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The achievements of the EORTC Lymphoma Group

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Abstract

From 1964 onwards, the EORTC Lymphoma Group has conducted seven consecutive randomised phase 3 trials on early stage Hodgkin's lymphoma aiming at increasing efficacy, while decreasing short- and long-term toxicity. Staging laparotomy is definitely abandoned and replaced by identification of prognostic subgroups based on pretreatment clinical characteristics. Event-free and overall survival significantly improved from about 50 and then 70%, in the early years, to over 80 and then 90% more recently. Radiotherapy fields have become more restricted, whereas chemotherapy has become standard. Longitudinal quality-of-life assessment has become an integral part of our studies. In advanced stages, overall outcome has improved as well with 6-year survival rates of over 80%. In aggressive types of NHL, the second generation chemotherapy schedule CHVmP-BV was superior to CHVmP. We could not show any advantage for intensification of upfront treatment with autologous stem cell transplantation.

Keywords: Hodgkin's lymphoma; Non-Hodgkin's lymphoma; EORTC

1. Hodgkin's lymphoma

From 1964 to October 2001, a total of 6180 patients have been enrolled in nine consecutive EORTC Lymphoma Group randomised phase 3 trials in patients with Hodgkin's lymphoma (HD). 85% of these patients had early-stage disease (seven trials) and 15% advanced stages (two trials). A dramatic change in therapeutic strategy is the result of a consistent search by our group to try to improve the efficacy of staging and treatment, while decreasing short- and long-term toxic effects. This basic concept of all our trials in HD had already been set up and applied in the first randomised trial (H1 study) in 1964, initiated by Maurice Tubiana, one of the founders of our group [1].

1.1. Early stages HD

In the *H1 trial*, 288 patients were entered in the period 1964–1971 [2]. All patients had clinical stage I or II disease. No staging laparotomy was performed. Patients received regional Radiotherapy (RT) (mantle field in case of supradiaphragmatic disease and inverted Y for subdiaphragmatic stage I/II disease). Patients who achieved a Complete Response (CR) were then randomised between no further treatment and 2 years of weekly monochemotherapy with vinblastine. The 15-year follow-up showed a definite advantage in disease-free survival (DFS) for the combined treatment compared with RT alone (60% versus 38%). However, the overall survival (OS) did not differ significantly between both arms (65% versus 58%). The advantage of the combined treatment regimen was more evident in patients with unfavourable initial characteristics. A high incidence of relapses occurred in the para-aortic nodes in patients who received supradiaphragmatic RT only,

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in line with the rationale for performing staging laparotomy to detect occult abdominal disease.

In the *H2 trial*, patients with supradiaphragmatic CS I/II were therefore randomised between staging laparotomy, including splenectomy, followed by mantle field and para-aortic RT, and mantle field, para-aortic and spleen RT (STNI) without staging laparotomy. A total of 300 patients were entered from 1972 to 1976. The results of the staging laparotomy did not change the treatment policy. One of the important results was the significant increase of the DFS, as well as the OS compared with the previous H1 trial [3]. The improvement could be attributed to the treatment directed to the para-aortic nodes and the spleen. The DFS and OS did not differ significantly between the laparotomy and the no-laparotomy groups of patients: 76% versus 68% and 79% versus 77%, respectively. The prognostic significance of the laparotomy findings was most evident in patients with otherwise favourable pretreatment characteristics: those with a positive laparotomy had a significantly increased risk of relapse indicating the need for more aggressive therapy. In those with a more adverse pretreatment profile, the findings of laparotomy did not add to the estimation of the risk of relapse. This H2 trial showed that staging laparotomy could be omitted in certain subsets of patients, provided STNI is given instead of mantle field only. In addition, together with data from the previous H1 trial, we could derive a set of clinical prognostic factors that could identify groups of patients with a more favourable or unfavourable prognosis [4]. This offered the opportunity to develop treatment regimens tailored to these prognostic factors, in keeping with our original starting points.

The H5 and H6 trials as well as the more recent H7–H9 trials, all aimed at minimising treatment intensity to as little as was considered safe in the favourable subgroups and improving efficacy in the unfavourable subsets. These trials had a paramount impact for changing standards of care for patients with early stage HD. In the *H5 trial* (1977–1982), we used prognostic factors to develop different treatment strategies [5]. Patients with favourable characteristics (age $\leqslant 40$ years and erythrocyte sedimentation rate (ESR) $\leqslant 70$ and clinical stages (CS) I or II without mediastinal involvement; lymphocyte predominant or nodular sclerosing histology) underwent staging laparotomy. In those with a negative laparotomy ($n=198$), treatment was randomised between either mantle field RT only or mantle field plus para-aortic RT: there was no significant difference in the 6-year DFS (74 and 72%, respectively) and OS (96 and 89%, respectively). In those with unfavourable characteristics, including those with a positive laparotomy ($n=257$), randomisation was performed between total nodal irradiation (TNI) and combined modality treatment consisting of Mitoxine, Vincristine, Procarbazine, Prednisone (MOPP)×3 cycles followed by mantle field RT followed by another three cycles of MOPP. The combined modality treatment resulted in a significantly better DFS than RT only: 83% versus 66%, respectively. However, the advantage in OS was less evident: 88% versus 75% respectively ($P=0.06$). Refinement of the stratification in favourable and unfavourable subsets was another result of this H5 trial and this improved stratification was used in its successor, the *H6 trial* (1982–1988) [6]. Patients with favourable characteristics now included: CS I or II with a maximum of two involved areas, and no bulky mediastinum, and ESR $\leqslant 50$ mm if no B-symptoms were present or ESR $\leqslant 30$ mm in case of B-symptoms. These patients ($n=262$) were randomised between staging laparotomy or immediate treatment with STNI. In case of negative laparotomy, patients received either mantle field RT (in case of lymphocyte predominant or nodular sclerosing histology) or STNI (in case of mixed cellularity or lymphocyte-depleted histology). No significant differences between the two treatment arms were found in DFS. In the unfavourable subset ($n=316$), combined modality treatment was considered the new standard, based on the results of the H5 trial, and patients were randomised between two different chemotherapeutic regimens, e.g. MOPP or Adriamycine, Bleomycine, Vinblastine, Dacarbazine (ABVD), both in a sandwich-schedule of three cycles, then mantle field RT, then another three cycles. Although the ABVD-arm had a superior DFS, this was not translated into a superior OS.

This consecutive series of four large randomised trials in early stages HD, provided a solid basis for future trials (Fig. 1). We had convincingly demonstrated that staging laparotomy can be safely omitted on the basis of pretreatment clinical characteristics. Those with unfavourable features need combined treatment anyway, whether or not occult abdominal disease is present. Those with favourable profiles can be treated by STNI with a similar outcome as obtained by staging laparotomy followed by mantle field RT. Importantly, overall results gradually improved over the years. (Fig. 2) [7–10]. Long-term follow-up data, however, indicated that in HD survivors there is a life-long excess of deaths due to other causes, including second malignancies and cardiovascular events. These important conclusions from our studies were corroborated in the report from the International Database of Hodgkin's Disease that was presented at an exciting meeting in Paris in 1989 [11]. In this enormous enterprise initiated by our group, almost all cooperative groups from all over the world participated by providing data from their trials. For example, the increase in the incidence of breast cancer in young women after treatment by mantle field RT before the age of 30 years has now led to the advice for yearly mammography starting 10–15 years after RT. Surely, adaptation of primary treatment for the HD itself should also be part of our activities by trying to

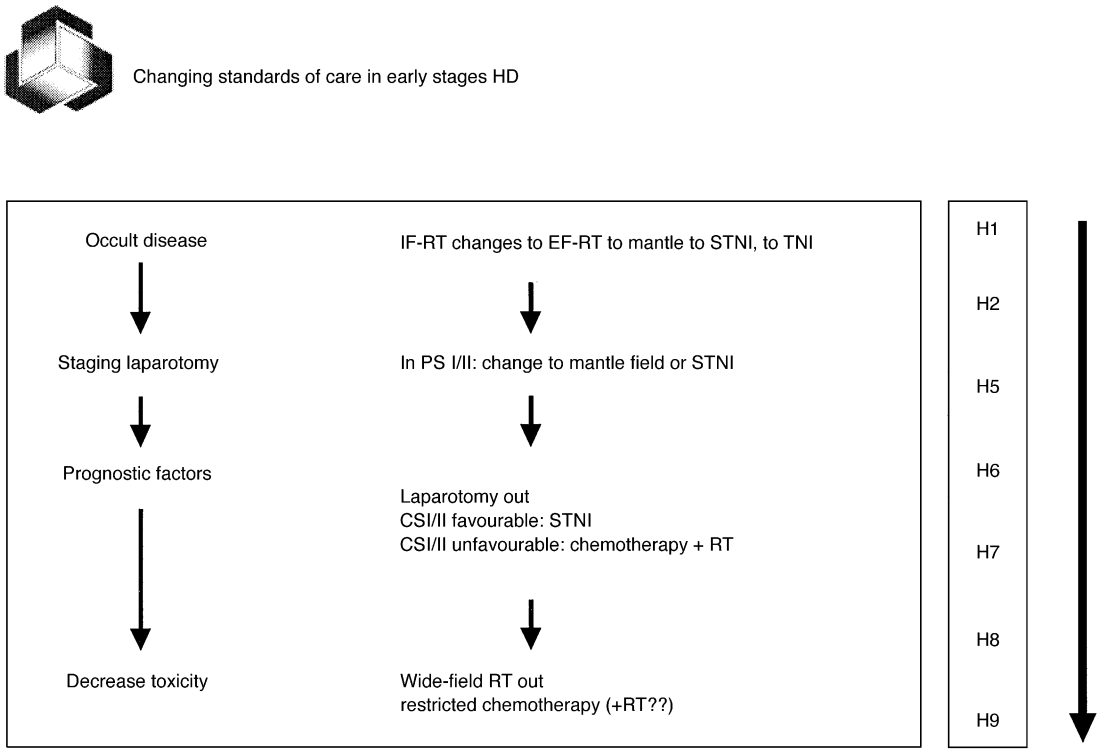

Fig. 1. Changing standards of care in early stages HD. RT, radiotherapy; HD, Hodgkin's disease; TNI, total nodal irradiation.

prevent—as much as possible—exposure to the identified toxic treatment regimens, without losing the efficacy. Very similar thoughts and considerations should be given to the prevention and management of other second malignancies (Acute Myeloid Leukemia (AML), Myelodysplastic Syndrome (MDS), lung cancer), as well as cardiovascular complications. Hopefully, effects on fertility, pulmonary and thyroid functions can also be modified [12–16]. The psychosocial effects, not only of having the disease, but also of the short- and long-term effects of treatment, are now increasingly being acknowledged as important parameters in the evaluation of our therapeutic interventions. Our group plays a major role in these evaluations by taking the lead in longitudinal *quality-of-life* monitoring in our more recent trials [17,18]. The EORTC H7–H9 trials are clear examples of this combined, multidisciplinary approach. In the meantime, demonstrating statistically significant improvements in for example CR rates, relapse-free survival (RFS) or OS require such enormous amounts of patients that co-operation with other groups is necessary. A fruitful collaboration with the French GELA group has been firmly established from the H8 trial on and facilitates the possibility of running large randomised trials with relevant and urgent questions in a short period of time.

In the *H7 trial* (1988–1993), staging laparotomy was definitely abandoned [19]. We defined three prognostic subgroups. The very favourable group consisted of female patients <40 years with lymphocyte predominant or nodular sclerosing HD and CS IA disease with ESR <50 mm and no mediastinal bulk. This small subset of patients (5–6%) was estimated to have a very low risk of infradiaphragmatic disease and was therefore treated by mantle field RT alone. On the other end of the spectrum was the unfavourable subgroup with age $\geqslant 50$ years or CS II disease with more than three involved areas, or A with ESR $\geqslant 50$ or B with ESR $\geqslant 30$ or bulky mediastinal involvement. These patients (about

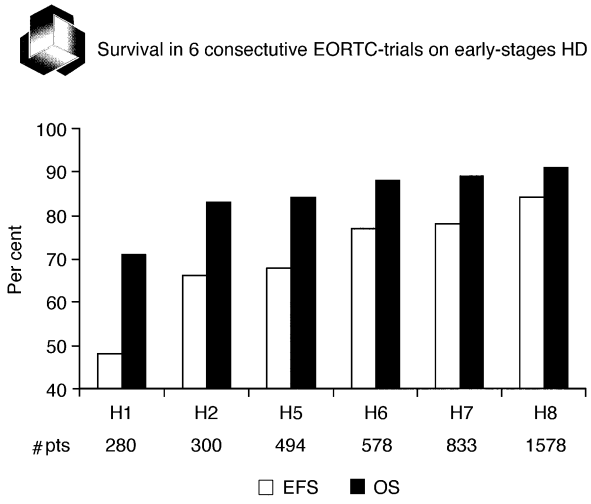

Fig. 2. Survival in consecutive EORTC Lymphoma Group trials on early stages HD. EORTC, European Organization for Research and Treatment of Cancer; HD, Hodgkin's disease; #pts, number of patients; EFS, Event-free Survival; OS Overall survival.

50% of patients) were treated right from the start with combined modality regimens. The remaining group of about 45% of patients belonged to the favourable subset. In the latter, the question was asked whether STNI could be replaced by the combination of a relatively non-toxic chemotherapy schedule and limited-field RT. The chemotherapy schedule used was the EBVP adaptation of ABVD: doxorubicin was replaced by epirubicin because of its presumed reduced cardiotoxicity, dacarbazine was omitted because there was considerable doubt about its efficacy in HD, prednisone was introduced instead. In addition, the schedule was changed from the days 1 and 15 scheme in ABVD to only day 1 every 3 weeks in the EBVP schedule. The same EBVP schedule was used in the unfavourable group: six cycles of MOPP/ABV (Adriamycine, Bleomycine, Vinblastine) + IF-RT was compared to with six cycles of EBVP + IF-RT. A total of 762 patients were enrolled. At the first analysis, with a median follow-up of 6 years, the EBVP + IF-RT (involved-field radiotherapy) treatment yielded a significantly better EFS than the STNI-treatment arm in the favourable subgroup. However, in the unfavourable group EBVP was inferior to the MOPP/ABV chemotherapy arm in terms of EFS. Therefore, we concluded that STNI was probably no longer the standard treatment for patients with supradiaphragmatic CS I or II HD with favourable clinical pretreatment characteristics. However, because of the restricted follow-up period at that first analysis, we could not yet draw more definite conclusions. For the unfavourable group, MOPP/ABV remained the standard chemotherapy. Unexpectedly, we encountered a relatively high relapse rate in the small group of patients with very favourable characteristics, treated with mantle field RT only. The relapse rate approached 40%, although the overall survival was excellent, reflecting the availability of good salvage treatments. Nevertheless, we decided to maintain this treatment in the next H8 trial before excluding this treatment option in future trials [20].

Based on the results of the H6, and preliminary data from the H7, we started the *Intergroup H8 trial* together with the Group d'Etude de Lymphomes Adultes (GELA) group. This very successful trial accrued 1578 patients between 1993 and 1998. The same prognostic factor profile as used in the H7 trial, was applied. A first analysis with relatively short follow-up has been performed already. In the very favourable patients treated with mantle field RT only, again a high relapse rate was noted. Therefore, we decided that the very favourable group was not adequately treated with mantle field RT alone, despite good salvage treatment results. In the favourable arm, we again tested STNI as the standard arm against a restricted number of cycles of standard chemotherapy (three cycles of MOPP/ABV) followed by IF-RT. The STNI arm was inferior to the combined modality treatment in terms of EFS as well as in OS. In the unfavourable group, three arms were tested: six cycles of MOPP/ABV + IF-RT, four cycles of MOPP/ABV + IF-RT or four cycles of MOPP/ABV + STNI. Preliminary analysis showed no differences between the treatment arms, neither in EFS nor in OS.

These results from H6–H8 trials, summarised in Figs. 1 and 2, gave the solid basis for the design of the *current H9 trial*, again in cooperation with GELA. In this study, we addressed the question whether RT can be decreased or even omitted in favourable patients. The STNI has been abandoned as standard treatment and the new standard is six cycles of EBVP followed by IF-RT (36 Gy). This standard arm is being compared with the same chemotherapy, but followed by 20 Gy IF-RT or even no RT, evidently only for those patients who have reached a CR or a CRu after six cycles of EBVP. The unfavourable category of patients are being randomised between six cycles of ABVD, four cycles of ABVD, or four cycles of the baseline Bleomycine, Etoposide, Adriamycine, Cyclophosphamide, Vincristine; Procarbazine, Prednisone (BEACOPP) schedule, all followed by IF-RT. The H9 trial started in 1998 and has already accrued more than 1000 patients after 2.5 years. Importantly, in these studies a quality assurance of RT is initiated. This huge effort was started in the French centres and supported by the French League for the 'Lutte contre le Cancer' and is now being extended to other countries as well. In addition, in these latest H8 and H9 trials, a complete prospective QOL monitoring is included which will provide unique long-term QOL data of patients with early-stage HD treated in prospective randomised trials in EORTC/GELA centres.

1.2. Advanced stages HD

For advanced stages of HD, stages III and IV, two consecutive trials have been performed and the third is scheduled to start at the end of 2001. In the *first H34 trial* [21], the concept of treatment adaptation according to rapidity of response was included. In general, a total of eight cycles of chemotherapy is considered standard treatment for patients with advanced stages HD. However, our group has pioneered the use of only six cycles in those patients who reached already a CR after four cycles, the so-called early responders. The results of this H34 trial supported this concept, although it was not part of the randomisation question. The patients were randomised between MOPP and MOPP alternated with ABVD. The study (1981–1988) showed superiority for the alternating chemotherapy schedule in terms of EFS and disease-specific survival. Therefore, MOPP was no longer standard chemotherapy and in the next trial MOPP was replaced by the hybrid schedule MOPP/ABV, at that time considered worldwide as probably the best chemotherapy schedule for HD.

In the *#20884 trial*, the main objective was to address the question whether RT is required after a chemotherapy-induced CR [22]. To this end, we applied IF-RT, including all originally involved areas of disease. The randomisation was performed between IF-RT and no further treatment for all patients who reached CR upon MOPP/ABV. Patients who achieved an early CR on four cycles of MOPP/ABV received a total of six cycles, and those with a late CR (after six cycles) received eight cycles. For patients who reached only a PR after six cycles, all received IF-RT. Despite a long accrual period of more than 10 years, we completed this important trial in 2001 and accrued over 700 patients. First detailed analysis showed that IF-RT did not improve RFS or OS in patients who already achieved a CR with MOPP/ABV. Remarkably, those who reached a PR and were treated with additional IF-RT, had comparable overall outcome as those who reached a CR. A detailed analysis including quality control of RT, is now being performed and will be finalised early 2002 (supported by the Dutch Ank van Vlissingen Foundation).

The forthcoming study on advanced stages HD will be a large transcontinental *intergroup effort (#20012)*. We will compare eight cycles of ABVD, versus the promising new schedule BEACOPP, four cycles of escalated doses followed by four cycles of baseline doses. This study is meant only for those with a poor-risk profile according to the International Prognostic Score for advanced HD. For those with a more favourable prognostic score, new concepts are being prepared.

2. Pathology

Right from the start, our group realised that a central review of pathology was absolutely required, not only to validate and standardise histological diagnosis, but also to have the opportunity to start scientific projects on the tissue specimens. A group of central pathologists was installed. The review of the HD cases has gradually led to the HD panel in which even pathologists from the British National Lymphoma Investigation (BNLI) actively participate. Studies on the prognostic significance of the subtyping of nodular sclerosing types of HD, BNLI types I and II, have been successfully performed. However, due to the efficacy of our treatment for patients with HD, the initially established poor prognostic subset identified by BNLI type II cases, could not be reproduced in the large randomised trials H7, H34 and H8.

In 1985, we reported on the reproducibility and prognostic value of different Non-Hodgkin's Lymphoma (NHL) classifications, e.g. the Kiel classification, the Rappaport and the International Working Formulation. Consensus rates of about 70% were reached [23]. Agreement on categorisation into nodular, nodular and diffuse, diffuse growth patterns even reached 93%. In 1996, we reported on the results of reclassifying 670 cases from two group trials according to the Revised European-American Classification of Lymphoid Neoplasm (REAL) [24]. Our data corroborated the recognition of several NHL entities with distinct clinical behaviour through this new REAL classification system [25]. In a separate study on mantle cell lymphomas, we evaluated the clinical outcome of these patients. Since some of these patients were enrolled in trials for low-grade NHL and others in trials for intermediate- and high-grade NHL, the impact of different treatment schedules could be analysed. Compared with the other low-grade NHL, survival was twice shorter, but initial response and PFS rates did not differ. In comparison to other intermediate- and high-grade NHL, mantle cell lymphoma patients showed a shorter duration of response and PFS. No optimal treatment for these patients could be identified [26].

3. Non-Hodgkin's lymphoma

3.1. Indolent subtypes

Several prospective randomised studies have been performed on the introduction of new drugs in the treatment of patients with indolent NHL (formerly: low-grade malignancy). In particular, the follicular subtype of NHL was the main focus of our interest. In 1985, a randomised trial was started on maintenance treatment with interferon-alpha for 1 year versus no further treatment in patients with stages III or IV who had reached a response upon induction treatment with eight cycles of Cyclophosphamide, Vincristine, Prednisone (CVP) chemotherapy [27]. A total of 242 patients were randomised. There was a modest, but significant, improvement of progression-free survival (PFS) of about 12 months in the IFN(interferon)-alpha-treated group of patients, but this did not translate into a better OS. In our next trial on indolent NHL, the purine analogue fludarabine was introduced in an intergroup study together with the British National Lymphoma Investigation Group, Dutch-Belgian HOVON, Italian Lymphoma and Swiss SAKK group in which previously untreated patients with stages III or IV were randomised between eight cycles of CVP and eight cycles of Fludarabine (1993–1997). Preliminary analysis of data of the 381 randomised patients showed a significantly higher CR rate in the fludarabine-treated group of patients. However, there were no differences in EFS or in OS.

New initiatives on indolent NHL include the recently opened randomised trial for patients with stages I or II, with a randomisation between IF-RT or IF-RT + low-dose total body irradiation (TBI). For advanced stages,

an intergroup study with the Dutch-Belgian HOVON group is being prepared. For relapsed patients, a large intergroup study is running in which patients with relapsed follicular NHL are randomised between CHOP chemotherapy and Cyclophosphamide, Adriamycine, Vincristine, Prednisone (CHOP) + anti-CD20 antibody therapy (Mabthera) with or without maintenance. In close conjunction with these indolent NHL trials, the biology theme group has conducted a quality control project between different labs concerning the quantitation of $t(14;18)^+$ cells in blood using the real-time Taqman Polymerase Chain Reaction (PCR) technique. Results on DNA samples showed high reproducibility and concordance between laboratories, offering the opportunity to incorporate these analyses in future trials.

Balancing between indolent and aggressive types of NHL, the mantle cell type deserves separate attention. A large European network on mantle cell lymphomas has been established in which our group actively participates in developing new intergroup trials and pathology projects for this relatively rare disease.

3.2. Aggressive subtypes

In 1975, the #20751 trial consisted of a mixture of patients with NHL who received various combinations of CHOP-like chemotherapy [28]. Because pathology subgroups were not yet recognised at that time, results are difficult to interpret. From 1980 to 1985, the second-generation chemotherapy schedule developed by our group CHVmP-BV (cyclophosphamide, doxorubicin, teniposide, prednisone combined with vincristine and bleomycin at mid-cycle intervals) was evaluated in a randomised prospective trial versus the CHOP-like variant CHVmP [29]. In this trial for previously untreated stages III/IV patients, 15–70 years of age, 141 patients have been enrolled. The CHVmP-BV schedule had a significantly higher CR rate than the CHVmP schedule: 74% versus 49%. Similarly, the freedom-from-treatment failure (FFTF) and OS were improved. This improvement persisted even after a follow-up of 10 years. With these results, we considered the CHVmP-BV schedule as our standard chemotherapy and in the successive study we compared it with the third-generation schedule ProMace (Prednisone, Methotrexate, Adriamycine, Cyclophosphamide, Etoposide)-MOPP. This randomised study failed to show any advantage for the third generation scheme, but instead increased toxicity of the new schedule [30].

In the group's next trial (#20901), we evaluated whether upfront intensification of treatment with autologous stem cell transplantation (ASCT) could improve the outcome [31]. Previously untreated patients with stage I bulky, II, III or IV aggressive types of NHL up to 65 years of age, were randomised between eight cycles CHVmP-BV or six cycles of CHVmP-BV followed by ASCT. Randomisation was performed only in those patients who had reached a CR or PR after three cycles of chemotherapy. From 1990 to 1998, 311 patients have been accrued. After a median follow-up of almost 5 years, the intention-to-treat analysis showed no significant differences between the two treatment arms in PFS nor in OS.

Elderly patients with aggressive types of lymphomas have an even worse prognosis than the younger ones. For this group of patients, almost one-third of all patients with aggressive NHL, CHOP is the standard treatment as well. Less toxic and preferably more efficacious treatment regimens are therefore needed. The VMP (etoposide, mitoxantrone, prednimustine) schedule pioneered at the Aviano Cancer Center, was a presumed candidate and this schedule was prospectively analysed in the randomised trial against CHOP. Between 1989 and 1994, 130 patients with aggressive types NHL over 70 years of age, stages II, III or IV were enrolled [32]. Unfortunately, no improvement was seen with the new VMP regimen. In contrast, CHOP remained the standard with a superior PFS of 55% versus 25% and OS of 65% versus 30%.

Obviously, these data show that we need innovative approaches for patients with aggressive NHL. New drugs have to be tested, so-called small molecules should be incorporated in regimens, and the concept of dose intensification should be carefully reconsidered. Probably, as shown in HD, the intelligent use of prognostic factors can guide and tailor treatment strategies in the near future. In this respect, the International Prognostic Index (IPI) could be very useful in identifying patients who can be treated safely by CHOP or CHVmP-BV and those for whom new treatment avenues are indicated. In addition, the recognition of distinct entities of NHL as reflected in the new pathology classification system of the World Health Organization (WHO), asks for differentiated approaches. For example, the treatment of patients with central nervous system NHL is now being addressed by our group and these initiatives will lead to further strengthening of the international cooperation with a prominent role for the EORTC.

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