ELSEVIER

European Journal of Cancer 40 (2004) 474–480

European Journal of Cancer

www.ejconline.com

Review

Long-term efficacy of the CHVmP/BV regimen used for aggressive non-Hodgkin's lymphoma in three randomised EORTC trials

E.C. Moser[a,b,*], E.M. Noordijk[b], M. van Glabbeke[a], I. Teodorovic[a], C. de Wolf-Peeters[c], P. Carde[d], J.W. Baars[e], U. Tirelli[f], J.M.M. Raemaekers[g], J.C. Kluin-Nelemans[h]

[a]*EORTC Data Center, Brussels, Belgium*
[b]*Department of Radiotherapy, Leiden University Medical Center, Albinusdreef 2, PO Box 9600, 2300 RC Leiden, The Netherlands*
[c]*Department of Pathology, U.Z. Gasthuisberg, Leuven, Belgium*
[d]*Department of Oncology, Institute Gustave Roussy, Villejuif, France*
[e]*Department of Medical Oncology, Antoni van Leeuwenhoekziekenhuis, Amsterdam, The Netherlands*
[f]*Department of Oncology, Centro di Riferimento Oncologico, Aviano, Italy*
[g]*Department of Hematology, University Medical Center Nijmegen, Nijmegen, The Netherlands*
[h]*Department of Hematology, University Medical Center, Groningen, The Netherlands*

Received 4 August 2003; received in revised form 30 September 2003; accepted 4 November 2003

Abstract

We analysed data from 936 newly-diagnosed patients with advanced, aggressive non-Hodgkin's lymphoma (NHL) treated in three randomised European Organisation for Research and Treatment of Cancer (EORTC) trials performed between 1980 and 1999 (median follow-up of 8.7 (0.2–20.4) years). The CHOP-like regimen CHVmP/BV (cyclophosphamide, doxorubicin, teniposide and prednisone with bleomycin and vincristine at mid-interval), was compared with CHVmP (CHVmP/BV without bleomycin and vincristine), ProMACE-MOPP (methotrexate, doxorubicin, cyclophosphamide, etoposide, mechlorethamide, vincristine, procarbazine and prednisone) and CHVmp/BV with additional, autologous stem-cell transplantation, respectively. Overall, treatment with CHVmP/BV resulted in a better long-term outcome with 63% complete responses being observed and an overall survival (OS) of 59 and 43% at 5 and 10 years, repectively. Remarkably, OS after CHVmP/BV improved across the trials, even after stratifying for the International Prognostic Index (IPI). This finding could not be directly related to better salvage treatments during the last decade. Selection bias appears to be responsible: stepwise corrections for small differences in inclusion criteria eliminated the difference in OS, especially when histological subgroups were studied. This systemic review underlines the difficulties encountered in retrospective sub-set analyses and the biases that can be introduced when recent studies are compared with older ones.

Keywords: Long-term outcome; Advanced aggressive NHL; CHVmP/BV regimen; Sub-set analyses

1. Introduction

Patients with advanced, aggressive non-Hodgkin's lymphoma (NHL) can be effectively treated with multi-agent chemotherapy. Although most (55–80%) patients below the age of 65 years will experience a complete remission (CR) after 6–8 courses of CHOP-like chemotherapy, less than 50% will be cured. Many trials have been performed, several within the European Organisation for Research and Treatment of Cancer (EORTC) [1], introducing new drugs and more aggressive approaches, with the aim of improving the outcome of this group of NHL patients. Since 1980, the CHVmP/BV scheme (eight cycles of cyclophosphamide, doxorubicin, teniposide and prednisone with bleomycin and vincristine in every cycle at the mid-interval), which contains cyclophosphamide, doxorubicin, teniposide and prednisone combined with vincristine and bleomycin, has been consistently used in three consecutive EORTC phase III trials [2–5]. Combining these trials resulted in a unique chance to review the efficacy of this regimen over a 20-year period. We observed remarkably large differences across the trials in long-term outcome data. By presenting our analyses, we want to underline the risk of comparing recent studies with older ones, showing the biases that can be introduced by retrospective sub-set analyses.

* Corresponding author. Tel.: +31-7152-63057; fax: +31-7152-66760.
E-mail address: e.c.moser@lumc.nl (E.C. Moser).

0959-8049/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2003.11.003

2. Patients and methods

2.1. Eligibility

Between 1980 and 1999, 936 newly-diagnosed and untreated patients with advanced, aggressive NHL were registered in three prospective, phase III randomised EORTC-trials (20802, 20855 and 20901). Follow-up was missing or incomplete in 23 patients. Therefore, altogether, 913 patients could be analysed. All three trials were designed for intermediate or high-grade NHL classified by the Working Formulation (WF) as D-J [6]. Histological classification (Table 1) was performed by the local pathologist and reviewed by a Lymphoma Pathology Panel after randomisation. The panel was supervised by the same person in all the trials, who reviewed all cases in the WF classification, so no new pathology review was performed for our systemic review. All cases, including 52 low-grade NHL, 22 Lymphoblastic and 15 Burkitt's lymphoma after panel review, were included in the analysis. In all patients, the WHO performance status was less than 3. The inclusion criteria regarding age and Ann Arbor stage were somewhat different throughout the three trials. Advanced disease was defined in trial 20802 as Ann Arbor stage III or IV, while in 20855 stage II patients were also accepted. In trial 20901, patients with stage I bulky (>10 cm) were included as well, if histology was classified as WF high grade. In trials 20802 and 20855, the age of the patient was limited to 15–70 years. In trial 20901, the initial upper age limit was 60 years, but this was increased during the course of the trial to include those aged up to 65 years.

2.2. International Prognostic Index (IPI)

The IPI [7] was computed (adding up points in case of age >60 years, WHO performance >1, Ann Arbor stage >II, raised lactate dehydrogenase (LDH) and more than one extranodal location at the time of diagnosis) in 867 patients and classified into low-, low/intermediate-, intermediate/high- and high-risk groups. In 38 patients, information on one or more of the five factors was missing (Table 2).

2.3. Treatment and review design

In the first trial (20802), 195 patients were randomised between 1980 and 1986 and 189 could be included in our systemic review. The CHVmP/BV regimen was compared with the old standard without the addition of bleomycin and vincristine (CHVmP).

In the next trial (20855), that ran from 1986 until 1990, 430 patients were randomised and 413 patients could be analysed. The new CHVmP/BV standard was compared with ProMACE-MOPP, also given for eight cycles. This third generation scheme consisted of doxorubicin, cyclophosphamide, mechlorethamine, vincristine, procarbazine, methotrexate and prednisone.

Trial 20901 ran between 1990 and 1999 and compared eight cycles of CHVmP/BV with six cycles of CHVmP/BV followed by consolidation with the BEAC regimen (BCNU, VP-16, Ara-C and cyclophosphamide) and autologous stem-cell transplantation (ASCT). In contrast to the previous two trials where upfront randomisation took place, here the patients were only randomised if either a partial response with a negative bone marrow sample or a complete response was obtained after the third cycle ($n=194$). In the systemic review, all 311 patients registered in trial 20901 were analysed (194 randomised and 117 non-randomised) together with the 189 and 413 randomised patients from trials 20802 and 20855.

In all three trials, radiotherapy was recommended for initial bulky disease (>10 cm) and partial response after three cycles. In 336 patients, areas of bulky disease and/or slow response were irradiated after protocol chemotherapy; a dose of 30–40 Gy was given.

2.4. Response criteria

Response was evaluated after three cycles and at the end of protocol therapy according to the WHO criteria [8]. Complete response was defined as the disappearance of all symptoms and lesions, including normalisation of

Table 1
Histological characteristics according to the Working Formulation

Working Formulation	Cell type	20802 *n* (%)	20855 *n* (%)	20901 *n* (%)	Total *n* (%)
Low grade	A, B or C	31 (16)	16 (4)	5 (2)	52 (6)
Intermediate grade	D	5 (3)	23 (6)	11 (3)	39 (4)
	E	23 (12)	52 (13)	20 (6)	95 (10)
	F	22 (12)	45 (11)	17 (5)	84 (9)
	G	57 (30)	181 (44)	165 (53)	403 (44)
High grade	H	15 (8)	45 (11)	4 (1)	64 (7)
	I (lymphoblastic)	14 (7)	7 (2)	1 (<1)	22 (2)
	J (Burkitt's)	6 (3)	7 (2)	2 (1)	15 (2)
Unclassified		16 (8)	37 (9)	86 (28)	139 (15)
	Total	189	413	311	913

Table 2
Distribution of IPI prognostic factors

	20802 ($n=189$) (%)	20855 ($n=413$) (%)	20901 ($n=311$) (%)
Age (years)			
$\leqslant 60$	131 (69)	267 (65)	303 (97)
>60	58 (31)	146 (35)	8 (3)
Ann Arbor stage			
I–II	12 (6)	145 (35)	122 (39)
III–IV	177 (94)	268 (65)	189 (61)
WHO performance			
$\leqslant 1$	147 (78)	342 (83)	270 (87)
>1	34 (18)	67 (16)	41 (13)
Missing	8 (4)	4 (1)	0
LDH			
Normal	141 (75)	385 (93)	142 (46)
Elevated	39 (21)	21 (5)	157 (50)
Missing	9 (5)	7 (2)	12 (4)
Extra nodal locations			
0–1 locations	172 (91)	375 (91)	293 (94)
>1	11 (6)	37 (9)	18 (6)
Missing	6 (3)	1 (<1)	0
IPI-score			
IPI low	78 (41)	251 (61)	176 (57)
IPI low/intermediate	68 (36)	44 (11)	81 (26)
IPI intermediate/high	25 (13)	98 (24)	40 (13)
IPI high	5 (3)	7 (2)	2 (1)
Missing	13 (7)	13 (3)	12 (4)

WHO performance, performance status classified as by the World Health Organisation; LDH, lactate dehydrogenase; IPI, International Prognostic Index.

blood values, X-rays and bone marrow. Partial response was defined as a decrease of at least 50% in the product of two perpendicular diameters in all lesions, a negative bone marrow and disappearance of symptoms. Progression was defined as an increase in size of at least 25% in one or more lesions or the occurrence of new lesions or symptoms. When the patient did not qualify for one of these three criteria, their response was defined as stable disease. Protocol treatment was stopped in cases of no change or progression after three cycles of chemotherapy.

2.5. Statistical analysis

Statistical analyses were performed according to the 'intention-to-treat principle' including all patients randomised in trials 20802 and 20855 or registered in 20901. Outcome was evaluated in terms of overall survival (OS), stated as the time between the date of randomisation and the date of death from any cause. Patients who were still alive when last contacted were censored at the date of their last follow-up. For the patients who were not randomly assigned, the OS was calculated as the time between the date of registration and the date of death. Survival curves were estimated by the use of the Kaplan–Meier method [9,10] and compared by the use of log-rank tests [11,12]. All statistical tests used were two-sided.

3. Results

3.1. Long-term efficacy

Out of 913 patients with advanced, aggressive NHL, 55 and 47% were still alive at 5 and 10 years, respectively (median follow-up of 8.7 (0.2–20.4) years). The median survival was 7.3 (0.2–20.4) years, with 388 (42%) patients still alive at the time of analysis. Protocol treatment was stopped in 168 (18%) patients after three cycles, showing no response; from the patients who continued protocol treatment, 63% of the patients treated with CHVmP/BV obtained a complete remission.

3.2. Randomised trials

Trial 20802 was updated with a median follow-up of 18 years. The previously established benefit of adding bleomycin and vincristine to CHVmP persisted in the prolonged follow-up, showing an overall survival rate at 10 years of 34 versus 21% ($P=0.009$, Hazard Ratio (HR) 1.56).

When CHVmP/BV (trial 20855) was compared with ProMACE-MOPP (median follow-up 12 years), a trend towards a better OS after CHVmP/BV was seen, but it was not statistically significant by the log-rank test (OS at 10 years 42 versus 37%, $P=0.064$, HR 1.27). How-

ever, in earlier analyses [3,4], it was clear that ProMACE-MOPP was associated with more (acute) toxicity.

In trial 20901 patients were randomised after 3 cycles between CHVmP/BV alone and CHVmP/BV plus ASCT. No benefit of the more aggressive approach was stated, even after a median follow-up of 8 years. Overall survival at 10 years was 70 versus 67% ($P=0.455$ HR 1.22).

3.3. Variation in patient outcome following treatment with CHVmP/BV

From the 529 patients treated with the CHVmP/BV regimen, 59 and 43% were still alive at 5 and 10 years, respectively. Comparison of results across the trials showed a remarkable improvement in OS over time ($P=0.001$, HR 0.73, Fig. 1). Our first hypothesis was that this variation could be due to improved rescue treatments in the last decade. Almost half of the patients (48%) in all three trials progressed or had recurrent disease and 82% of them received salvage treatment. Comparing the various initial rescue regimens, those containing ASCT resulted in a better OS ($P=0.011$ HR 1.26) and were more often used in patients registered in the 20901 trial. When long-term outcome after rescue treatment in trial 20901 was compared with outcome in trials 20802 and 20855, a trend in favour of patients in 20901 was seen ($P=0.066$ HR 1.27). However, if the rescue treatment given was not taken into account (1/3 did not receive this treatment) and all patients who failed after protocol treatment were analysed across the trials: a difference was no longer apparent ($P=0.887$). Thus, the variation in outcome across the trials could not be explained by improved salvage treatment(s) alone.

3.4. Role of selection

An obvious explanation for the better outcome of patients in trial 20901 could have been the late randomisation resulting in the selection of good responders. Therefore, we included for further analysis all registered patients in this trial, and not just the randomised patients. However, the overall patient outcome remained superior in trial 20901 to that of the other two trials. Differences in inclusion criteria might have been responsible for the better outcome over time. We assumed that the IPI should correct for differences in stage and age, but when the 430 patients with a low and low/intermediate risk profile treated with CHVmP/BV were selected, the patients in trial 20901 still did significantly better ($P=0.002$ HR 0.72). In contrast, for patients with an intermediate/high or high risk IPI (more than 3 points added up), survival ($n=99$) was poor irrespective of which trial they had been included in ($P=0.34$; HR 0.82).

Therefore, we corrected stepwise for the seemingly small differences in the inclusion criteria; age and stage (Table 3, Fig. 2). Patients were generally younger in trial 20901 (the upper age limit was initially 60 years and this was later extended to 65 years; however, only 8 patients

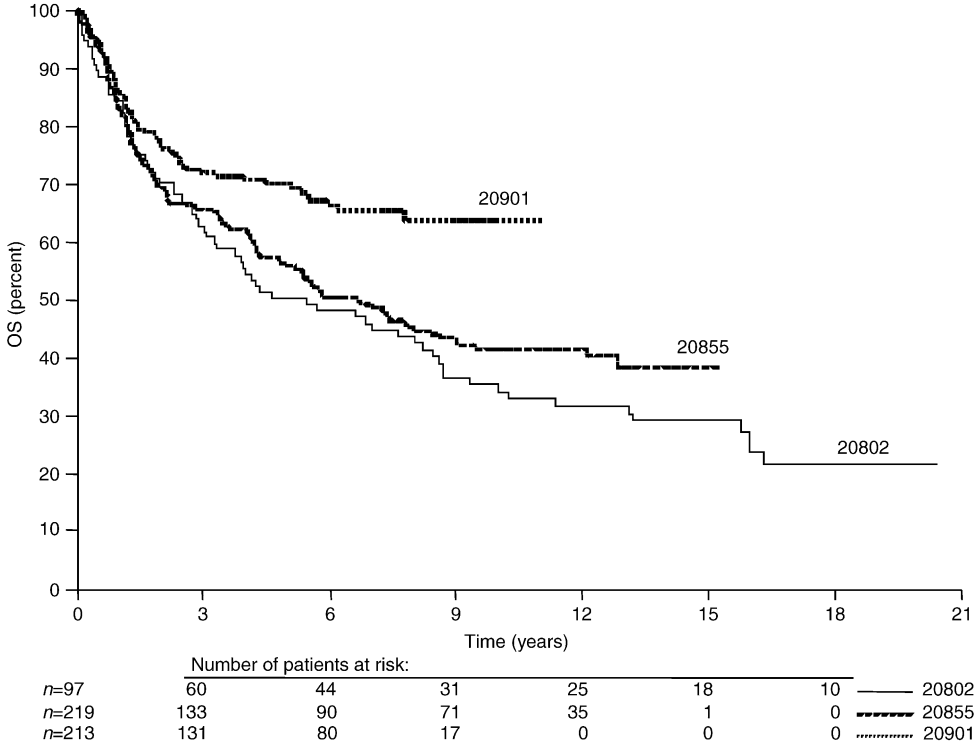

Fig. 1. Comparison of overall survival after CHVmP/BV across the three trials.

Table 3
Comparison of overall survival across trial; patients, all treated with the same CHVmP/BV regimen are step-wise matched for age, age and stage, age, stage and histology after comparison by International Prognostic Index

Comparison	Trial	% alive at 5 years	95% Confidence Interval	Log-rank *P* value	Hazard ratio	90% Hazard Confidence	Number of patients
CHVmP/BV in:	20802	50	40–60				97
	20855	56	49–63				219
	20901	70	64–77	$P=0.001$	0.73[a]	0.61	213
CHVmP/BV if IPI	20802	56	44–68				73
low and low/intermediate risk	20855	59	51–66				178
	20901	74	68–81	$P=0.001$	0.72[a]	0.63	173
CHVmP/BV if IPI	20802	32	13–51				24
intermediate/high and	20855	44	29–60				41
high risk	20901	54	38–70	$P=0.473$	0.82[a]	0.70	40
CHVmP/BV if age	20802	32	42–66				66
$\leqslant$60 years	20855	44	53–69				141
	20901	54	64–76	$P=0.032$	0.77[a]	0.71	208
CHVmP/BV if age	20802	53	40–65				59
$\leqslant$60 years and stage >II	20855	49	38–61				79
	20901	65	56–73	$P=0.195$	0.85[a]	0.68	133
CHVmP/BV if age	20802	60	42–77				30
$\leqslant$60 years and stage >II	20855	37	23–51				48
and WF pathology F, G or H	20901	54	42–66	$P=0.265$	1.02[a]	0.78	74

WF, Working Formulation; CHVmP/BV, eight cycles of cyclophosphamide, doxorubicin, teniposide and prednisone with bleomycin and vincristine in every cycle at the mid-interval.
[a] 20901 compared with 20802 and 20855.

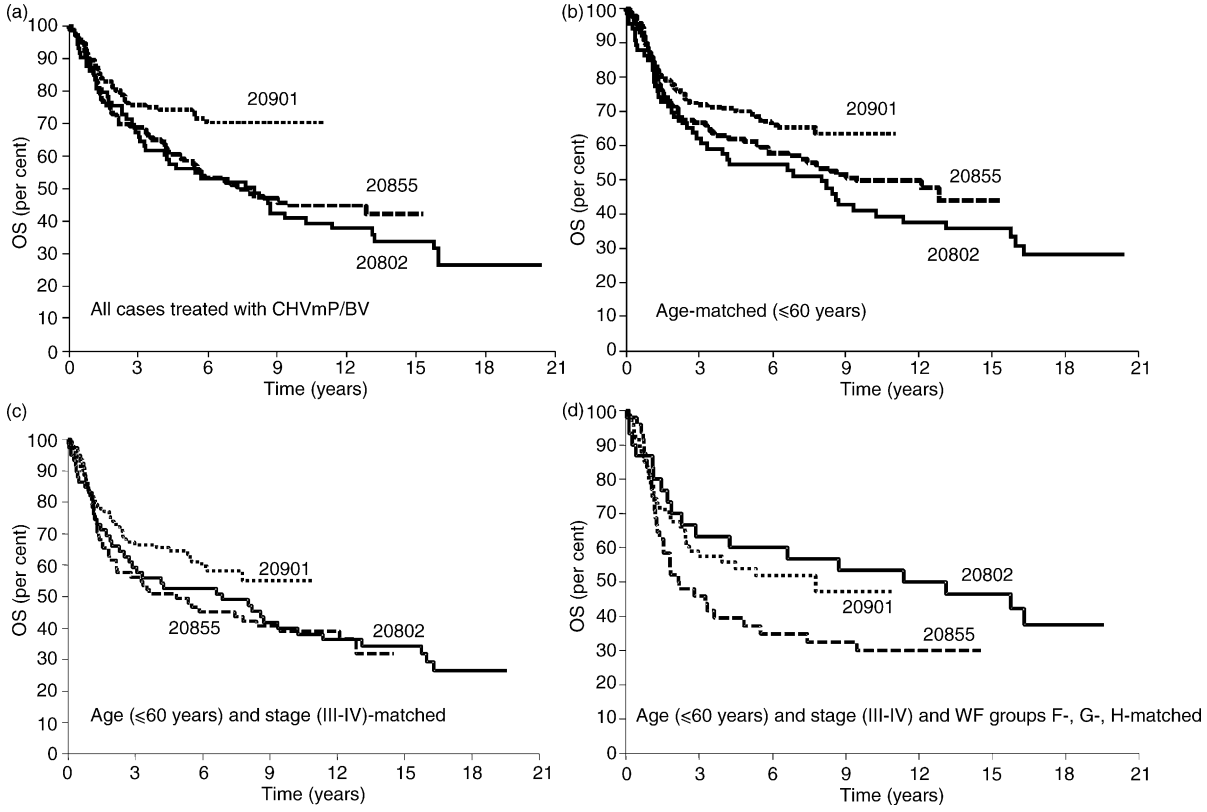

Fig. 2. Comparison of overall survival (OS) with CHVmP/BV across three trials when matching for International Prognostic Index (low and low/intermediate IPI) (a), age (b), age *and* stage (c) or age, stage *and* histology (Working Formulation F, G and H).

>60 years were included) and stages I bulky and II were excluded in trial 20802. We re-analysed the data by matching for age (60 years or younger) and stage (III and IV). Comparing outcome in trial 20901 to 20802 and 20855, while matching for age did increase the Hazard Ratio (HR), but differences in OS were still apparent ($P=0.032$, HR 0.77). Matching for age *and* stage raised the HR and *P*-value further and no significant differences in OS were now seen ($P=0.195$, HR 0.85). After comparing the patients aged 60 years or younger, *and* stage III or IV *and* with histology classified as group F, G or H (diffuse, mixed, small and large cell or diffuse large cell or large cell immunoblastic NHL) by the WF, the HR normalised to 1.02 ($P=0.265$).

Altogether, we observed a significant improvement in outcome across the trials that persisted when grouping patients with the same IPI-risk profile. However, this difference disappeared when patients were matched for age, stage and histology (Table 3).

4. Discussion

Several different regimens have been applied in patients with advanced aggressive NHL. Fisher and colleagues [13] compared third generation regimens (m-BACOD, ProMACE-CytaBOM, MACOP-B) with the classical CHOP, and found no difference in outcome between all four regimens. Our findings were similar when we compared ProMACE-MOPP, as a third generation regimen, with the EORTC-based CHVmP/BV regimen. However, by adding bleomycin and vincristine to the CHVmP scheme, we improved the survival outcome significantly. Fisher [13] described a 3-year overall survival of 54% for the CHOP regimen. In our study, we observed an overall survival rate at 5 years of 59% with the CHVmP/BV regimen. Although the only way to prove the superiority to CHOP is in a randomised trial, CHVmP/BV seems to be at least equivalent to classical CHOP regimens.

We observed large differences in outcome following treatment with the CHVmP/BV regimen between the trials. Rescue treatment and, more importantly, age and stage distributions biased the outcome data in the trials. This bias persisted when stratifying by the IPI risk profile. When the distributions of the five factors that form the basis of the IPI (especially age and stage) are not balanced within a population, sub-set analysis using this prognostic tool can be very misleading.

Besides the factors found in the IPI-score, histology also plays an important role in the prognosis of NHL patients [14]. The histological classification of NHL has changed considerably over the last two decades, the period during which our data were collected. In our trials, NHL categories were defined as intermediate- and high-grade histology following the WF, including subgroups like Lymphoblastic and Burkitt's lymphoma. Other sub-groups, such as anaplastic large cell lymphoma, were not yet recognised as different entities in this Formulation. Subgroups should be seen as separate entities with their own prognostic impact [15]. An overview of the revised pathology showed that a considerable number of patients were ineligible because of (low-grade) histology. When analysing accordingly to the 'intention-to-treat principle', these cases were included. In the sub-set analysis, we selected cases using the WF (F, G and H) with the aim of creating a more homogeneous category of aggressive NHL, that, in part, is comparable with the diffuse large B-cell category of the Revised European and American Lymphoma (REAL) and WHO classifications. Evidently, our goal was not to define outcome within histology sub-groups, but to stress both that diversity in histology can also lead to selection bias and the importance of a correct diagnosis.

Altogether, interpretation of retrospective sub-group analyses and comparison of recent trials with previous ones, has to be done with great care. Patients with advanced, aggressive NHL differ not only in the factors defined within the IPI, but also in their histology. They often progress and undergo rescue treatments, and these factors also influence outcome. Implementation of new therapeutic approaches should only be done after prospective, randomised confirmation within a selected sub-set, as this is the only way to prevent selection bias in this heterogeneous group of patients.

Acknowledgements

This project was partly financed by the Dutch Cancer Foundation. The help of all participating centres and local investigators is gratefully acknowledged (see the Appendix for details).

Appendix

The names of the participants (with institutional affiliations, who entered more than 5 patients) are as follows: P. Carde (Institute Gustave Roussy, Villejuif, France; 126 patients); U. Tirelli. (Centro Di Rifferimento Oncologico, Aviano, Italy: 124 patients); J. Baars (Antoni van Leeuwenhoekziekenhuis, Amsterdam, The Netherlands; 94 patients); J. Thomas (U.Z. Gasthuisberg, Leuven, Belgium; 89 patients); D. Bron (Institut Jules Bordet, Brussels, Belgium; 64 patients); J.C. Kluin-Nelemans (Leiden University Medical Center, Leiden, The Netherlands; 58 patients); W. Schroyens (Universitair Ziekenhuis Antwerpen, Antwerp, Belgium; 31 patients); K.J. Roozendaal (Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands;

29 patients); M. Monconduit (Centre Henri Bequerel, Rouen, France; 29 patients); J.M.M. Raemaekers (St. Radboud University Hospital, Nijmegen, The Netherlands; 27 patients); A.M. Peny (Centre Regional Francois, Baclesse, Caen, France; 24 patients); C.M. Blanc (Hotel-Dieu de Paris, Paris, France; 24 patients); G.J. Creemers (Catherina Ziekenhuis, Eindhoven, The Netherlands; 21 patients); M.B. van't Veer (Rotterdam Cancer Institute, Rotterdam, The Netherlands; 21 patients); W. Gerrits (Integraal Kankercentrum West, The Netherlands; 18 patients); G.J. Goverde (St. Ignatius Ziekenhuis, Breda., The Netherlands; 18 patients); A. van Hoof (A.Z. St. Jan, Brugge, Belgium; 16 patients); R. Debock (Algemeen Ziekenhuis Middelheim, Antwerp, Belgium; 14 patients); M. Fickers (Atrium Medisch Centrum, Heerlen, The Netherlands; 8 patients); G. Rosti (Ospedale Sta Maria Delle Croci, Ravenna, Italy; 8 patients); H.P. Muller (Streekziekenhuis Gooi-Noord, Blaricum, The Netherlands; 7 patients); H.C. Schouten (Academisch Ziekenhuis Maastricht, Maastricht, The Netherlands; 7 patients); H.N.L.M. Bron (Maaslandziekenhuis, Sittard, The Netherlands; 7 patients); J.J. Keuning (St. Josef Ziekenhuis, Veldhoven, The Netherlands; 7 patients); J. Michel (Centre Hospitalier de Tivoli, Louviere, Belgium; 6 patients): A.C. Tagnon (M.C. De Tournai, Tournai, Belgium; 6 patients).

References

1. Raemaekers JM, Kluin-Nelemans JC, Teodorovic I, *et al*. The achievements of the EORTC Lymphoma Group. *Eur J Cancer* 2002, **38**(Suppl. 4), S107–S113.
2. Carde P, Meerwaldt JH, van Glabbeke M, *et al*. Superiority of second over first generation chemotherapy in a randomised trial for stage III–IV intermediate and high-grade non-Hodgkin's lymphoma (NHL): the 1980–1985 EORTC trial. The EORTC Lymphoma Group. *Ann Oncol* 1991, **2**, 431–435.
3. Somers R, Carde P, Thomas J, *et al*. EORTC study of non-Hodgkin's lymphoma: phase III study comparing CHVmP-VB and ProMACE-MOPP in patients with stage II, III, and IV intermediate- and high-grade lymphoma. *Ann Oncol* 1994, **5**(Suppl. 2), 85–89.
4. Meerwaldt JH, Carde P, Somers R, *et al*. Persistent improved results after adding vincristine and bleomycin to a cyclophosphamide/hydroxorubicin/Vm-26/prednisone combination (CHVmP) in stage III–IV intermediate- and high-grade non-Hodgkin's lymphoma. The EORTC Lymphoma Cooperative Group. *Ann Oncol* 1997, **8**(Suppl. 1), 67–70.
5. Kluin-Nelemans JC, Zagonel V, Anastasopoulou A, *et al*. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomised phase III EORTC study. *J Natl Cancer Inst* 2001, **93**, 22–30.
6. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas. Summary and description of a working formulation for clinical usage. *Cancer* 1982, **49**, 2112–2135.
7. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993, **329**, 987–994.
8. World Health Organisation. *WHO Handbook for Reporting Results of Cancer Treatment*. Geneva, Switzerland, WHO, 1997.
9. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457.
10. Breslow N. Comparison of survival curves. In Buyse ME, ed. *Cancer Clinical Trials Methods and Practice*. Oxford, UK, Oxford Medical Publications, 1988, 382–406.
11. Cox DR. Regression models and life-table. *J R Stat Soc* 1972, **34**, 187–220.
12. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966, **50**, 163–170.
13. Fisher RI, Gaynor ER, Dahlberg S, *et al*. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med* 1993, **328**, 1002–1006.
14. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Blood* 1997, **89**, 3909–3918.
15. Teodorovic I, Pittaluga S, Kluin-Nelemans JC, *et al*. Efficacy of four different regimens in 64 mantle-cell lymphoma cases: clinicopathologic comparison with 498 other non-Hodgkin's lymphoma subtypes. European Organisation for the Research and Treatment of Cancer Lymphoma Cooperative Group. *J Clin Oncol* 1995, **13**, 2819–2826.