOP-14 with or without R. Six cycles of R-CHOP-14 significantly improved event-free survival (EFS), progression-free survival (PFS) and OS compared with six cycles of CHOP-14. In addition, there was no benefit from extending treatment to eight cycles of R-CHOP-14.[44] This established R-CHOP-14 as the preferred regimen for elderly patients in Germany. A Phase II study assessed the feasibility and efficacy of a bi-weekly regimen, R-COMP-14 (rituximab, cyclophosphamide, non-pegylated liposome-encapsulated doxorubicin, vincristine and prednisone) in elderly patients (median age 73, range 62–82) with poor-risk DLBCL who also had moderate-to-high cardiac co-morbidity.[45] Time to progression and OS at four years were 77 and 67 %, respectively. The age-adjusted Charlson Co-morbidity Index correlated with treatment failures, with patients scoring ≤7 having a longer time to treatment failure (66 versus 29 %; p=0.009). The incidence of cardiac grade 3–5 adverse events was 17 %. This demonstrates that R-COMP-14 is feasible in patients with cardiac co-morbidity, and provides an alternative for such patients.

The results of a randomised study comparing R-CHOP-14 to the standard R-CHOP-21 were presented at the American Society of Clinical Oncology conference in 2011.[46] In this trial, DLBCL patients (52 % >60 years of age) were randomised to either eight cycles of standard R-CHOP-21 or six cycles of R-CHOP-14 plus granulocyte colony-stimulating factor (G-CSF) with two additional cycles of single-agent R (similar to RICOVER-60). Overall response rates were similar between the two arms and, after a median follow-up of 37 months, PFS and OS were not significantly different. Subgroup analyses failed to identify a population of patients that benefited from the dose-dense R-CHOP. In particular, there was no benefit from R-CHOP-14 in the older age subgroup of DLBCL patients. At the 2011 American Society of Hematology meeting, Dr Pfreundschuh described a pharmacokinetically optimised schedule of R-CHOP-14 that achieves high R levels early and maintains optimal serum levels over a prolonged period of time with eight doses of R (SMARTE-R-CHOP-14).[47] This trial showed a benefit from SMARTE-R-CHOP-14 when compared with historical controls (RICOVER-60) and suggested that prior trials of R-CHOP-14 may have been compromised by the shorter exposure to R when eight applications are given every two weeks. However, randomised data are needed to determine whether pharmacokinetically optimised R-CHOP-14 may provide benefits for elderly patients over R-CHOP-21.

Important to highlight is the reference to elderly patients in these trials, which has often been defined as older than 60 years and less than 80 years of age, but limited data exist regarding the treatment of patients >80 years. The Groupe d'Étude des Lymphomes de l'Adulte has performed a prospective, multicentre, Phase II study of low-dose CHOP chemotherapy regimen and R in patients aged 80 years and older (median age 83, range 80–95) with DLBCL.[48] Patients received six cycles of R-miniCHOP (375 mg/m^2 rituximab, 400 mg/m^2 cyclophosphamide, 25 mg/m^2 doxorubicin and 1 mg vincristine on Day 1 of each cycle, and 40 mg/m^2 prednisone on Days 1–5) at three-week intervals. The intention to treat population included 149 patients. After a median follow-up of 20 months, median OS was 29 months and two-year OS was 59 %. Median PFS was 21 months, with a two-year PFS of 47 %. The majority of deaths (57 %) were secondary to lymphoma progression, 12 of 58 (21 %) deaths were attributed to treatment toxicity. The most frequent side effect was haematological toxicity (grade ≥3 neutropenia 40 %, febrile neutropenia 7 %). Prophylactic G-CSF was left to the discretion of the treating physician. However, in the event of severe neutropenia or neutropenic fever, G-CSF was recommended from Day 6–13 of the subsequent cycle or until neutrophils were ≥1.0×109/l. In a multivariate analysis, the only parameter associated with worse outcome was low serum albumin concentration. Included in the initial assessment was the instrumental activities of daily living scale. Without systematic comparison and in the absence of a control arm, this study suggests that in selected patients older than 80 years with a good performance status (0–2), R-miniCHOP offers a compromise between efficacy and safety. However, PFS and OS at two years in this trial were lower than would be expected for standard CHOP-21 in patients >60 years, thus this approach would benefit from a comparison with standard CHOP-21 in this population, given that most deaths were due to lymphoma progression.

Future Directions

Prospective studies directed at elderly patients are needed, particularly for guiding treatment decisions. A particular area of need is the relapsed or refractory setting. Younger patients who experience relapse will be evaluated for salvage therapy and high-dose therapy (HDT) with autologous stem cell transplant (ASCT). With better supportive care, consideration of HDT-ASCT in elderly DLBCL patients who are medically fit is an option.[49–51] Certain salvage therapy regimens also can be difficult to administer in this patient population; for example, platinum therapy is impractical in patients with diminished creatinine clearance. Given the limited options for elderly patients, referral to clinical trials is appropriate for many patients. Numerous small molecule inhibitors, antibodies and other approaches are under study, and these therapies may provide the advantage of minimal toxicity.[52]

Several novel agents are under investigation, many of which are rationally designed from knowledge gained from GEP analysis. Enzastaurin, a protein kinase c-beta inhibitor, has been demonstrated in a Phase II study to prolong PFS in a subset of patients,[53] and a Phase III trial incorporating this drug in first remission maintenance has been completed and is awaiting analysis. Several other pathway inhibitors have demonstrated activity in DLBCL targets and include spleen tyrosine kinase, Brutons tyrosine kinase, phosphoinositide 3-kinase and mammalian target of rapamycin. Navitoclax is a high-affinity small molecule inhibitor of the anti-apoptotic activity of BCL-2 and BCL-XL under investigation in DLBCL. Studies of aurora kinase inhibitors both as single agents and in combination are ongoing, based on the finding that aurora kinases are upregulated by c-Myc.[54] Overexpression of NF-κB is a potential target of the ABC subtype of DLBCL, and bortezomib has been used to exploit this concept.[55] Lenalidomide has shown significant activity in relapsed DLBCL, with higher responses also seen in the

non-GCB subtype.[56] As discussed, these strategies hold promise for elderly patients, as most appear to have limited toxicity or toxicity that does not overlap considerably with prior chemotherapy.

Conclusions

Although a number of retrospective analyses have been performed reporting outcomes in elderly patients, prospective data are limited. With the ageing population, the prevalence of DLCBL, particularly in elderly patients, is expected to increase. Future research is needed not only to address treatment strategies but also to define the biologic heterogeneity between younger and older patients with DLBCL, so that more rational therapeutic design can be investigated. Several issues arise when addressing worse outcomes seen with elderly patients compared with their younger counterparts. Elderly patients often have more co-morbid illnesses, worse performance status, less haematologic reserve and altered pharmacokinetics related to decreased metabolism and clearance of drugs. Clinical judgement clearly contributes to determination as to whether patients are fit for aggressive treatment. Since it is well established that aggressive chemoimmunotherapy can provide cure to elderly patients, what is needed are objective tools to identify patients who will safely benefit from aggressive therapy. Currently, there are no validated methods to prospectively identify elderly patients fit enough to receive the same treatment as younger patients. The first question that should be asked by healthcare providers is whether or not their patient can be treated with R-CHOP, as this is the current standard induction therapy for medically fit patients. For those who are not candidates for R-CHOP, prospective data support the use of R-miniCHOP or R-COMP-14 as possible alternatives. Supportive measures such as prophylaxis with G-CSF are recommended. Novel agents that are currently under investigation are promising, in that they offer a rational approach for biologically targeted therapy with the advantage of improved tolerability. Prospective studies are needed that include elderly patients (including those over the age of 80) to further guide treatment decisions. ■

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