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Diffuse large B-cell lymphoma in the older

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Abstract

The incidence of diffuse large B-cell lymphoma (DLCL) in the older is growing to the point of becoming a health priority in the next decades. Prognostic factors and the biology of the tumor are not very different between younger and older populations. Furthermore, it seems that the response rate is basically similar in both populations, provided an appropriate dose of chemotherapy is administered. However, there seem to be differences with regard to a lower tolerance to treatment and a higher relapse rate in responsive older patients. To analyze these problems we review the most important differences between young and older DLCL patients in terms of immunologic status, treatment toxicity and the presence of other concomitant diseases or organ dysfunctions. We also consider the most relevant clinical studies that may allow us to make the appropriate decisions regarding DLCL therapy in this older population.

Keywords: Diffuse large B-cell lymphoma; Older; Treatment; Toxicity; Comorbidity

1. Introduction

The definition of older people includes biological but also social, cultural, geographical and chronological aspects. However, in the present review we will use 60 years of age and

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older as the general definition of an older person. In the next decades, an increase in the number of older patients with non-Hodgkin lymphoma (NHL) is expected. Most of them will be cases of diffuse large B-cell lymphoma (DLCL). Multiple factors, including an increase in life expectancy, may play an important role in this situation. In fact, the median age of DLCL patients is in the 7th decade and it is expected that the current number of affected persons older than 65, 75 and 85 years will be at least doubled by 2030 [1]. Furthermore, more than half of the DLCL patients are 60 years of age or older.

The outcome of older patients with aggressive lymphoma is worse than that of the corresponding younger ones [2–5]. In fact, age itself is considered an adverse prognostic factor in the worldwide used International Prognostic Index (IPI) system in this kind of lymphoma [6,7].

Multiple causes related with the tumor itself, the treatment and also differentiated host biology of the host are considered contributors to this different outcome. In this review we focus on the differences in the prognostic factors, immunologic status, toxicity and the presence of other comorbidities or organ dysfunctions, which may explain this difference. We also consider the most relevant clinical studies that may allow us to make the appropriate decisions regarding DLCL therapy in this older population.

2. Why do older patients have a different outcome?

Most investigators claim that the vast majority of differences in outcome between younger and older patients do not depend on intrinsic tumor variations, but rather on other factors. These factors are: a more unfavorable IPI prognostic factor distribution in older patients, the presence of comorbid conditions, treatment-related factors that result in less effective therapy and a worse host immune system unable to control minimal residual disease [2,3,8–10].

2.1. Prognostic factors

As aforementioned, advanced age is per se an adverse prognostic factor of IPI [6]. So, the main question is why age confers a poorer independent prognosis in these patients. One possible explanation is that the median age of patients with activated B-cell (ABC) subtype of DLCL, which is the worst prognostic subtype, is around 65 years versus the other germinal centre B-cell (GCB) subtype of better prognosis that occurs at an earlier age [11]. Whether this difference contributes to the generally poorer results in the older with respect to the younger may need clarifying [12]. The question about the effect of age on therapeutic outcome cannot yet be answered from the genetic or molecular point of view since very few data about genetic or molecular abnormalities in older patients are available.

Some biological tumor-related factors have changed their prognostic value while others have retained it with the addition of rituximab to standard induction regimens. Table 1 shows main biologic DLCL-related prognostic factors in older patients treated with chemoimmunotherapy in a recent GELA study [13], some of them having a differential effect in patients receiving or not receiving rituximab.

Table 1
Main biological tumor-related prognostic factors in older patients receiving chemoimmunotherapy (R-CHOP).

Prognostic factor	Favorable	Unfavorable
Profile	GC subtype	ABC subtype
Genes	LMO2	APOBEC3G[a]
	MME	FOXP1
	LPP	
	RAB33A*	

GC: germinal centre profile; ABC: activated B-cell profile.
[a] Differential effect between in patients receiving or not rituximab.

Another important aspect assessed in other studies is whether the disease is more aggressive in older patients, giving them a poorer prognosis. Solid tumors in older patients show less aggressive parameters and a lower proliferative rate than the corresponding ones in younger people [14]. In contrast, lymphoma in older patients shows higher proliferative rates [15]. This may be explained because these disorders are immune system tumors, and are therefore associated with a more profound immunodeficiency than solid tumors, which have a higher propensity to grow and disseminate [16].

Differences between younger and older populations in well-known prognostic factors in this type of lymphoma have also been evaluated. In general terms, most predictive variables in younger patients also apply to the older [7,17]. The only difference is that older patients seem to present with more adverse prognostic factors. Interestingly, in one study a larger number of older patients with this type of lymphoma presented with a higher risk IPI distribution than the corresponding younger patients. Indeed, more than 50% of the patients presented with 2 or 3 adverse prognostic parameters of the adjusted-IPI (a-IPI) [18].

One of the adverse prognostic factors of IPI is having more than 1 extranodal involvement. Therefore a higher extranodal involvement, such as gastrointestinal, brain or testes, has been suggested, in the older [19]. Another important adverse prognostic factor of IPI in the older is the performance status. Some studies have found similar outcomes with similar treatment between younger and older patients. Grogan et al. retrospectively analyzed the outcome of 192 patients with aggressive NHL treated in a single institution, where 37% of the patients were older than 65 years. Patients were treated with standard doses of m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and prednisone) or CHOP. The authors reported similar response rates, disease-free survival (DFS) and overall survival (OS) in both younger and older patients. In addition, comparable prognostic factors were reported. However, older patients had a significantly worse PS ($P < 0.02$) with 42% having a PS of 2 or more compared to 22% in those younger than 65 years. No other important variable was different in both populations.