Unmet needs in the scientific approach to older patients with lymphoma

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Lymphomas in older patients require special attention because these patients have potentially curative diffuse large B-cell lymphomas (DLBCLs) but may have other diseases that could alter their ability to tolerate treatment. The incidence of lymphomas in older patients has increased in recent years. As detailed in Table 1, most of the subtypes of lymphomas, with the exception of Burkitt lymphoma, lymphocyte predominant nodular Hodgkin lymphoma and classical Hodgkin lymphoma, increase after the age of 50, with a median age of onset of 67 years. Most frequent entities in this age group are DLBCLs, followed by marginal zone lymphomas and follicular lymphomas. Because of the predominance of DLBCLs, this review will focus mainly on this subtype.

For optimal management of older patients with lymphoma, three types of issues have to be taken into account. These are: 1) patient-related; 2) disease-related; 3) treatment-related.

Patient-related issues

Aging is a natural process leading to the progressive loss of physiological functions, increased inflammatory status, decreased naïve immune T-cell population, increased mutational events and epigenetic modifications resulting in an impaired health status. With the aging of the population, the number of older patients with lymphoma will continue to increase, namely, very old patients over 80 years of age. This population is characterized by its heterogeneity in terms of comorbidities, life expectancy, physical fitness and socio-economic situation.

It is clear today that chronological age alone is meaningless, as it is even in very fit patients; marrow reserve and renal function are decreased, and neurological tolerance to toxic drugs is severely impaired.

A common characteristic of older patients is the presence of comorbidities that necessitate polymedication, increasing the risk of interaction between these drugs and those used to treat lymphoma. In very old patients, we also have to be mindful of geriatric syndromes (falls, cognitive disturbances, incontinence, dementia and loss of autonomy) that are correlated with a shorter life expectancy. This population should be protected from treatment-related toxicity and be allowed to benefit from optimal supportive care to preserve their quality of life. The socio-economic situation of these patients is also a concern, as it can significantly impair the way the patient deals with unexpected adverse events, hospital visits and the high cost of new medications.

The median age of patients with non-Hodgkin lymphoma (NHL) is 67 years and in many international prognostic scoring systems, such as the International Prognostic Index (IPI) or the Follicular Lymphoma International Prognostic Index 2 (FLIPI 1-2), age over 60 remains an adverse risk factor correlated with lower response to chemotherapy and poorer survival.[1,2] However, according to the publications from the Groupe d'Etude des Lymphomes de l'Adulte (GELA), the benefit of R-CHOP compared to CHOP is significant in all categories of older patients, including very old selected patients aged between 75-80 years.[3] Since life-expectancy for an 80 year-old patient can vary between 3 and 11 years according to his health status, it is of major importance to identify patients without irreversible comorbidities who have a significant life-expectancy and who would benefit most from the optimal treatment regimen.

We know from the exhaustive multivariate analysis from Hamaker that there are 3 major predictive factors for mortality in the treatment of older patients with malignant hemopathies[4] (Table 2). These factors are: 1) the physical capacity of the patient, such as performance status or the "up and go" evaluation; followed by 2) nutritional deficiencies; and finally 3) the comorbidity index. Therefore, functional, physiological, psycho-cognitive and socio-economic evaluations should be part of the multidimensional geriatric assessment of patients over 70 years of age, taking into account the patient-related, and not only the disease-related, comorbidities.

While physicians are quite good at evaluating functional status, comorbidities or nutritional status, the psycho-cognitive function is usually poorly investigated and the socio-economic status rarely evaluated. The value of a multidimensional geriatric assessment was prospectively investigated in 2000 successive Belgian patients.[5] This study confirmed that multidimensional geriatric assessments gave prognostic information in terms of overall survival (OS), morbidity and loss of quality of life, but more importantly, they detected multiple problems that influenced the choice of a better targeted treatment.

In a population of clinically fit lymphoma patients sent by their physician to receive chemotherapy treatment, we observed that cognitive problems were completely underestimated: 30% of the patients had an abnormal Mini Mental State Evaluation (MMSE) test and 51% had an abnormal Montreal Cognitive Assessment (MoCA) test (which is more sensitive in its evaluation of executive functions), which could reach 70% in patients over 80

years. In this clinically "fit" population, admitted for the treatment of hematologic malignancies, we observed a significant deleterious impact on the 2-year overall survival rate when the MoCA test was below 26 or the MMSE test was below 23/27 (P<0.01).[6]

Therefore, to better evaluate the fitness of older patients, close collaboration between geriatricians and hematologists is highly recommended. However, a prerequisite should be the harmonization of the terminology. Indeed, many trials conducted in patients aged over 60

use the term "elderly patients", while geriatricians consider "elderly patients" as those having severe comorbidities, loss of autonomy and requiring a lot of attention. At the same time, a patient onco-hematologists would call "vulnerable" would be considered "frail" by geriatricians, leading to confusion in the interpretation of "frailty" in the population receiving chemotherapy and potentially excluding them from clinical trials.

An optimal, easy-to-use screening tool is essential to determine patient "fitness". The G8 screening tool has been validated in solid tumors and malignant

Table 1. Non-Hodgkin lymphoma histological subtypes according to age.
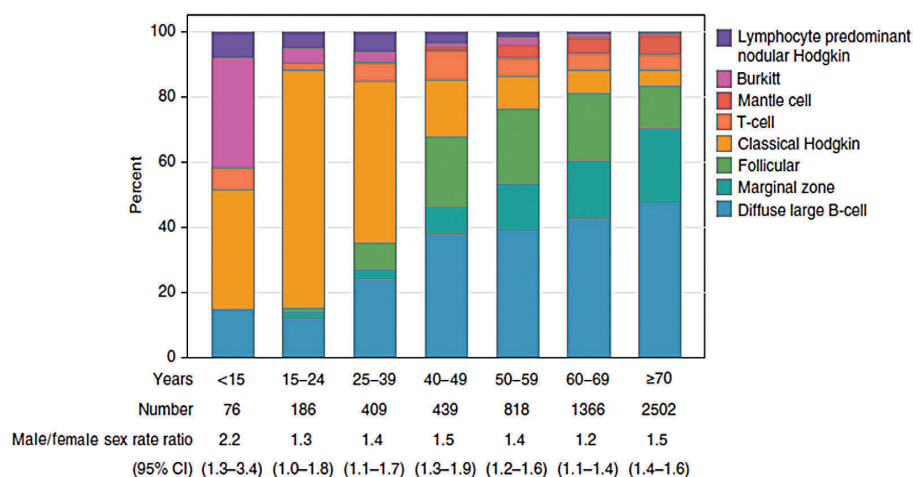
Numbers of cases and sex-rate ratios by sub-type and age: Haematological Malignancy Research Network (HMRN) 2004–2012.

Table 2. Prognostic factors for mortality. Hematologic malignancies in the elderly.[4]

ADL: activities of daily living; IADL: instrumental activities of daily living; AML: acute myeloid leukemia; MDS: myelodysplastic syndromes; RAEB: refractory anemia with excess blasts; DLBCL: diffuse large B-cell lymphoma.

hemopathies.[7,8] However, in "clinically fit" patients, the weight of nutritional and psychological status is too important. Indeed, many DLBCL patients experience weight loss, and often feel tired and in poor health. The score of their G8 questionnaire one week after steroids shows a complete improvement across all categories by the reversibility of these lymphoma-related comorbidities. The strict application of the G8 screening, completed by a Comprehensive Geriatric Assessment (CGA), could lead to under-treatment of patients, undermining their chances to be cured.

Disease-related problems

The paradigm in diffuse large B-cell lymphomas is that we are facing a curable disease with adequate immuno-chemotherapy in a population for whom this adequate treatment can lead to life-threatening side effects. We also know that the OS of lymphoma patients is correlated with achievement of complete remission (CR) and that a minor reduction in the dosage or dose intensity compromises their chances to be cured. In addition, older NHL patients present with more advanced stages at diagnosis, a more unfavorable biological profile (non-germinal center vs. germinal center), more genetic mutations (MYC positive), and an increased incidence of anemia, which is an adverse prognostic factor whatever the cause. However, the disease remains the major cause of death. The GELA study and the German study have both demonstrated that R-CHOP21 is superior to CHOP14 and to CHOP21 in terms of OS and toxicity.[3,9,10] The benefit of rituximab was observed in all age categories (60-70, 70-75, 75-80 years of age) but this trial was limited to "fit" patients under 80.

In a prospective phase II trial, Peyrade and colleagues investigated the R miniCHOP regimen in a population of DLBCL patients aged 80 or over.[11] This trial confirmed the feasibility and efficacy (49% OS at 4 years) of this reduced R-CHOP in very old patients, as reported also in retrospective studies.[12] However, this population was also selected on the basis of comorbidities and an interesting retrospective study reported by Marchesi et al. showed that "frail" patients [aged 85 years or over, activities of daily living (ADL) < 6, 1 geriatric syndrome or > 3 comorbidities] did not benefit from any chemotherapy.[13]

Indeed, there have been no randomized clinical trials (RCT) in frail DLBCL patients nor in other subtypes of lymphomas (HL, Burkitt, T lymphoma, etc.). A recent review outlines the reasons for this.[14]

Treatment-related problems

The treatment of older patients with NHL, and specifically the R-CHOP regimen, is associated with short-term toxicity: primarily hematologic toxicities with the increased risk of febrile neutropenia, cardiac toxicity and neurotoxicity. This regimen also results in long-term toxicity with secondary myelodysplasia or acute myeloblastic leukemia (MDS or AML), functional and cognitive decline, and cardiomyotoxicity, leading to the loss of autonomy. If the toxic death rate is important in all clinical trials, in older patients this rate is exacerbated. The prognostic factors associated with poor survival are discussed by Hamaker and are usually patient-related. Screening tests to predict this toxicity, mostly used in oncology, are the Chemotherapy Risk

Assessment Scale for High-Age Patients (CRASH) test and the Vulnerable Elders Survey (VES-13).[15,16] However, they have not yet been validated in hematologic patients and are thus rarely used.

Soubeyran reviewed predictive factors for unacceptable toxicities such as early toxic death, loss of autonomy and unplanned hospitalization (P Soubeyran, unpublished data, 2017) identified in 3 recent trials. The significant predictive factors were: Mini Nutritional Assessment (MNA) < 24, "up and go" test > 20 sec, the Lawton Instrumental Activities of Daily Living (IADL) < 8, and Geriatric Depression Scale-15 (GDS15) > 5.

The major side effect of chemotherapy in older patients is neutropenia (>60% over 80 years) with a mortality ranging from 9% to 23%. Marrow reserve is reduced in patients aged over 60 but their response to granulocyte-colony stimulating factor (G-CSF) is similar to that of younger patients. Although it has been known for more than ten years that the addition of G-CSF as primary prophylaxis reduces mortality in the treatment of NHL, in fact, only 36% of older patients receive G-CSF as primary prophylaxis; 20% receive a G-CSF as secondary prophylaxis and up to 30% receive no growth factor at all.[17]

Another event causing early death is tumor lysis syndrome during the first cycle. This risk can be significantly reduced by a pre-phase treatment using steroids for one week with or without rituximab,[18] as confirmed at the Lymphoma Study Association (LYSA) meeting (F Peyrade, unpublished data, 2017).

Other concerns after treatment with R-CHOP are cardiovascular problems and late heart failure, diabetes and high sensitivity to neurotoxic drugs such as vincristine. One should be very careful when monitoring heart rate, glycemia and searching for peripheral neuropathies. Older patients are also more sensitive to secondary tumors such as lung cancers and MDS. Pharmacokinetic data are dramatically lacking in very old patients and trials such as the GELA trial, with reduced doses of anthracycline leading to a similar CR rate and OS rate, suggest that older patients may have an increased half-life of drugs or drug metabolites.

Table 3. Unmet needs in the multidisciplinary approach of lymphoma patients.

Patient-related
- Harmonization in language (older vs. elderly, frail vs. vulnerable)
- Simple tool to evaluate patient fitness that allows optimal curative treatment
- Better distinction between patient-related and disease-related comorbidities (multidisciplinary approach)

Disease-related
- RCT adapted to "real life"
- Informed consent of the patient after cognitive evaluation
- Patient-centered RCT with "OS with quality of life" as a primary end point!

Treatment-related
- Primary prophylaxis with G-CSF
- Pre-phase treatment before aggressive chemotherapy
- Optimal survey of neuropathies
- Involvement of family caregivers

RCT: randomized clinical trials; OS: overall survival; G-CSF: granulocyte-colony stimulating factor.

Another group published similar data in DLBCL patients above 80 years where less than 85% anthracycline relative dose intensity achieved a better overall survival.[19]

Finally, as pointed out by Hamaker, most of the ongoing trials for elderly patients with hematologic malignances are not addressing the right end points.[20] Indeed, the outcomes of primary importance for this population, such as quality of life, health care utilization and loss of functional capacity, were only measured in 8%, 4% and 0.7% of the trials!

As a scientific community, we must support patient-focused cancer care in RCT to further elucidate all these unresolved issues in order to significantly improve our knowledge of the optimal treatment of older patients.

Conclusion

The treatment paradigm in aggressive NHL is, on the one hand, an effective conservative treatment that preserves quality of life and controls the disease, and on the other, an intensive potentially curative treatment with more toxicities. A multidisciplinary approach using harmonized language is mandatory (Table 3).

It is important to determine the risk-benefit ratio for each patient. We are entering an era in which the patient-physician relationship has evolved from paternalism to a face-to-face dialogue. The patient is involved in the decision-making process and expresses his wishes regarding his quality of life. However, this patient involvement is conditioned by his ability to understand the risk-benefit ratio of the treatment, and to read and sign an informed consent.

Today, the management of lymphoma in older patients is a multistep approach starting with the prognostic evaluation of the lymphoma and the potential severe adverse events induced by the treatment. A second step evaluates the physical, physiological, cognitive and socio-economic status of the patient, raising the question of life expectancy with or without the tumor. Finally, and probably more importantly, the patient should express his expectations in terms of quality of life.

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