Eur J Haematol 2005: 75 (Suppl. 66): 63–67

EUROPEAN
JOURNAL OF HAEMATOLOGY

An international approach to the treatment of Hodgkin's disease in the elderly: launch of the SHIELD study programme

Proctor SJ, White J, Jones GL. An international approach to the treatment of Hodgkin's disease in the elderly: launch of the SHIELD study programme
Eur J Haematol 2005: 75 (Suppl. 66): 63–67. © Blackwell Munksgaard 2005.

Abstract: Utilising the Scotland and Newcastle Lymphoma Group population data for Hodgkin's disease (HD), collected over a 20-year period, it is evident that 20% of patients are over the age of 60 yr at diagnosis. Data from 674 patients are available. This group comprised 346 men and 328 women. Median follow-up was 9.5 yr. In total 361 patients had stage I/II disease. In this cohort overall response and complete response (CR) rates were 88% and 79%, respectively, for treated patients. Overall 308 patients had stage III/IV disease. Among treated patients in this cohort, overall and CR rates were 78% and 59%, respectively. Response data were missing for 26 patients with stage I/II disease and 43 patients with stage III/IV disease. The chlorambucil, vinblastine, procarbazine and prednisolone, mechlorethamine, vincristine, probarbazine and prednisolone and doxorubicin, bleomycin, vinblastine and decarbazine were the commonest chemotherapy regimens, in descending order of frequency, used to treat this cohort of patients. Outcome did not vary with these regimens. Thirty-four other chemotherapy combinations were used, some curative others palliative. These data and all other published studies confirm the need for a prospective, age-defined approach to HD in the elderly. Such an approach needs to be closely linked to issues of comorbidity, an assessment of frailness and the tailoring of specific protocols for the elderly to allow full dose delivery. The Study of Hodgkin Lymphoma In the Elderly/Lymphoma Database programme has now been launched and attempts to address these issues (http://www.shieldstudy.co.uk).

Stephen J. Proctor[1], Jo White[2], Gail L. Jones[1]

[1]Department of Academic Haematology, Medical School, University of Newcastle, Newcastle upon Tyne, UK; [2]Medical Statistics Unit, PHS, University of Edinburgh, Teviot Place, Edinburgh, UK

Key words: Hodgkin's Lymphoma, Elderly, Population-based, Treatment Comorbidity.

Correspondence: Stephen J. Proctor, Department of Academic Haematology, Medical School, University of Newcastle, Newcastle upon Tyne, UK
Tel: +44-191-2824261
Fax: +44-191-2225542
e-mail: s.j.proctor@ncl.ac.uk

In 2001, at the Fifth International Hodgkin Lymphoma (Hodgkin's disease; HD) meeting in Cologne, the subject of HD in the older patient came under intensive discussion for the first time in such a context (1). During a workshop session, issues were identified which delineated the problems faced by the elderly as separate from the difficulties encountered in younger patients. Many chemotherapy regimens, so successful in younger patients, could not be used to treat the majority of patients aged over 60 yr. The toxic effects of such chemotherapy prevented its administration at optimal dose intensity in this group of patients. As a result, with lower remission rates, the outcomes were inevitably worse (2–6).

To address these difficulties, it seemed necessary to introduce an effective therapy or therapies specifically designed for the older person, aiming at full dose delivery in a defined time frame but with a toxicity profile, which was acceptable. At that time it was recognised that such treatment could only be defined if difficulties in the objective evaluation of frailty in the elderly could be overcome. It was clear that an approach founded on the Comprehensive Geriatric Assessment, based on standard interviews and validated scales must be used (7). Such an assessment would include an objective comorbidity index, linked to measures of functional activity such as 'Activities of Daily Living (ADL)' and the 'Instrumental ADL' to

provide an objective frailty assessment for inclusion in prospective studies (8, 9). At the time, the only prospective study in progress to identify and address these issues was the Intergroup Italian study (IIL), which utilised a specifically designed chemotherapy regimen, vinblastine, cyclophosphamide, procarbazine, prednisolone, etoposide, mitoxantrone and bleomycin (VEPEMB). The data from this study are now published (10), and are discussed in detail below. The phase II study in the Study of Hodgkin Lymphoma In the Elderly/ Lymphoma Database (SHIELD) programme builds on this Italian experience with VEPEMB. This seems a logical approach given that this is the only prospectively constructed intervention to date on a defined patient population.

To further set the scene, with respect to the clinical problems associated with treating this group of patients, the experience of the Scotland and Newcastle Lymphoma Group (SNLG) are described including outcome data for almost 700 patients. We conclude with a description of the practicalities of the electronic SHIELD registration and study programme.

Population-based data for 674 elderly patients with HD: the SNLG experience

The SNLG have been collecting population-based data with respect to the incidence and outcome of patients with lymphoma since 1979. Between 1979 and 2003 data were accrued from 3373 patients with HD, of these 674 (20%) were aged ≥60 yr at diagnosis. The median follow-up was 115 months (9.5 yr). Over that time period various regional groups, within Scotland and northern England, gradually became involved in the registration process. After analysis of the rate of registration of lymphoma cases and cross-referencing with other relevant cancer registries, we believe that the SNLG database became truly population-based for Scotland and northern England (population 8 million) from 1994 (Fig. 1). In total 399 patients aged ≥60 yr were diagnosed with HD in the 10 yr from 1994. Using data from the relevant censuses (11, 12) the age-specific incidence of HD in this population is calculated to be 2.3 cases per 100,000 individuals aged ≥60 yr per annum.

Demographic data for the 674 patients diagnosed since 1979 are displayed in Table 1. The primary therapeutic modalities used to treat these patients can broadly be divided into radiotherapy alone ($n = 178$), chemotherapy alone ($n = 351$), combined modality treatment with chemotherapy and radiotherapy ($n = 87$), surgery alone ($n = 4$) and no treatment ($n = 49$). Primary treatment modalities, with respect to disease stage at presentation, are displayed in Table 2. Overall, 438 patients received chemotherapy as part of their primary therapy. The most commonly used chemotherapeutic regimens were chlorambucil, vinblastine, procarbazine and prednisolone (13) (ChlVPP; $n = 157$, 35.8%), mechlorethamine, vincristine, probarbazine and prednisolone (14) (MOPP; $n = 83$, 18.9%), doxorubicin, bleomycin, vinblastine and decarbazine (14) (ABVD; $n = 42$, 9.6%) and prednisolone, chlorambucil, vincristine, mitozantrone and etoposide (15) (PCOME; $n = 39$, 8.9%). Treating physicians reported the use of an additional 34 chemotherapeutic approaches including the use of various single agents and drug combinations.

Amongst treated patients with stages I and II disease (16) ($n = 343$), the overall response rate and complete response (CR) rates were 88% and 79%, respectively. Amongst treated patients with stages III and IV disease ($n = 277$) the overall response

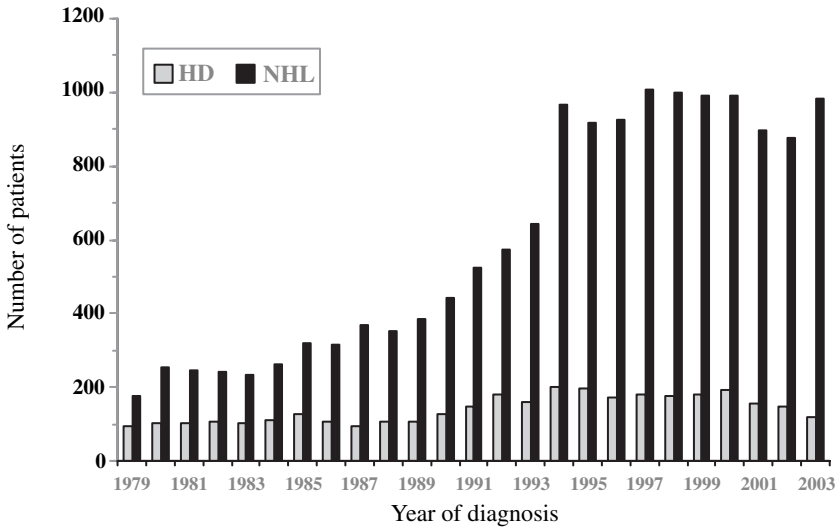

Fig. 1. Graph representing cases of lymphoma reported to the SNLG registry 1979–2003. Registration data are included from 3373 patients with HD and 12 709 patients with NHL. In total 694 of the patients with HD and 7948 of the patients with non-Hodgkin's lymphoma (NHL) were aged ≥ 60 yr at diagnosis.

Table 1. Patient characteristics and histological subtypes by clinical stage

	Male	Female	LP	NS	MC	LD	LRCHD	UC	Missing
CS I–II	175	186	47	124	132	26	7	21	4
CS III–IV	170	138	19	86	119	47	1	32	4
CS unknown	1	4	0	1	0	1	0	3	0

This table demonstrates the demographic features of the population-based cohort studied.
CS, Ann Arbor clinical stage; LP, lymphocyte predominant; NS, nodular sclerosing; MC, mixed cellularity; LD, lymphocyte depleted; LRCHD, lymphocyte-rich classical Hodgkin's disease; UC, unclassified.

Table 2. Treatment modality by clinical stage at presentation

	CS I–II ($n = 361$)	CS III–IV ($n = 308$)
Radiotherapy alone	163	15
Chemotherapy Alone	114	237
Combined modality	62	25
Surgery alone	4	0
No treatment	18	31

CS, clinical stage.

and CR rates were 78% and 59%, respectively. Data pertaining to response to therapy were missing for 26 patients with stages I and II disease, 43 patients with stages III and IV stage disease and one patient for whom clinical stage at presentation was also unknown. Median overall survival (OS) for patient's aged ≥60 yr in this cohort was 28 months, 45 months for those with stages I and II disease and 13 months for those with stages III and IV disease ($P < 0.0001$). The OS at 5 yr post-diagnosis was 35%, 44% and 24%, respectively (Fig. 2).

During the follow-up period there were 462 deaths; 221/361 patients (61%) with stages I and II disease and 237/308 patients (77%) of patients

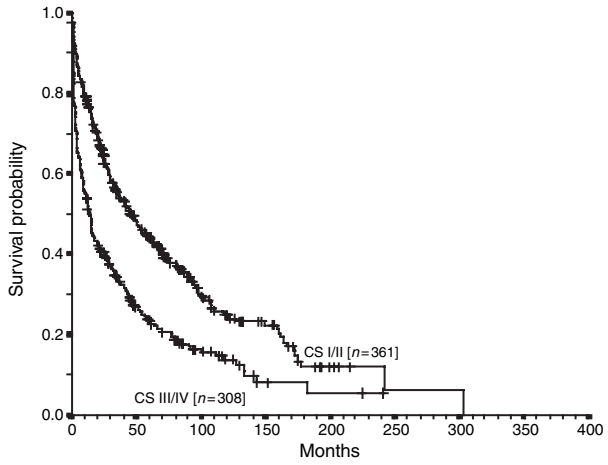

Fig. 2. The OS by clinical stage. This figure demonstrates the probability of OS for patients aged ≥60 yr old in this population-based patient cohort with time after diagnosis. The curves are significantly different ($P < 0.0001$). Abbreviations: CS, clinical stage.

with stages III and IV disease died ($P < 0.0001$). Data pertaining to initial staging investigations was missing for four patients who subsequently died. Death was reported, by the treating physician, as being due to HD in 88/221 (40%) of deaths amongst patients with stages I and II disease and 149/237 (63%) of patients with stages III and IV disease ($P < 0.0001$).

The age-specific incidence of HD, as determined by these data, is very similar to that defined in our group's study of HD within the Northern region of England (15). It must be noted, however, that 102 of 694 (15%) patients described in the current study were also included in the earlier publication. It can be concluded that HD in the elderly is clearly a relatively rare condition with only 399 cases occurring in a population of 8 million over a 10-year period. These data clearly demonstrate marked heterogeneity of therapy delivered to this cohort of patients. This heterogeneity seems likely to be due, at least in part, to the relative rarity of the disease; individual physicians are likely to see relatively few elderly patients with HD. In concordance with several previous studies (15, 17–19), this registry-based analysis demonstrated that most of the deaths in this cohort were due to HD, particularly amongst patients with higher stage disease. These factors make this condition an ideal candidate for an international registration-based approach, particularly if therapeutic guidelines can be incorporated.

Launch of the SHIELD programme

The detailed analysis of the SNLG data (15) and the paucity of information from prospective studies (10, 20–23) demonstrate that the idea conceived in Cologne 3 yr ago, to develop a prospective strategy of assessment, treatment and outcome, was correct. Progress to date has included a meeting of European partners in Lugano 2002; the concept of an on-line registry linked to defined phase II studies was agreed. Required data fields at registration and the principle of collecting fixed tissue and serum from patients at diagnosis were also agreed.

A plan was formulated to develop the basic elements of the programme in the UK, which were to include a trial protocol and a web-based data collection system for registration of cases. This latter system would also be used for data collection during and analysis after the study. Initially a randomised trial between ABVD vs. VEPEMB was proposed but the consensus in the UK was that the majority of patients in the age group concerned would not be able to tolerate ABVD. It was agreed, therefore, to assess the Italian regimen VEPEMB prospectively in a cohort of 150 patients in conjunction with performance status and quality

of life data. In addition, the registry would be used to collect data pertaining to patients considered too frail for curative therapy. Concurrent with this approach, the German group planned to develop a phase II study using a modification of the bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone (BEACOPP) schedule termed bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone (BACOPP) and a phase I/II study of a regimen incorporating gemcitabine (prednisolone, vincristine, procarbazine and gemcitabine; PVAG). The aim of this strategy was to use data from these studies to inform the design of a subsequent randomised trial.

During the time of the development of this programme, Levis *et al.* (10) have reported on their initial study of VEPEMB on 105 patients. The treated patients had a mean age of 71 yr (range 66–83) and 48 patients had early stage (stages I and II) disease. This group, treated with three courses of chemotherapy and radiotherapy, had a CR rate of 98% and 5 yr OS of 95%. Fifty-seven patients had advanced stage disease. This group included 18 patients with significant comorbidity and for whom treatment had to be modified. Nevertheless a CR rate of 58% for the unselected group was acceptable and was substantially better amongst those able to receive full dose-intensity therapy. The overall 5 yr survival for this group was 34% but of those remitting the 5 yr relapse free survival was 66% indicating that if CR can be achieved the survival rate is good. Clearly these results are of great value and represent the largest prospectively treated series. In addition this group concluded that comorbidity is a prognostic factor more important than age itself and suggested that alternative therapies need to be assessed for such frail patients.

Subsequent progress had to take into account the development of the new European Research Directive but all aspects of ethical approval and all elements of the on line system are now in place and can be viewed at http://www.shieldstudy.co.uk Presently the SHIELD programme aims to do two things:

(i) To register patients ≥ 60 yr who have developed HD. To collect clinically relevant data on presenting features, record treatment modalities and outcome linked to a defined detailed performance status (frailty index) including comorbidity data. We are aware that some patients, aged 60–65 yr in particular, may be eligible for treatments typically used to treat patients < 60 yr but we still wish to assess the outcome and tolerability of such treatments on the registry as well as the outcome of palliative regimens used to treat frail patients who are not considered eligible for curative therapy.

(ii) To offer a single arm study identical to that by Levis *et al.* (10) utilising VEPEMB and to assess the outcome of the medication in a defined non-frail population.

In Germany two additional phase II studies are currently active with BACOPP and PVAG and data comparing patient populations and outcome from these studies will inform the best way forward for randomised studies in the future.

The broader and long-term aims of SHIELD are to create international cooperation and eventually improve cure rates for HD within this age group and to use prognostic parameters (clinical and laboratory) to assess outcome prediction. The key for a rare disease in a vulnerable age group is to have a system that is purpose built to investigate the particular problems of the patient group; this is what SHIELD aims to do.

Published studies describe a number of different approaches to the management of elderly patients with HD. Data from the Omaha group suggest that patients treated with anthracycline-containing regimens have better outcomes than those treated with ChlVPP (24). In a retrospective study from the Vancouver group, the ODBEP regimen (vincristine, doxorubicin, bleomycin, etoposide and prednisolone) was reported to produce survival outcomes similar to those seen with MOPP/ABV, though with reduced toxicity (23). More recently, data from the German study group has shown that BEACOPP baseline or COP-ABVD can be given to a proportion of patients aged over 65 yr with CR rates of 76% and OS of 50% (22). Clearly these results are good but these regimens proved difficult to tolerate for many patients in this age group; 11/68 patients in this study died of therapy-related causes.

The intention of the SHIELD programme is to evaluate several possible regimens for non-frail patients with HD, in particular VEPEMB, PVAG and BACOPP. Our intention is to use these evaluations to design a randomised controlled trial for commencement in approximately 3-year time. For the more frail patients the aim is to evaluate outcome and toxicity of therapies used on the registry-based programme and in the longer term to develop a 'menu' of therapeutic options (25–27) including the best palliative interventions.

We would welcome involvement from all countries worldwide, and encourage you to contact us via the contact information on the SHIELD website at http://www.shieldstudy.co.uk

Acknowledgements

The authors wish to thanks all members of the Scotland and Newcastle Lymphoma Group, without whose cooperation this study would have been impossible. We acknowledge the contribution of Mrs. Jennifer Wilkinson the SHIELD administrator and study manager.

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