Hodgkin's Lymphoma in the Elderly: A Different Disease in Patients Over 60

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With improved prognosis for patients with Hodgkin's lymphoma (HL), interest has increasingly focused on high-risk groups such as elderly patients. Advanced age at presentation is still one of the strongest negative risk factors. Many different factors influence the prognosis in elderly patients. These include biologic differences such as more aggressive histology, different distribution of disease, more frequent diagnosis of advanced stage, and shorter history of disease. In addition, however, aging itself and associated factors such as comorbidity, reduced tolerability of conventional therapy, more severe toxicity and treatment-related deaths, failure to maintain dose intensity, shorter survival after relapse, and death due to other causes contribute to the poorer outcome in elderly patients. Besides the evaluation of specific causes and risk factors, this review highlights recent and ongoing studies for elderly patients with HL as well as international approaches and recommendations for this age group.

Treatment and prognosis of patients with Hodgkin's lymphoma (HL) has substantially improved during the past few decades, rendering this entity one of the most curable of human cancers. This success is mainly attributed to the introduction and optimization of effective chemotherapy regimens and progress in radiation techniques. However, these improvements have so far not been extended to the group of elderly patients presenting with HL.

In contrast to younger patients, elderly patients with HL still have an unsatisfactory prognosis. Advanced age at presentation is one of the strongest negative risk factors. Different study groups showed significantly poorer outcome for elderly HL patients compared with younger patients when similar treatments were given.[1-14] Many different factors influence the prognosis in elderly patients. These include biologic differences such as more aggressive histology, different distribution of disease, more frequent diagnosis of advanced stage, and shorter history of disease. But aging itself and associated factors such as comorbidity,[4] reduced tolerability of conventional therapy,[5] more severe toxicity and treatment-related deaths, failure to maintain dose intensity,[6-9] shorter survival after relapse,[10,11] and death due to other causes[12] also contribute to the poorer outcome in elderly patients.

Within population-based studies, the proportion of patients older than 60 years ranges from 20% to 44%.[6,9,15] However, the number of elderly patients participating in prospective trials is considerably lower than that of younger patients. This is mainly due to the fact that most clinical trials have age limits or study entry criteria that exclude older patients with severe comorbidity or poor performance status. Although some retrospective analyses have enrolled selected elderly patients in standard treatment protocols, data from larger randomized studies designed for this age group are lacking.

Thus, besides the evaluation of toxicity, response, and outcome of established therapies, new strategies with sufficient efficacy and better tolerability are needed for elderly patients. Different modified or new regimens specifically targeted at elderly patients are currently being evaluated by different study groups.[16-19]

Here, we review the literature on elderly HL patients, including biologic and clinical prognostic factors as well as clinical studies and future approaches for this group of patients.

Biologic Differences in the Elderly

Incidence

In Europe and the United States, the annual incidence of HL is about 2 to 3 per 100,000 persons at risk, and has remained remarkably constant over the past few decades.[20] In industrialized countries, the age at onset has historically shown two peaks—one in the third decade and a second for patients older than 50 years. However, in more recent analyses, the second peak seems to
disappear, since many cases of non-Hodgkin's lymphoma (NHL) were misclassified as HL in the past.[21]

The incidence of HL in patients older than 60 years is still not exactly clear. The proportion of elderly patients participating in prospective trials is usually low, mostly due to age restraints for the trials or the fact that exclusion criteria are not met. Generally, more elderly HL patients were represented in studies performed in the 1970s or 1980s. For example, in earlier Cancer and Leukemia Group B (CALGB) studies, 19% of patients were older than 60 years.[3] However, central pathology review was not performed in these studies. Given that a more recent retrospective reevaluation of elderly HL patients diagnosed decades ago indicates that a substantial proportion of elderly patients with B-cell lymphomas were initially misdiagnosed as having HL,[21] meaningful studies in elderly patients require a reference pathology expert diagnosis. Accordingly, elderly patients represented 8% of all diagnoses in the follow-up CALGB trial, which included pathology review.[22]

Within population-based studies, the proportion of elderly HL patients ranges from 20% to 44%: In a Swedish study, 163 of 202 patients treated between 1979 and 1988 were confirmed HL cases after histopathologic review. Of these, 61 (31%) were older than 60 years.[9] Another study from England prospectively evaluated the incidence and outcome of HL patients in the Northern Health Region (population of 3 million) between 1991 and 1998, irrespective of entry into a specific trial. Of the newly diagnosed HL patients, 20% were older than 60 years. The age-specific incidence was 1.97/100,000 for those aged 60 to 69 and 2.18/100,000 for those aged 70 years or older.[15,23]

**Histologic Subtype and Disease Characteristics**

A retrospective analysis from the German Hodgkin Study Group (GHSG) revealed statistically significant differences in disease-related characteristics between younger and older HL patients. Elderly patients presented more frequently with B symptoms, elevated sedimentation rate, mixed cellularity (MC) histologic subtype, and poorer Karnofsky performance score. Less frequently found in this group were bulky disease, large mediastinal mass, and nodular sclerosis (NS) subtype. Although the MC subtype was present more often in elderly patients (35% vs 19%), NS histology was most frequently observed in both age groups (41% vs 66%).[13]

In smaller case series, others have reported similar findings.[5,8,22] As an example, a recent study from the Nebraska Lymphoma Study Group found sex, stage, Karnofsky performance score, lactate dehydrogenase, number of extranodal sites, B symptoms, size of largest mass and histologic subtype prognostically relevant.[5] More recent studies or those using pathology expert review[7,12,22] observed fewer patients with lymphocyte-predominant and lymphocyte-depleted subtypes.[1,3,8,24] This reflects improved histomorphology allowing a more precise classification of different HL subtypes and the distinction of HL from NHL.

In accordance with the findings of the GHSG and the Nebraska Group, the difference in outcome between young and elderly patients seems to be due, at least in part, to an intrinsic difference in the disease. Elderly patients present more often with poorer risk factors such as B symptoms or a shorter history of disease.[24-27] Furthermore, although staging procedures have usually been more comprehensive in the young, many studies found advanced stages more often in elderly patients.[2,9]

**Clinical Differences in the Elderly**

**Treatment-Related Toxicity**

It is unlikely that biology and disease-related factors alone explain the differences in outcome between younger and elderly HL patients. Treatment-related factors such as reduced tolerability of conventional therapy,[5] more severe toxicity and treatment-related deaths, failure to maintain dose intensity,[6-9] and shorter survival after relapse[10,11] further worsen the prognosis of the elderly age group.

The GHSG analysis including 373 elderly HL patients (≥ 60 years) found more treatment-associated toxicity. Higher mortality during treatment as well as lower dose intensity were the major factors explaining the poorer overall outcome.[13] Elderly patients were less likely to complete the full intended course of treatment. The most frequent reason for premature termination of chemotherapy or radiotherapy was excessive toxicity. Considering only the intended number of treatment cycles, fewer elderly patients received the full number of cycles. Dose adjustment was necessary significantly more often in older patients, especially during treatment for advanced-stage disease. The administration of more intensive treatment resulted in even more dose reductions and early
withdrawals in elderly patients. Thus, the dose intensity delivered was generally lower, explaining
the poorer outcome of elderly patients, particularly those in advanced stages of disease. All relevant
adverse effects occur more often in elderly patients. Above all, leukopenia, infections, and
cardiopulmonary toxicity were the limiting factors in treatment delivery and contributed substantially
to the higher treatment-related mortality in the elderly.[13]

Other investigators have also observed this increased toxicity and reduced tolerance of treatment
associated with higher mortality and a worse outcome in elderly HL patients.[3,7-9,12,27] Levis et al
showed that in the group of elderly patients treated with a conventional hybrid MOPP/ABVD regimen
(mechlorethamine [Mustargen], vincristine [Oncovin], procarbazine [Matulane], prednisone,
doxorubicin [Adriamycin], bleomycin, vinblastine, dacarbazine), acute toxic death occurred in 19% of
patients compared with 4% in the group treated with CVP/CEP (cyclophosphamide, vincristine,
prednisone, caraboplatin, etoposide, bleomycin).[16] Among patients treated with VEPEMB
(vinblastine, cyclophosphamide, procarbazine, prednisolone, etoposide, mitoxantrone, bleomycin),
3% died during therapy.[17] Another population-based study reported a 21% treatment-related
death rate in patients over 60 years old treated with curative intent.[9]

In the HD9elderly study of the GHSG, elderly patients with advanced-stage HL suffered from
considerably more severe hematologic toxicity than younger patients when being treated with
intensified chemotherapy (BEACOPP; bleomycin, etoposide, doxorubicin, cyclophosphamide,
vincristine, procarbazine, prednisone) compared to a standard treatment (COPP-ABVD;
cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, and
dacarbazine). Acute toxic deaths occurred in 21% of patients treated with BEACOPP compared with
8% for COPP-ABVD recipients. As a result, in contrast to younger patients, there was no benefit in
changing to the more effective treatment for the older age group.[14]

Comorbidity and Death From Other Causes

Although most authors describe treatment-related toxicity and mortality as major obstacles in this
age group, patient-related factors such as comorbidity[4] and death from unrelated causes[12]
further contribute to the poorer outcome of elderly patients.

In a population-based series comprising more patients with serious comorbidity than allowed in
clinical trials, van Spronsen et al studied the age-specific prevalence of comorbidity and its
relationship to treatment and outcome in 194 HL and 904 NHL patients diagnosed between 1993 and
1996. The most common comorbid conditions were cardiovascular disease (18%), hypertension
(13%), chronic obstructive pulmonary disease (13%), and diabetes mellitus (10%) for elderly HL
patients. Serious comorbidity was found in more than half of all lymphoma patients who were 60
years and older. Elderly patients with serious comorbidity received chemotherapy less often, which is
likely to adversely affect survival, as was especially indicated by a decreased survival within the first
4 months after diagnosis.[4]

Guinee et al compared the clinical course of 136 previously untreated HL patients aged 60 to 79
years with that of 223 patients aged 40 to 59 years, treated between 1977 and 1983. When the
prognosis of all patients was examined, a definite change in the pattern of survival appeared in the
60- to 69-year-old cohort. The entire group of elderly patients (60 to 79) had twice the risk of dying
from HL and four times the risk of dying from other causes, compared with the younger group. The
authors concluded that HL should have the same natural history and similar risk factor pattern in the
elderly and should be amenable to existing therapeutic approaches. Thus, the prognosis of older
patients with HL has been obscured in previous studies by the inclusion of deaths due to other
causes in survival estimates.[12]

Another adverse factor might be an inadequate staging and treatment in elderly patients. In a study
of 52 patients 60 to 75 years old who were treated for HL at Stanford between 1968 and 1980, the
5-year survival rate in the adequately staged and treated group was 86%, compared with only 35%
in the inadequately staged group.[2] Another study found that patients over the age of 50 years
were more likely to receive suboptimal doses of chemotherapy, which was associated with more
treatment failure and relapse.[28]

Treatment in the Elderly

Response and Outcome

Generally, adequately staged elderly patients receiving and tolerating appropriate doses of
treatment should achieve responses comparable to those in younger patients.[5,7,13,29]
et al.[27] described 31 HL patients who were more than 60 years old and who were treated with standard chemotherapy regimens. They observed a complete remission rate of 87% and an overall survival of 58%, with a median follow-up of approximately 5 years.

Specht and Nissen[11] found age to be a significant prognostic factor in HL patients, with higher age being related to the inability to tolerate intensive therapy. Erdkamp[8] et al found that older patients with HL were less likely to receive adequate treatment compared to younger patients and were less likely to achieve a complete remission. However, patients who achieved a complete remission had equally durable remissions. The conclusion of these authors was that elderly patients who were sufficiently fit to tolerate standard therapy had a response and treatment outcome comparable to that of younger patients.

In the GHSG analysis, elderly patients had a significantly poorer outcome compared with younger patients in terms of freedom from treatment failure (60% vs 80%) and overall survival (65% vs 90%). Other recent studies including selected patients show a similar 5-year overall survival ranging from 30% to 60% in the elderly age group.[1,5,16-18] Data from retrospective population-based studies reported even poorer response and survival in elderly patients.[2,3,7-9,22,24] However, in these series, a large proportion of patients received no treatment, radiotherapy only, or a variety of chemotherapy regimens without an anthracycline or a reduced anthracycline dose.

Radiotherapy

Before the introduction of chemotherapy into the treatment of early disease stages, radiotherapy was often applied in higher doses and larger radiation fields (eg, extended-field, subtotal or total lymphoid irradiation). Large radiation fields were also used in elderly patients, often preceded by staging laparotomy and splenectomy.[2,30] This often led to a reduced tolerance and applicability of treatment due to substantial side effects.

Patients with early-stage favorable or early-stage unfavorable HL are currently being treated with combined-modality strategies including two to four cycles of chemotherapy (ABVD) followed by radiotherapy to the involved field in most centers. The treatment for advanced stages of disease usually consists of six to eight cycles or of a more intensive regimen, plus consolidating radiotherapy to residual lesions. Very similar approaches are being used for elderly patients in good physical condition. FIGURE 1

Radiotherapy Techniques and Fields

In the GHSG HD8 trial, patients were randomized to four cycles of chemotherapy plus radiotherapy to either an extended field (arm A; EFRT) or involved field (arm B; IFRT). The final results at 5 years did not show significant differences between the two arms in terms of freedom from treatment failure or overall survival.[31] These results and parallel trials by the European Organisation for Research and Treatment of Cancer (EORTC) led to the worldwide acceptance of the less toxic involved-field technique in a combined-modality setting for early favorable and unfavorable stages of disease. An example of the different radiotherapy fields is given in Figure 1.

In a recent analysis of the HD8 data, younger patients were compared to those older than 60 years. Elderly patients more often suffered from severe toxicity, especially those assigned to the EFRT arm. At 5 years, freedom from treatment failure and overall survival were remarkably lower for elderly compared with younger patients (freedom from treatment failure: 64% vs 87%; overall survival: 70% vs 94%). Furthermore, elderly patients had a significantly inferior outcome when treated with EFRT as compared with IFRT, in terms of both freedom from treatment failure (EFRT: 58%; IFRT: 70%) and overall survival (EFRT: 59%; IFRT: 81%). Radiation-induced effects including nausea and hematologic, pharyngeal, and gastrointestinal toxicity were observed more often in elderly patients undergoing EFRT. Taken together, in this group of elderly HL patients, application of EFRT instead of IFRT resulted in significantly lower rates of freedom from treatment failure and survival and should be avoided in future studies.[32]
Chemotherapy and Clinical Trials

TABLE 1

Selected Chemotherapy Regimens Used in Clinical Trials for Elderly Patients With Hodgkin's Lymphoma

In young patients, the superiority of doxorubicin-containing regimens such as ABVD or BEACOPP over MOPP is now well established.[33,34] Elderly patients have been reported to tolerate combination chemotherapy less well than younger patients.[11,25,27] Because of concerns of cardiotoxicity, doxorubicin has often been avoided. However, it seems that elderly patients with HL benefit from the inclusion of doxorubicin in their treatment. This was shown recently by the Nebraska Lymphoma Study Group when comparing ChlVPP (chlorambucil [Leukeran], vinblastine, procarbazine, prednisone) and ChlVPP-ABV hybrid regimens. In 56 patients over 60 years old, the doxorubicin-containing ChlVPP-ABV (see Table 1) was associated with a better outcome, leading to a 5-year overall survival of 67% for patients receiving ChlVPP-ABV compared to 30% for those treated with ChlVPP alone.[5]

Other data on 88 consecutive elderly patients diagnosed in Sweden support these findings: Landgren et al report that elderly patients who received ABVD-based treatment and a relative dose intensity of more than 65% had a significantly better overall survival than those who had a relative dose intensity of less than 65% or who received a MOPP-like therapy, irrespective of received dose intensity.[6] Other results from Canada on 99 elderly patients showed that the ODBEP regimen (vincristine, doxorubicin, bleomycin, etoposide, prednisone), resulted in a similar overall survival and disease-specific survival compared to MOPP/ABV type chemotherapy, but appeared to be less toxic.[18]
Further intensification of treatment associated with better outcome in younger HL patients cannot easily be applied to elderly patients. In an attempt to improve the poor prognosis of elderly HL patients with advanced-stage HL, the GHSG conducted the HD9elderly trial, the only prospectively randomized trial in this age group. Patients with advanced-stage disease aged 60 years and more were randomized between eight courses of COPP-ABVD or eight courses of BEACOPP baseline. The disease-specific freedom from treatment failure at 5 years was 74% after BEACOPP and 55% after COPP-ABVD. However, the better tumor control achieved with the intensified chemotherapy was offset by higher toxicity and did not translate into better outcome (overall survival at 5 years: 50% for both regimens, Figure 2).[14]

In an attempt to reduce hematotoxicity and infections, two new regimens for elderly patients are currently being evaluated by the GHSG in phase I/II trials: PVAG (prednisone, vinblastine, doxorubicin, gemcitabine [Gemzar]; see Table 1) and BACOPP (bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; see Table 1).[19,35] In the Intergruppo Italiano Linformi, regimens such as CVP/CEB (chlorambucil, vinblastine, procarbazine, prednisone, cyclophosphamide, etoposide, bleomycin), and VEPEMB (vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone, bleomycin, see Table 1) were administered to elderly patients in a nonrandomized setting. CVP/CEB (administered to 25 patients from 1990 to 1993) produced event-free and overall survival rates of 32% and 55%, respectively. Levis et al concluded that CVP/CEB was a well-tolerated low-toxicity regimen associated with an outcome comparable to that of other patients treated conventionally at that time.[16] VEPEMB is a reduced-intensity anthracycline-containing regimen that was evaluated in 105 elderly HL patients from 1995 to 2001. Results were better in early disease stages than in advanced stages: CR rates were 98% vs 58% and 5-year failure-free survival rates were 79% vs 34%. In this study, comorbidity proved to be a more important prognostic factor than age itself.[17]

Since data on elderly patients are still rare and relatively few patients enter randomized trials, the international pooling of data and treatment evaluation in these patients was encouraged in a workshop held during the 5th International Symposium on HL.[23] Proctor et al introduced the SHIELD project (Study of Hodgkin's lymphoma in the Elderly Lymphoma Database; www.shieldstudy.co.uk), providing online registration for ongoing studies in the elderly as well as guidance on obtaining ethical approval for participation. Objective assessments of comorbidity, activities of daily living, and instrumental activities of daily living were built-in to define objective frailty, linked to physician treatment choice or inclusion on the study protocol. An additional aim of the program is to develop palliative treatment for patients too frail for potentially curative therapy.[36,37] TABLE 2
Selected Clinical Trials in Elderly Patients With Hodgkin’s Lymphoma

The optimal treatment regimen for the elderly patient population remains uncertain, and randomized studies are eagerly awaited. It may be even more important that anthracyclines be included in the treatment of elderly patients than for those who are younger. This possibility is in contrast to common practice, whereby older patients are sometimes treated with less intense chemotherapy, such as COPP or CHLPP, due to its comparative ease of administration. Whether the results of new approaches such as CHLPP-ABV, ODBEP, PVAG, BACOPP, or VEPEMB would be equal, inferior, or superior compared with ABVD is currently a matter of speculation. From these data, however, it seems that elderly patients with HL who require chemotherapy should be treated with an anthracycline-containing regimen. Recent and ongoing clinical trials in the elderly are summarized in Table 2.

Special Considerations

Clearly, new strategies are needed for elderly patients, especially for those with advanced HL. In light of the increased comorbidity and decreased functional reserve, an assessment of patient frailty and ability to tolerate treatment should be introduced before treatment decisions are made. As proposed by Levis et al.\[17\] the most efficient tool for evaluating the clinical importance of comorbid conditions and functional limitations is provided by the Comprehensive Geriatric Assessment, which is based on standardized interviews and validated scales.\[38\] The unsatisfactory high early mortality due to acute toxicity might be reduced by modification or reduction of cytostatic drug doses and by better monitoring of toxicity at the onset of therapy. In addition, a short initial course of steroids for patients with advanced disease might reduce the rate of complications and early deaths. Since systematic dose reduction can affect outcome, primary prophylactic use of granulocyte colony-stimulating factor (G-CSF, Neupogen) for all elderly patients receiving curative myelotoxic chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or CHOP-like regimens was suggested by the EORTC. In their Elderly Task Force guidelines, they advocated a risk-adapted strategy with primary prophylactic G-CSF administration in high-risk patients. Dose intensification by treatment interval shortening can be facilitated by G-CSF and improve survival in elderly patients with various malignancies.\[39\]

There is a need for further well-designed studies to identify elderly patients who will benefit most from prophylactic G-CSF. However, the routine use of G-CSF remains controversial. In a recently published study from the Dutch-Belgian Hemato-Oncology Cooperative Group, prophylactic use of G-CSF with CHOP in elderly patients who had aggressive NHL did not lead to better response or survival.\[40\] In addition, G-CSF failed to reduce serious infections and acute toxic deaths. These findings are in line with the results of a large meta-analysis investigating the impact of G-CSF on outcome and toxicity of lymphoma patients treated with standard-dose chemotherapy with or without G-CSF.\[41\]

Conclusion and Perspective

Generally, elderly patients without major comorbidities who are sufficiently fit to tolerate standard therapy have a treatment outcome comparable to that of younger patients. Whenever possible, elderly patients should be treated with a doxorubicin-containing regimen and large radiotherapy fields should be avoided. Elderly patients ought to be enrolled into clinical trials, or information should at least be gathered. In order to successfully balance effectiveness and toxicity, the future
treatment of elderly patients with HL should be based on an objective evaluation of the individual patients' frailness. In future basic research, planned investigations will correlate biomarkers in tissue and serum with outcome, with the aim of producing a prognostic index in the elderly. Furthermore, novel therapeutic approaches following relapse, such as immunotherapy or small molecules, are needed.

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