

Aggressive lymphoma - Section 3

Treatment of aggressive lymphomas focused on elderly patients

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Take-home messages

- Elderly patients present more often with known risk factors and DLBCL subtypes associated with poor prognosis
- Severity of frank pathologic dysfunction and comorbidity increase with age and many chemotherapies cannot be given at dose intensities possible in young patients, thus further worsening the outcome of elderly DLBCL patients.
- Curative treatment should be pursued for the majority of elderly patients with special emphasis on supportive measures.

Abstract

Elderly patients are often diagnosed with more aggressive diffuse large B-cell lymphoma (DLBCL) subtypes and present with more clinical risk factors than younger patients. Comorbidities and organ dysfunctions often prohibit the consequent adherence to standard immunochemotherapy regimens. Specific supportive measures, however, can improve the tolerability for intensive treatments and increase the cure rates of elderly patients with DLBCL.

Introduction

Age is the most prominent factor for survival after the diagnosis of lymphoma and is recognized in the International Prognostic Index for diffuse large B-cell lymphoma (DLBCL). Though 60 years is the cut-off point in IPI, the cut-off point between young and elderly patients in prospective trials is usually set between 60 and 65 years, even though the more clinically relevant breakpoint is closer to 75 years, where comorbidity, dependency and geriatric symptoms become more prevalent. Elderly patients present more often with other commonly accepted risk factors like advanced stage, multiple extralymphatic sites of involvement, elevated LDH and poor performance status. Moreover, the morphologically defined immunoblastic variant which is associated with a poor prognosis is also more frequent in elderly patients as are the prognostically inferior DLBCL cases derived from activated B-cells (ABC subtype) in contrast to the GC (germinal center) cell-derived DLBCL. Moreover, BCL-2 expression, and cytogenetic complexity increase with age at diagnosis, and EBV+

DLBCL, an EBV+ clonal B-cell lymphoid proliferation with poor prognosis rarely occurs in patients <50 years.¹

Diagnosis and staging: Because aggressive lymphoma is life-limiting also for elderly patients, but at the same time is curable in a significant proportion of elderly and very old patients, the guidelines developed for younger patients regarding diagnosis and staging of DLBCL must be consequently adhered to,² except in patients with a clearly palliative situation.

General treatment approach

Severity of frank pathologic dysfunction or comorbidity increases with age. The association between comorbidity and survival was demonstrated by Charlson³ who showed that comorbidities are independent predictors of survival. Therefore, a basic geriatric screening is indicated in all patients >70 year old. Comorbidities and polymedications for the treatment thereof can further compromise the tolerability of therapy. The hematopoietic reserve is often reduced and a decrease in liver function can alter the metabolism of many drugs in elderly patients. Many older patients have a decreased glomerular filtration rate and a delay in drug excretion, necessitating adaption of cytotoxic drugs to creatinine clearance. The physiological increase of body fat and reduction in lean body mass also contribute to an increased toxicity. Many elderly patients have a reduced emotional tolerance to stress and need closer guidance in order to maintain treatment compliance, in particular with oral anti-cancer drugs. All these facts explain why many chemotherapies cannot be given to elderly patients at doses and treatment intervals for young patients thus compromising the responses of and worsening the outcome of elderly DLBCL patients.



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Specific measures

Of particular importance are specific supportive measures for elderly patients. All elderly patients should receive prednisone 100 mg p.o. for several days (depending on the tumor load) as a “prephase” treatment to avoid tumor lysis syndrome and ameliorate the side effects of the first chemotherapy cycle which has the most pronounced myelotoxicity and is associated with the highest treatment-related death rate. Dose reductions due to hematological toxicity should be avoided, and hematopoietic growth factors should be given to all elderly patients starting with the first CHOP. In addition to floxazines during days of severe neutropenia, anti-infective prophylaxis with acyclovir is recommended which significantly reduced the rate of severe infections and treatment-related deaths of elderly DLBCL in an ongoing trial of the DSHNHL (Figure 1).⁴ Finally, patients with severe fatigue between treatment cycles after tapering of prednisone should receive hydrocortisone substitution.

Treatment regimens

All principles of curative DLBL treatment must be applied to elderly patients and treatment strategies should be stratified

according to IPI. Whether less intensive / shorter chemotherapy can be given to the subgroup of elderly patients without bulky disease and with no IPI risk factor other than age is addressed in ongoing prospective trials. Best results have been obtained with 8 cycles of R-CHOP-21 and six cycles of R-CHOP-14 +2R. Both regimens have equal efficacy and acute toxicity.⁵ 6xR-CHOP-14+2R⁶ has the advantage over 8xR-CHOP-21 of a much shorter duration under chemotherapy (71 vs. 149 days), which has particular psychological importance for elderly patients, and of less (2/3) cumulative drug exposure compared to 8xR-CHOP-21, which is relevant with respect to the rate of cardiomyopathies and second neoplasms. Whether extended rituximab exposure by increasing intervals between rituximab applications later in the treatment course⁷ can indeed improve the outcome of elderly DLBCL patients, is the objective of an ongoing trial.

Radiotherapy

Radiotherapy to bulky disease is recommended, because it eliminates bulky disease as a risk factor. Abandonment of radiotherapy to bulky disease led to an inferior outcome, including a significant reduction of overall survival in elderly patients with bulky disease.⁸ Early results from a prospective

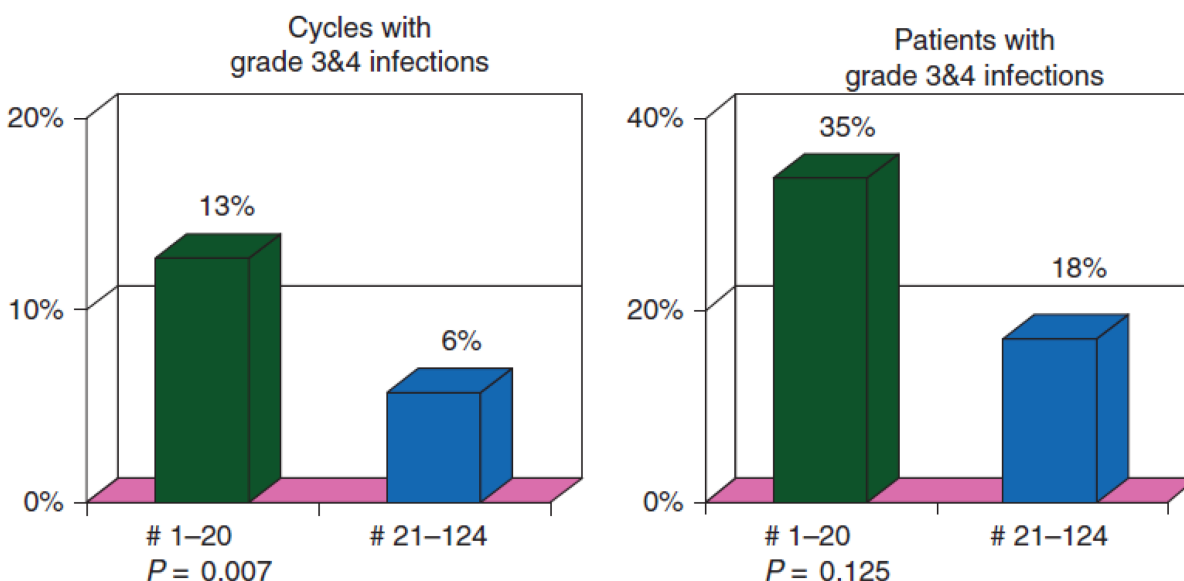


Figure 1. Grade 3 and 4 infections without and with anti-infective prophylaxis in the DENSE-R-CHOP-14 trial.¹⁵ Starting with patient #21 (light grey (blue online) columns), patients received anti-infective prophylaxis with aciclovir and cotrimoxazole. This resulted in a significant reduction of chemotherapy cycles with grade 3 and 4 infections (left graph), and a considerable decrease of patients with grade 3 and 4 infections (right graph). Adapted from Murawski *et al.* Ann Oncol 2014;25:1800–6; with permission.

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trial suggest that radiotherapy can be spared in patients with a negative PET after immunochemotherapy.⁹

Patients aged more than 80 years

A geriatric assessment in order to ascertain comorbidities and functional decline is recommended to help choice of treatment in these patients.² R-CHOP treatment can usually be given to fit patients up to 80 years of age. The combination of rituximab with attenuated chemotherapy, such as R-mini-CHOP, can induce complete remissions and long-term survival in fit patients older than 80 years.¹⁰ Whether substitution of doxorubicin by gemcitabine, etoposide or liposomal doxorubicin, or even its omission, can be considered in patients with cardiac dysfunction or those who are otherwise unfit, must be shown in larger prospective studies. Alternative chemotherapy regimens such as GemOx¹¹ or CEMP,¹² which have proven efficacy in the treatment of elderly patients with relapsed and refractory DLBCL, can also be considered in such situations.

Elderly patients with refractory / relapsed DLBCL

Elderly patients or those with comorbidities who are not candidates for high-dose chemotherapy face a dismal prognosis. ESMO guidelines recommend treatment of such patients in prospective trials addressing new drugs and treatment strategies. Outside such trials, immunochemotherapy with low-toxicity regimens such as GemOx (gemcitabine, oxaliplatin)¹¹ is an option, with pixantrone achieving some responses in heavily pretreated patients.¹³ Numerous conventionally dosed chemotherapies for relapsed or refractory aggressive lymphoma have been studied, most of them in a limited number of patients, but no standard has been established for elderly DLBCL patients in a randomized trial. R-ICE and R-DHAP might be too toxic for many of the elderly patients, but gemcitabine, dexamethasone and cisplatin (GDP), which was compared with R-DHAP in a large randomized NCIC-CTG LY.¹² trial and proved to be as efficacious, but considerably less toxic than R-DHAP, might be an option.¹⁴

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