Hodgkin’s disease in the elderly: current status and future directions


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Introduction

Data in the literature on patients aged >60 years with Hodgkin’s disease (HD) is confused and largely incomplete. There are only a few single centre studies indicating a poorer prognosis for elderly patients compared with the younger, and representing a heterogeneous cohort of patients [1–4]. It is clear that while some patients in this age group will enter standard randomised trials, a major level of selection occurs such that the overall pattern of treatment and outcome within this group is indistinctly defined [5]. During the Fifth International Symposium on Hodgkin’s Lymphoma, 22–25 September 2001, in Cologne, it was decided that a review workshop should be convened to assess features of this particular problem from the point of view of population studies, clinical trials, co-morbidity issues, histopathological variation and other clinically relevant features, in order to define a potentially prospective way of studying this particular population. This report distils the main features of this discussion.

Workshop participants

Participants in the workshop were individuals who had specific interest and involvement, having previously performed studies on HD in patients >60 years old, and are the presenters and co-authors of this report.

HD in the elderly: incidence

In an unselected, population-based study of HD, conducted by the Scotland & Newcastle Lymphoma Group, patients have been registered and assessed for treatment and outcome, irrespective of entry into a specific trial [6]. This has allowed an assessment of the incidence of HD in patients >60 years of age from the population base. Figure 1 shows that 20% of the population are in the >60 age group.

In a very detailed study from the Northern Region Health Authority, within the Scotland & Newcastle Lymphoma Group, over an 8-year period, from a population of 3 million people, 521 cases of confirmed HD were diagnosed. Of these, 112 were in the >60 years age bracket. In contrast, in the randomised trials of the German Hodgkin Study Group (GHSG) the proportion of patients >60 years of age was only 10% [7].

Prognosis

Utilising therapeutic modalities available in the 1990s, it can be seen that in the Northern Region Haematology Group Study for patients <60 years of age, survival outcome was very good (Figure 2), but decays rapidly in patients >60 years of age. Figure 3 shows this population-based cohort of patients compared with a survival curve conducted for fit and healthy patients aged >60 years [6].

In detailed description of this patient cohort it was clear that in the 60–69 years group with early stage disease the outcome was very good, but advanced-stage demonstrated a 50% survival at 3 years. In patients aged >70 years early and advanced stages showed poor outcome with a median survival at 2 years in early stage disease of 50% and median survival for advanced-stage <6 months. Clearly, there is substantial room for improvement. Findings in comparable studies were similar [2, 3, 7–9].

Histopathological aspects

The Workshop discussed detailed review of histopathology of patients >60 years and essentially it was noted, again from
population-based studies, that the patterns of lymphocyte predominant mixed cellularity and nodular sclerosing were not dissimilar [7, 10, 11]. Whilst lymphocyte rich classical HD was really quite uncommon in all age groups, there was an increased incidence in patients >60 years of age. It was also noted that when histopathological grading was performed, using the two variants for nodular sclerotic disease, NS1 versus NS2, there was a highly significant reduction in survival for the NS2 variants. Similarly, when account was taken comparing outcome for the lymphocyte rich classical versus mixed cellularity, there was a substantial advantage for those patients with the former histology.

By far the most striking feature that emerged at the Workshop from a number of studies was that in this particular age group, where the Reed-Sternberg cells were positive for Epstein–Barr virus (EBV) markers, patients had a particularly poor outcome on conventional treatment. EBV-negative patients faired much more satisfactorily. It was noted with interest that is was the reverse to findings in patients in younger age groups [12].

It is therefore clear that in any future studies of HD these various characteristics would need to be taken into account in terms of stratification for any trials to avoid misleading results.

**Co-morbidity and therapy dose intensity**

A key point within discussions about proposed treatment strategies related to those patient characteristics that prevent appropriate treatment being delivered to this particular patient group. Attention was drawn to the fact that in the <60 years of age population, between 13% and 20% of patients will have an associated co-morbidity necessitating reduced drug dose intensity. In the >60 years of age group, >50% of patients have
such co-morbidities, usually involving cardio-vascular disease, hypertension, pulmonary disease or diabetes. In the study of a large number of patients by van Spronsen et al., it was noted that with co-morbidity, 50% less chemotherapy was administered to elderly patients with HD [13, 14].

The conclusion drawn from these discussions was that the extent of co-morbidity is not represented in current clinical trials, and that inclusion criteria for trials with Hodgkin’s patients >60 years of age must be modified. It is clear that co-morbidities have a great impact on treatment, and therefore any treatment guidelines within trials have to be more detailed in older patients to avoid toxic deaths. It is also quite clear that co-morbidities do cause dose reduction, and therefore treatment has to be tailored to the specific needs of the older patient to avoid this dose reduction.

**Which chemotherapy in the over 60s?**

Relatively few studies are available in this age group that have been conducted on unselected populations [1, 2–4, 15–17]. At the present time it is considered that there is no true gold standard against which any new treatments might be assessed. In fact, it was concluded that there is a substantial need to create a standard of approach, and it was generally considered that ABVD (doxorubicin, bleomycin, vincristine and dacarbazine) given in full curative doses with granulocyte colony-stimulating factor (G-CSF) support should be the main regimen against which others might be tested. Concern was expressed about the acceptability of full-dose adriamycin in these patients, particularly those with cardiac co-morbidity, but weighed against this was the issue of giving fully effective Hodgkin’s treatment to create an initial baseline against which other treatments could be measured [18].

It was noted that in patients, particularly between the ages of 60 and 70 years, in various studies where regimens were introduced and dose intensity maintained, remission rates were very good (but less good than in the <60 years age group) and survival rates improved.

Levis et al. [15] described the treatment of a cohort of 80 patients, utilising the VEPEMB (vinblastine, cyclophosphamide, procarbazine, prednisone, etoposide, mitoxantrone, bleomycin; Figure 4) regimen and made comparisons with the efficacy and acceptability of the regimen in comparison with the retrospective delivery of ABVD on another cohort of patients. This regimen, described in Figure 4, links the utilisation of drugs commonly used in HD in a sequential fashion, aimed at giving moderate dose intensity over a 19-day period, with cycles every 28 days. Current data utilising this regimen suggest a CR rate of 100% for low-risk patients and 65% for high-risk patients, with acceptable toxicity.

An alternative approach is the concept of utilising ABVD but excluding one of the key elements associated with the toxicity, i.e. DTIC (dacarbazine), substituting prednisolone, and potentially to use such a combination in comparison with ABVD and a new regimen such as the VEPEMB if sufficient patients could be recruited in a pan-European programme.

**Pan-European Working Group: study of HD in the elderly**

The end point of the Workshop was to agree a specific way forward for study in this group of patients throughout Europe (Figure 5).

It was noted that from the population studies there are approximately five cases/million/year, and therefore within Europe substantial numbers of patients will present. The plan was proposed by the group to build a working organisation in which co-operating groups or nations would register all cases of HD in the elderly in a uniform way, utilising uniform data-sets. That way, for all cases a detailed histological review would be undertaken and sufficient information would be collected to provide the possibility of developing different forms of prognostic index in this particular age group [19, 20].

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*Every 28 days*

*Figure 4. VEPEMB regimen.*
It would then be possible, using this baseline information, to monitor how early stage patients were treated, utilising the national guidelines of the groups concerned with a view towards moving to a uniform pan-European approach. It was not considered that a specific trial should be introduced for this group of patients in the first instance.

In the advanced-stage patients, it was felt that there were three potential approaches:
1. Patients >60 years of age who were quite fit, where it was possible to use the aggressive treatment used for patients <60 years of age, should be entered into their appropriate national or regional studies, but information should be kept on how the patients performed with such an approach.
2. Conversely, it was felt that there would also be a population in the >70 years age group where the patients were very frail and had associated co-morbidity, and it was anticipated that an approach using an all-oral chemotherapy, aimed at disease control, could be introduced. The suggestion of using lomustine-based therapy in this age group was to be discussed.
3. It was considered that for all patients not in the categories described above, it would be highly advantageous to have a pan-European or possibly an international randomised controlled trial, and initial suggestions related to the use of a comparison between six cycles of ABVD plus GCSF versus six cycles of VEPEMB plus GCSF and, if a sufficient number of patients were anticipated to be available, to have a third arm of a modified ABVD regimen plus GCSF. Modification of the ABVD regimen could be decided by the national groups involved.

There was sufficient uniformity of view to agree in principle the issues discussed above and that the Scotland & Newcastle group would take the lead in formulating a protocol in the first instance.

Summary and conclusions

In general, it was agreed that high rates of toxicities during treatment occur in the elderly and that there is a frequent occurrence of early relapse. It is clear that different combinations of effective therapies with lower toxicity are required. It was felt, however, that certainly in the 60–70 year age group, approaches should be vigorous to and the same diagnostic and staging procedures as in younger individuals, but with much closer monitoring of toxicity and response to treatment. It was felt that as part of the approach, liberal support with haematopoetic growth factors (G-CSF) was necessary to reduce prolonged neutropenia.

It is important to understand that age in general is not a contrary indication for aggressive treatment and that biologically younger patients under the age of 65 years, in good physical and mental condition, often should be given with stage-adapted treatment, analogous to conventional treatment protocols for the <60 years age group.

It was also considered that, in patients who clearly could not accept conventional treatment, study groups could begin to define the best palliative care for patients with pre-existing organ impairment, and that in all situations of assessment, whether in trial or not, there should be a detailed prospective assessment of quality of life parameters.

References