Approach to therapy of diffuse large B-cell lymphoma in the elderly: the International Society of Geriatric Oncology (SIOG) expert position commentary

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Diffuse large B-cell lymphoma (DLBCL) is a treatable and potentially curable malignancy that is increasing in prevalence in the elderly. Until recently, older patients with this malignancy were under-represented on clinical treatment trials, so optimal therapeutic approaches for these patients were generally extrapolated from the treatment of younger patients with this disorder. Because of heightened toxicity concerns, older patients were sometimes given reduced dose therapy, potentially negatively impacting outcome. Geriatric considerations including functional status and comorbidities often were not accounted for in treatment decisions. Because of these issues as well as the lack of treatment guidelines for the elderly population, the International Society of Geriatric Oncology convened an expert panel to review DLBCL treatment in the elderly and develop consensus guidelines for therapeutic approaches in this patient population. The following treatment guidelines address initial DLBCL therapy, in both limited and advanced stage disease, as well as approaches to the relapsed and refractory patient.

Key words: large cell lymphoma, B-cell lymphoma, chemoimmunotherapy, radiation therapy, elderly, frailty

introduction

Non-Hodgkin’s lymphoma (NHL) is a common malignancy in the elderly, affecting both genders equally. Over the past two decades, NHL incidence has been increasing up to 8–10% per year, with greatest increases in patients >60 years. Although patients >65 years of age represent 13% of the population, 53% of all new NHL cases occur in this age group, with median age at diagnosis of 67 years. With the population >75 and 85 years of age tripling and doubling, respectively, by 2030, the occurrence of NHL in these patients will pose an increasing problem. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL in the elderly. Treatment with anthracycline-based chemotherapy is complicated by comorbidities and alterations in functional status in older adults. Fortunately, in the past decade, prospective clinical treatment trials in older DLBCL patients have resulted in significant therapeutic advances. An expert committee was formed under the auspices of the International Society for Geriatric Oncology (Société Internationale d’Oncologie Gériatrique, SIOG) to assess current approaches to care of elderly DLBCL patients. An electronic medical subject headings search of available literature was done through Medline using PubMed interface for clinical articles, with the following key search words: elderly, geriatrics, diffuse large cell lymphoma, chemotherapy, and radiation therapy. The review and opinions of this SIOG Task Force are those of the informed experts and a consensus of the group. No formal levels of evidence are ascribed. We will specifically address approaches to therapy in the treatment-naive and salvage settings for these patients. The topics of demographics, staging, prognosis, impact of comorbidities, role of geriatric assessment, and supportive care measures are covered in a separate manuscript.

initial therapy of DLBCL in the elderly

For decades, the standard treatment approach for DLBCL was cyclophosphamide, Adriamycin, vincristine, and prednisone (CHOP) chemotherapy [1–3]. Complete response (CR) rates were 50% in those aged 65–75 years, but 40% in those >75 years. Median remission duration was 16 months; cure rates were 50–60% in younger and 25–30% in older patients. CHOP
therapy as a standard was established based on a randomized trial comparison to other regimens (m-BACOD, Pro-MACE-CytaBOM, MACOP-B), with no significant difference in efficacy [CR rate, progression-free (PFS) and overall survival (OS)] but with a better toxicity profile [4]. The outcome of older patients receiving full-dose anthracycline-based chemotherapy was similar to younger patients; more toxicities, as well as a higher death rate from intercurrent illnesses, was noted in some reports [5–11]. The feasibility of delivering full-dose CHOP therapy to elderly patients with myeloid growth factor support was demonstrated [12–14]. Subsequent prospective randomized trials examined the role of anthracyclines, etoposide, and alternative CHOP dosing for older patients receiving non-rituximab-containing regimens, as well as dose-dense biweekly CHOP (CHOP-14) [15–19] (Table 1). Initially, patients were randomized to CHOP-14 versus CHOP-21 (CR, 70% versus 60%, respectively), then later to CHOEP-14 (CHOP plus etoposide) or CHOEP-21 (CR, 72% versus 76%, respectively). These trials demonstrated the importance of anthracyclines, as well as greater toxicity with etoposide.

In the past decade, initial therapy with R-CHOP for older DLBCL patients, as well as younger with favorable prognostic characteristics, was established as standard of care (Table 2) [20–26]. In the Groupe d’Etude des Lymphomes de l’Adulte (GELA) trial, treatment-naive DLBCL patients, age 60–80 years, were randomized to R-CHOP (rituximab on day 1 each cycle) or CHOP therapy, with CR rates of 76% and 63% (P = 0.005), 10-year PFS of 36.5% and 20%, and 10-year OS of 43.5% and 27.6%, respectively [20–22]. Eight cycles of R-CHOP/CHOP therapy were administered to 80% and 72% of patients, respectively. Deaths due to other causes, secondary malignancies, and late relapses were comparable among the two groups.

The benefit of R-CHOP therapy was also demonstrated in the US intergroup trial, in which two rituximab doses were given before cycle 1, with a single dose before cycles 3, 5, and 7 [23]. Responding patients [CR, partial response (PR)] had a secondary randomization to maintenance rituximab (weekly for 4 weeks, repeated every 6 months for 2 years) or observation. Overall response rate (ORR) to induction therapy was comparable (R-CHOP, 77%; CHOP, 76%). With median follow-up of 9.4 years, the 9-year failure-free survival (FFS) was 35% (R-CHOP) and 25% (CHOP) (P = 0.008) [24]. Maintenance rituximab resulted in prolonged FFS following CHOP (P = 0.003), but any benefit was abrogated when R-CHOP was used for induction (P = 0.79). Ultimately, maintenance rituximab had no significant impact on OS (9-year OS: R-CHOP, 44%; CHOP, 37%, P = 0.11). With CHOP induction, median time to treatment failure (TTF) was 9.5 years with maintenance rituximab and 2.0 years with observation (P = 0.003). However, with R-CHOP induction, median TTF was comparable with maintenance rituximab or observation (8.5 and 7.5 years, respectively, P = 0.79). In this trial, 79% of patients received at least six cycles of induction therapy.

The RICOVER-60 trial examined patients aged 61–80 years, who were randomized to six or eight cycles of CHOP-14 or CHOP-R-14, with CR rates after six cycles of 68% and 78%, respectively [27]. With median follow-up of 35 months, 3-year event-free survival (EFS) was 47% and 67%, respectively. Improvements were also seen in PFS (CHOP-14, 56.9%; R-CHOP-14, 73.4%, P = 0.0001) and OS (CHOP-14, 67.7%; R-CHOP-14, 78.1%, P = 0.0181). Median relative doses of myelosuppressive agents received was at least 95%. Outcome was not better with eight, versus six, treatment cycles. When CHOP-14 patients were stratified into high-risk [age ≥75 years and performance status (PS) ≥3] and standard-risk (age 60–75 years and PS <3, or age <60 years) subgroups, frequency of hospitalization was greater in the high-risk group (88% versus 68%), mainly due to infection, malnutrition, and declining PS [30].

The issue of central nervous system (CNS) relapse was examined in the RICOVER-60 trial [31]. CNS prophylaxis (intrathecal methotrexate on days 1 and 5 of the first two cycles) was utilized for patients with involvement of bone marrow, testes, upper neck, or head. Involvement of >1 extranodal site and B symptoms were significant risk factors for CNS disease. However, with the addition of rituximab, the relative rate of CNS disease was reduced.

### Table 1. Randomized trials in older patients: pre-rituximab era

<table>
<thead>
<tr>
<th>Reference</th>
<th>Therapy (n)</th>
<th>Age (median)</th>
<th>PS</th>
<th>CR (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer [15]</td>
<td>CHOP n = 38, age ≥65 years (71)</td>
<td>PS 2.3–50%</td>
<td>68%</td>
<td>2-year PFS 2-year OS</td>
<td></td>
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<tr>
<td></td>
<td>Chop</td>
<td>PS 2.3–50%</td>
<td>74%</td>
<td>57%</td>
<td>74%</td>
</tr>
<tr>
<td>Sonneveld [16]</td>
<td>CHOP n = 148, age ≥60 years (71)</td>
<td>PS 2.3–18%</td>
<td>49%</td>
<td>3-year DFS 3-year OS</td>
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<tr>
<td></td>
<td>CNOP</td>
<td>PS 2.3–18%</td>
<td>31%</td>
<td>17%</td>
<td>42%</td>
</tr>
<tr>
<td>Bastion [17]</td>
<td>CVP n = 453, age ≥69 years (75)</td>
<td>PS ≥2–31%</td>
<td>33%</td>
<td>5-year OS (median, 13 months)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVP + pirarubicin</td>
<td>PS ≥2–31%</td>
<td>48%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Tirelli [18]</td>
<td>CHOP n = 120, age ≥70 years (75)</td>
<td>PS 2.3–42%</td>
<td>45%</td>
<td>2-year PFS 2-year OS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VMP</td>
<td>PS 2.3–42%</td>
<td>27%</td>
<td>55%</td>
<td>65%</td>
</tr>
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</table>

PS, performance status; CR, complete response; OS, overall survival.
and intrathecal prophylaxis was not beneficial except for those with testicular involvement. In another report, intrathecal prophylaxis alone was inadequate for high-risk patients, and systemic high-dose methotrexate was recommended [32]. Although dose-dense therapy appeared beneficial, a direct comparison of R-CHOP-21 and R-CHOP-14 was necessary to confirm any potential benefit in the rituximab era [28, 29].

The GELA trial included patients aged 60–80 years with at least one other adverse prognostic factor [28]. With median follow-up of 56 months, 3-year PFS did not differ by treatment (R-CHOP14, 60%; R-CHOP21, 62%, \(P = 0.04\)), nor did 3-year OS (69% and 72%, respectively, \(P = 0.7487\)); side-effects were comparable. In another trial in which patients aged 18–88 years (56%, >60 years) were enrolled, no efficacy differences were seen (2-year OS 83% with R-CHOP-14, 81% with R-CHOP-21) [29]. With R-CHOP-14, grade 3/4 thrombocytopenia, febrile neutropenia, and infection were more common.

Alternative approaches to R-CHOP-21 for more frail elderly patients have been examined in phase II trials (Table 3) [33–42]. Alternative regimens studied include: liposomal doxorubicin; R-mini-CHOP; a dose-adjusted infusional regime (DA-POCH-R); induction R-CNOP or R-CVP for three cycles, followed by maintenance rituximab in responders; substitution of gemcitabine for anthracycline in a R-CHOP-like regimen; vinorelbine plus prednisone; COP [33–38, 41, 42]. Bendamustine-rituximab (BR) has been examined in small series [39, 40]. An ORR of 69% (CR 54%) to BR with favorable toxicity profile was demonstrated in very elderly patients [39]. Another retrospective study examined BR as an alternative to R-CHOP in unfit DLBCL patients [40].

<table>
<thead>
<tr>
<th>Reference</th>
<th>Therapy (n)</th>
<th>Median age, years (range)</th>
<th>% patients ECOG PS-2</th>
<th>Efficacy</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Coiffier [20–22]</td>
<td>CHOP versus R-CHOP (21-day cycle) (n = 399)</td>
<td>69 (60–80)</td>
<td>20%</td>
<td>CR rate</td>
<td>76% 63% 0.005</td>
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<td>10-year PFS</td>
<td>37% 20% &lt;0.0001</td>
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<td>10-year OS</td>
<td>44% 28% &lt;0.0001</td>
</tr>
<tr>
<td>PfleischhauSch [27]</td>
<td>CHOP versus R-CHOP (14-day cycles); 6 versus 8 cycles (n = 1222)</td>
<td>68 (61–80)</td>
<td>14%</td>
<td>CR rate (6 cycles)</td>
<td>78% 68% 0.007</td>
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<td>3-year PFS</td>
<td>73% 57% 0.0001</td>
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<td>3-year OS</td>
<td>78% 68% 0.018</td>
</tr>
<tr>
<td>Habermann [23, 24]</td>
<td>CHOP versus R-CHOP (21-day cycle); responders randomized to maintenance rituximab versus observation (n = 632)</td>
<td>69 (60–92)</td>
<td>15%</td>
<td>Overall response rate</td>
<td>77% 76% NS</td>
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<td>9-year FFS</td>
<td>35% 25% 0.008</td>
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<td>9-year OS</td>
<td>44% 37% 0.11</td>
</tr>
<tr>
<td>Delarue [28]</td>
<td>R-CHOP-21 versus R-CHOP-14 (8 cycles) (n = 602)</td>
<td>70 (60–80)</td>
<td>22%</td>
<td>Overall response rate (CR rate)</td>
<td>86% (74%) R-CHOP-21 R-CHOP-14 NS</td>
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<td>3-year EFS</td>
<td>60% 56% NS</td>
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<td>3-year PFS</td>
<td>62% 60% NS</td>
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<td></td>
<td></td>
<td>3-year OS</td>
<td>72% 69% NS</td>
</tr>
<tr>
<td>Cunningham [29]</td>
<td>R-CHOP-21 versus R-CHOP-14 (8 cycles) (n = 1080)</td>
<td>61 (19–88)</td>
<td>13%</td>
<td>Overall response rate (CR rate)</td>
<td>88% (63%) R-CHOP-21 R-CHOP-14 NS</td>
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<td></td>
<td></td>
<td>2-year PFS</td>
<td>75% 75% NS</td>
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<td>2-year OS</td>
<td>81% 83% NS</td>
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</table>

PS, performance status; CR, complete response; EFS, event-free survival; FFS, failure-free survival; PFS, progression-free survival; OS, overall survival.
Initial ‘pre-phase treatment’ with prednisone for 7 days, alone or with a 1 mg dose of vincristine, may be considered for DLBCL patients of all ages, but especially for the more frail elderly [43]. An alternative pre-phase option is oral cyclophosphamide (400 mg on days 1, 3, 5). Its use decreases first cycle effects of deep neutrophil nadir, longer neutropenia duration, tumor lysis, and therapy-associated deaths with R-CHOP-based therapy. The benefit of pre-phase treatment should be weighed against pre-existing comorbidities such as diabetes.

In summary, six cycles of R-CHOP-21 therapy should be offered to fit older patients, with appropriate supportive care measures. In large phase III trials, it has been demonstrated that the majority of elderly patients are able to receive full-dose therapy. As patients with more favorable performance status were enrolled on to these trials, selection bias does exist. The use of geriatric assessment tools will be important in evaluating older/frail patients and choosing appropriate therapies. For very elderly (>80 years) patients or those unfit for R-CHOP-21, phase II study alternative regimens demonstrate efficacy and tolerability. Such treatment, accompanied by supportive measures and frequent toxicity monitoring, can be more than palliative and add meaningful quality/quantity of life. The introduction of novel therapeutic agents (lenalidomide, ibrutinib, idelalisib) may be especially applicable for the older/frail population, in terms of tolerability and improving outcome.

### the role of radiation therapy in limited stage disease or bulky disease

Approximately 25%–30% of DLBCL patients will present with limited stage disease, defined as stage I or non-bulky stage II (<10 cm in greatest diameter) [44]. With involved field radiation therapy (IFRT), although CR rates approached 90%, 5-year disease-free survival (DFS) for stage I and II disease was 50% and 20%, respectively, with relapses common outside the

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**Table 3. First-line therapy for DLBCL in older patients: alternative regimens from phase II trials**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Therapy (n)</th>
<th>Median age, years (range)</th>
<th>% patients ECOG-PS ≥2</th>
<th>Efficacy</th>
<th>Reasons for non-CHOP therapy</th>
</tr>
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<tbody>
<tr>
<td>Visani [33]</td>
<td>R-COMP-21 (20)</td>
<td>73 (61–82)</td>
<td>45%</td>
<td>ORR 90%</td>
<td>CR 65%</td>
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<td>Cardiac issues frailty</td>
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<tr>
<td>Corazzelli [34]</td>
<td>R-COMP-14 (41)</td>
<td>73 (62–82)</td>
<td>32%</td>
<td>ORR 73%</td>
<td>CR 68%</td>
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<td>Cardiac issues frailty</td>
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<tr>
<td>Peyrade [35]</td>
<td>R-mini-CHOP-21 (150)</td>
<td>83 (80–95)</td>
<td>34%</td>
<td>ORR 73%</td>
<td>CR 62%</td>
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<td>Age ≥80 years</td>
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<tr>
<td>Musolino [36]</td>
<td>DA-POCH-R (23)</td>
<td>77 (70–90)</td>
<td>74%</td>
<td>ORR 90%</td>
<td>CR 57%</td>
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<td>3-year EFS 54%</td>
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<td>3-year OS 56%</td>
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<tr>
<td>Hainsworth [37]</td>
<td>R-CN0P or R-CVP,</td>
<td>78 (61–90)</td>
<td>37%</td>
<td>ORR 61%</td>
<td>CR 39%</td>
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<tr>
<td></td>
<td>with maintenance rituximab (51)</td>
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<td>2-year PFS 50%</td>
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<td></td>
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<td></td>
<td>2-year OS 56%</td>
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<tr>
<td>Fields [38]</td>
<td>R-GCVP (62)</td>
<td>77 (52–90)</td>
<td>50%</td>
<td>ORR 69%</td>
<td>CR 54%</td>
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<td>Median PFS 8 months</td>
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<td>Median OS 8 months</td>
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<tr>
<td>Weidmann [39]</td>
<td>BR (14)</td>
<td>85 (85–90)</td>
<td>29%</td>
<td>ORR 61%</td>
<td>CR 38%</td>
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<td>Median PFS 6 months</td>
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<td>Median OS 9 months</td>
</tr>
<tr>
<td>Walter [40]</td>
<td>BR (15)</td>
<td>79 (68–92)</td>
<td>33%</td>
<td>ORR 69%</td>
<td>CR 54%</td>
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<td>Median PFS 8 months</td>
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<td>Median OS 8 months</td>
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</table>

PS, performance status; ORR, response rate; CR, complete response; DFS, disease-free survival; EFS, event-free survival; PFS, progression-free-survival; OS, overall survival.
radiation field and in extranodal sites [45–49]. At present, sole use of IFRT may be considered for patients unfit for chemotherapy.

**trials in the pre-rituximab era**

In Southwest Oncology Group (SWOG) trial 8736, 400 patients, median age 59 years, with stage I (68% of patients), IE, or non-bulky stage II, IIE disease were randomized to eight cycles of CHOP or three cycles of CHOP followed by IFRT [50]. With initial 5-year follow-up, the combined modality arm was more favorable than CHOP alone (5-year PFS, 77% and 64%, \( P = 0.03 \); 5-year OS 82% and 72%, \( P = 0.02 \), respectively). However, at 7-year follow-up, the curves overlapped for PFS, and overlapped for OS at 9 years, due to lymphoma relapses from years 5 to 10 in the CHOP-IFRT group [51]. Adverse risk factors were stage II disease, elevated LDH, PS 2, and age >60 years. Five-year OS was 95%, 77%, and 50%, for 0, 1–2, or 3 risk factors, respectively (\( P = 0.01 \)). Five-year OS in bulky stage II disease patients (49%) was similar to that of advanced stage patients, supporting similar treatment approaches. In the Miller modification of the International Prognostic Index (IPI), stage II/IIE disease replaced advanced stage disease in the IPI [52]. In a retrospective review, 308 patients, median age 64 years, with stage I (61%) or non-bulky IIA disease received three cycles of doxorubicin-based chemotherapy followed by IFRT [53]. Outcomes were similar to SWOG 8736, with 5- and 10-year PFS of 94%/89% (no risk factors), 79%/73% (1–2 factors), and 60%/50% (3–4 factors), using the Miller-modified IPI. Corresponding OS was 97%/89% (no factors), 77%/56% (1–2 factors), and 58%/48% (3–4 factors).

The impact of IFRT consolidation following chemotherapy has been examined [54–56]. In ECOG 1484, eight cycles of CHOP was followed by observation (\( n = 179 \)) or consolidative IFRT (\( n = 173 \)) with CR (\( n = 219; 61\% \)) or PR (\( n = 98; 28\% \)); all PR patients received IFRT [54]. Although 31% of PR patients converted to CR following IFRT, this did not impact relapse rate (47% for PR, 46% with PR converted to CR) or survival (6-year DFS 63%, 6-year OS 69%). Comparing CR patients with CHOP alone to those in CR with IFRT, 6-year DFS was 56% and 73%, \( (P = 0.05) \), and 5-year OS was 73% and 73% (\( P = 0.24 \)), respectively, with no difference in 10- or 15-year OS. In another series of patients age >70 years with stage IA/contiguous IIA non-bulky disease, three cycles of reduced intensity CHOP (80%) followed by IFRT resulted in 3-year PFS and OS of 83% [56]. In GELA trial LNH-93–4, good risk patients (60–80 years of age, 95% with age-adjusted IPI of 0, 65% stage I, 35% stage II) were randomized to four cycles of CHOP alone, or followed by IFRT, with no differences in toxicities or 5-year EFS and OS with CHOP ×4 versus CHOP ×4 + IFRT (61% and 64%, \( P = 0.6; 72\% \), and 68%, \( P > 0.05 \), respectively) [56]. Relapse patterns also varied between CHOP ×4 (47% exclusively initial disease site; 16% local and distant sites; 37% exclusively distant) and CHOP ×4 + IFRT (21%, 13%, and 66%, respectively).

**trials in the rituximab era**

Subsequent phase II SWOG trials sought to improve upon CHOP ×3 + IFRT, with a primary survival end point. In SWOG 0014, 60 patients (median age 69 years, 57% stage I disease, stage-modified IPI 1 in 70%) with ≥1 adverse risk factor received CHOP ×3 + IFRT, plus four doses of rituximab [57]. With median follow-up of 5.3 years, 2- and 4-year PFS and OS were 93% and 88%, 95% and 92%, respectively. Two subsequent trials examined the role of yttrium-90 ibritumomab tiuxetan (zevalin) consolidation. In SWOG 0313, 44 patients (median age 61 years, 48% stage I disease; stage-modified IPI of 1 (66%), 2 (25%), three (9%)) received CHOP ×3, followed by IFRT and ibritumomab tiuxetan consolidation [58]. Grade 3/4 neutropenia occurred in 30%, with 8% grade 3 febrile neutropenia. With 2-year median follow-up, 2-year PFS and OS were 92% and 95%, respectively. In ECOG 3402, four to six cycles of R-CHOP was followed by ibritumomab tiuxetan consolidation, and by IFRT if residual disease was present, with final results pending.

IFRT should be considered for improved in-field control and EFS for any stage bulky disease (≥10 cm) patients with equivocal positron emission tomography (PET) scan findings after chemotherapy [59–62]. The role of IFRT to bulky disease sites in elderly patients (age 61–80 years) was recently reported from the RICOVER-60 trial [63]. Patients receiving six cycles of R-CHOP, followed by two additional rituximab doses, then IFRT to sites of initial bulky (≥7.5 cm) disease and extralymphatic involvement, were compared with those who received therapy without IFRT. EFS was superior with IFRT (\( P = 0.005 \)); there were trends for superior PFS and OS in those receiving IFRT. The use of IFRT thus abrogated bulky disease as a risk factor. In an ongoing trial, the role of IFRT is being examined in older DLBCL patients who have a negative PET scan after induction therapy (OPTIMAL >60 trial).

In a retrospective review of 469 patients (40% stage I–II, 60% stage III–IV) who received IFRT after R-CHOP, 5-year PFS (90% versus 75%) and OS (91% versus 83%) were superior with IFRT [64]. In limited stage patients, 5-year PFS and OS were 82% and 92%, respectively, with R-CHOP followed by IFRT, compared with 68% and 73%, respectively, with R-CHOP alone. In a SEER-based review of 13 000 limited stage patients of whom 41% received radiation therapy, improvement in DFS and OS was seen [65].

The role of PET scans was examined in 65 patients, median age 67 years, with non-bulky stage I (58%) or II disease who underwent PET scan after three cycles of R-CHOP [66]. A fourth cycle of R-CHOP was given to 48 (74%) PET-negative patients; 17 (26%) PET+ patients received IFRT. With median follow-up of 17 months, only one PET-negative patient relapsed and 2-year DFS and OS was 97%. In contrast, 3 of 17 PET+ patients relapsed (all outside the radiation field), with 2-year DFS/OS of 83%/76%, respectively. This group also retrospectively examined the impact of IFRT compared with involved node RT (INRT; radiation to prechemotherapy involved nodes with margins ≤5 cm) [67]. From 1981 to 2007, 288 limited stage (stage I, II, no B symptoms, bulk <10 cm) patients received three cycles of chemotherapy followed by IFRT (1981–1996) (\( n = 138; 48\% \)) or INRT (1996–2007) (\( n = 150; 52\% \)); 56% were >60 years of age, 34% had stage II and 55% extranodal, disease, and 15% received rituximab. With median follow-up of 117 (IFRT) and 89 (INRT) months, there was no difference in time to progression (TTP), PFS, or OS. The most common site of failure was distant relapse. Thus, reducing the radiation field size resulted in low marginal recurrence risk with no impact on outcome.
In summary, the use of IFRT improves local disease control and reduces relapses at original disease sites. There appears to be no excess therapy-related myelodysplasia. Second malignancy risk in the radiation field is 11–15%, but decreases with advancing age [68–72]. Although the role for IFRT in advanced stage disease patients remains controversial, recent data suggest that it may be beneficial in older patients with bulky disease. Data from an ongoing prospective trial examining the role of IFRT in patients with PET-negative disease will be of interest in potentially resolving this controversy.

**Maintenance therapy**

With the utility of maintenance therapy in indolent NHL, its potential role in DLBCL has been examined. Maintenance interferon alfa 2b therapy was examined in 223 DLBCL patients, half >65 years of age, with high- (80%) or high-intermediate (20%) risk disease who achieved a CR to CHOP-bleomycin therapy [73]. Patients were randomized to maintenance interferon (5 million units, three times weekly for a year) or observation. With median follow-up of 45 months, no advantage to maintenance interferon was seen, with estimated 5-year EFS and OS of 71% and 54%, respectively, compared with 69% and 54% in those observed (P = 0.2). In a subsequent study, 169 DLBCL patients with high-intermediate or high-risk disease who achieved a CR to induction therapy were randomized to maintenance interferon alfa 2b, cyclophosphamide, and prednisone, or to observation [74]. No advantage in 5-year EFS and OS was found (71% and 84% with maintenance, 63% and 83% with observation, respectively, P = 0.2).

The utility of maintenance rituximab was examined in the US intergroup trial, with 632 patients ≥60 years of age randomized to induction CHOP or R-CHOP therapy [23]. The 451 induction therapy responders (CR, PR) were then randomized to maintenance rituximab (weekly for 4 weeks, every 6 months for 2 years) or observation. With median follow-up from the induction and maintenance randomizations of 9.4 and 9.0 years, respectively, 9-year EFS and OS by induction therapy were 35% and 44% with R-CHOP, and 25% and 37% with CHOP, respectively [24]. Overall, maintenance rituximab resulted in prolonged EFS (P = 0.014), but not OS. Maintenance rituximab prolonged EFS after CHOP (P = 0.003), but not after R-CHOP induction, and had no impact on OS. Median time to failure (TTF) for CHOP plus maintenance rituximab and CHOP observation was 9.5 and 2.0 years, respectively. With R-CHOP induction, median TTF was similar with maintenance rituximab or observation (8.5 and 7.5 years, respectively). In a retrospective study of 228 patients who received maintenance rituximab (monthly for a year, then every 3 months for another year) following R-CHOP induction, PFS was improved in all IPI subgroups [75]. In another trial, maintenance rituximab (weekly for 4 weeks, every 6 months for 2 years) was given to 51 elderly (median age 78 years) patients with no disease progression following three cycles of induction R-CNOP or R-CVP therapy [37]. With 4-year median follow-up, 2-year PFS and OS were 71% and 72%, respectively.

However, preliminary data from a phase III multicenter trial raises the issue that maintenance rituximab may benefit certain subgroups [76]. The 683 treatment-naive patients who achieved a CR to induction R-CHOP-like therapy were randomized to maintenance rituximab (one dose every 2 months for 2 years) or observation. Both EFS and PFS were superior in male patients receiving maintenance rituximab, especially those with IPI <1.

In summary, there is presently no proven role for maintenance therapy in DLBCL induction therapy responders. However, there may potentially be select subgroups (very elderly/frail, those not receiving full-dose standard induction therapy, possibly males with IPI <1) in which maintenance rituximab may confer benefit.

**Management of relapsed and refractory DLBCL in the older patient**

Despite improvements in survival of older DLBCL patients treated with chemoimmunotherapy, 30%–40% of patients will have relapsed/refractory disease [20]. The majority of relapses occur in the first 2 years following initial therapy, with 10% having primary refractory disease. Suspected relapses should be biopsy-confirmed, to rule-out alternative histologies, second neoplasms, or inflammatory processes. Patients should have complete restaging, including functional imaging with PET scans [77]. If clinical suspicion of CNS involvement, imaging and lumbar puncture with cytology and flow cytometry should be carried out. The second-line age-adjusted IPI [lactate dehydrogenase (LDH), stage, PS] is predictive of outcome at relapse [78].

Patients with disease failing to respond to initial therapy can be categorized into three groups: (i) primary refractory disease with <50% reduction in lesions or new lesions during induction, (ii) PR with >50% reduction but persistent disease postinduction, and (iii) relapsed disease occurring after achieving a CR [79]. Primary refractory disease has a poor outcome with infrequent benefit from salvage regimens. Some partial responders may be appropriate for non-cross-resistant second-line therapy (SLT) with high dose therapy and autologous stem-cell rescue (HDT/ASCR) consolidation. Relapsed patients have the best outcomes, especially if remission duration is >12 months. Disease biology is also predictive of outcome, as relapsed DLBCL in the elderly is increasingly associated with non-germinal center (ABC phenotype) biology with inferior outcomes [21, 80–85]. In the French LNH 98–5 trial, relapsed patients had 2-year OS of 26% with median OS <9 months [21]. Late relapers with no prior rituximab had improved outcome with rituximab-containing salvage regimens.

For many relapsed/refractory older DLBCL patients, care goals shift from curative intent to disease control, symptom palliation, and quality of life. A minority may be suitable for more intensive SLT with HDT/ASCR.

**Relapsed and refractory disease: the role of HDT/ASCR**

There is a paucity of data concerning HDT/ASCR in older patients. Younger patients with relapsed/refractory disease typically receive platinum-based salvage therapy (R-ICE, R-DHAP) and if chemosensitivity is demonstrated, consolidation with HDT/ASCR [80, 86]. Decisions regarding feasibility of HDT/ASCR in older patients are increasingly based on ‘biologic age’ assessment. Comorbidity risk scoring, assessment of IADLs,
and comprehensive geriatric assessment (CGA) are useful tools, helping to define transplant-related mortality (TRM) as well as overall treatment risk [87–93]. Assessment of cardiac and pulmonary function is essential to identify potential HDT/ASCR candidates before initiating intensive SLT, as well as critical review of psychosocial support networks, and early referral to a transplant center.

Despite advances in supportive care during HDT/ASCR, relapse risk and non-relapse mortality (NRM) is higher in older patients. A CIBMTR review of older (>55 years) agressive lymphoma transplant patients identified 5-year TRM rates of 15% and relapse rates of 66% (DFS, 19%; OS, 30%) [94]. In a retrospective review of 463 DLBCL patients ≥60 years of age at transplant, the EBMT reported a TRM 1.6 times that of younger patients; comparable data from the CIBMTR registry found TRM 1.86 times that of younger patients [94, 95]. In a smaller series, 35% non-relapse mortality in patients aged ≥70 years, compared with 8% in patients aged 65–69 years, was reported [96]. For the select older patients considered fit for HDT/ASCR, there is no clear standard SLT. Rituximab is generally included given potential improvement in response rates [97, 98]. The Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study demonstrated equivalent outcomes and response rates (ORR 63%) with both R-ICE and R-DHAP [80]. Considerations for renal toxicity with cisplatin and neurotoxicity with ifosfamide, both age-dependent, may guide therapeutic choice. Alternative second-line regimens incorporating gemcitabine or oxaliplatin have been reported in phase II studies [99–101]. If chemosensitivity to SLT is not achieved, outcomes are poor and clinical trial consideration or supportive care are appropriate [102]. In the few reported small series of older individuals >70 years undergoing HDT/ASCR, outcomes suggest long-term disease control (>1 year) in 48%–59% [103, 104]. In the seminal CORAL study (median 54–55, range 19–65 years), 3-year PFS and OS are 37% and 49%, respectively [80]. However, most relapses occur following a rituximab-containing induction and within 12 months of last treatment. This very group, by intent-to-treat analysis in the CORAL study, has 3-year PFS of only 23%, with similar data from EBMT registry assessment [105].

**non-transplant approaches for relapsed/refractory DLBCL**

For patients not candidates for intensive salvage therapy, including most >70 years of age, front-line therapy represents the only chance for cure. At relapse, palliative therapy is instituted for disease control, with no standard regimen established and durable remissions uncommon. In general, if transplant is not a consideration, R-ICE/R-DHAP should not be administered, given toxicity. Potential therapeutic options include best supportive care, single-agent therapy, and consideration for clinical trials. Although single-agent rituximab has modest activity at best, including it in salvage regimens may improve outcome. Relapsed GELA study patients treated with rituximab-containing salvage regimens had 2-year survival of 58%, versus 24% without rituximab ($P = 0.00067$) [21]. This benefit, however, was limited to rituximab-naïve patients; rituximab may have limited utility in patients relapsing <6 months from their last rituximab exposure.

### Table 4. Representative guidelines appropriate for consideration in the care of the older lymphoma patient

<table>
<thead>
<tr>
<th>Organization</th>
<th>Guideline</th>
<th>Website</th>
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<tr>
<td>ASCO</td>
<td>ASCO Provisional Clinical Opinion: The Integration of Palliative Care into Standard Oncology Care</td>
<td><a href="http://www.asco.org/quality-guidelines/asco-provisional-clinical-opinion-integration-palliative-care-standard-oncology-care">http://www.asco.org/quality-guidelines/asco-provisional-clinical-opinion-integration-palliative-care-standard-oncology-care</a></td>
</tr>
<tr>
<td>NCCN</td>
<td>Senior Adult Oncology</td>
<td><a href="http://www.nccn.org/professionals/physician_gls/pdf/senior.pdf">http://www.nccn.org/professionals/physician_gls/pdf/senior.pdf</a></td>
</tr>
<tr>
<td>SIOG</td>
<td>International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency</td>
<td><a href="http://siog.org/index.php?option=com_content&amp;view=article&amp;id=1478&amp;Itemid=92">http://siog.org/index.php?option=com_content&amp;view=article&amp;id=1478&amp;Itemid=92</a></td>
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A number of well-tolerated combinations regimens are often employed for disease control, including CEPP(B), gemcitabine-based therapy (R-Gem-Ox), bendamustine, and CVP +/- rituximab [106–127]. In a small phase II study of bendamustine therapy for relapsed/refractory DLBCL patients, ORR was 44% (CR, 17%) [114]. With BR therapy, ORR was 51% (CR, 15%) [113]. In another BR trial in pretreated DLBCL patients, ORR in patients ≥65 years of age was 62% (CR, 38%) [115]. Several oral regimens utilize single-agent etoposide given continuously, and low-dose ‘metronomic therapy’ with prednisone, etoposide, procarbazine, cyclophosphamide (PEP-C) [116, 117]. Lenalidomide has activity with 33% ORR and 10.2-month median response duration [118–121]. The regimen choice is determined by prior therapy and toxicity expectations based on comorbidity and functional reserves. Radiation therapy to sites of symptomatic disease, as well as corticosteroids, can be effective for symptom palliation. Supportive care, palliative care, and treatment guidelines currently exist from organizations as SIOG, ASCO, and NCCN which are germane to the older lymphoma patient (Table 4).

conclusions
Significant advances in the initial therapy of elderly DLBCL patients have been made over the past decade with prospective randomized trial data. Alternative regimens may be considered for those unable to tolerate R-CHOP due to comorbidities or frailty. There is presently no clear-cut role for maintenance therapy of DLBCL. In the relapse setting, select elderly patients may be candidates for high-dose treatment approaches, and palliative treatment approaches should be considered for those unable to tolerate such therapy. With the evolution of novel agents and future treatment trials in the elderly, it is anticipated that continued advances will be made in the care of this patient population.

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references


