Current clinical trials for the treatment of advanced-stage Hodgkin’s disease: BEACOPP

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Background: The bleomycin–etoposide–doxorubicin–cyclophosphamide–vincristine–procarbazine–prednisone (BEACOPP) regimen was developed to investigate the potential of moderate dose escalation of conventional polychemotherapy to improve the unsatisfactory treatment results in advanced-stage Hodgkin’s lymphoma (HL). Following pilot studies, the randomised trial HD 9 demonstrated that BEACOPP (baseline dose) attained superior failure-free survival to COPP/ABVD, and that dose escalation made a further marked improvement. Toxicity was severe but manageable.

Patients and methods: The current GHSG multicentre randomised trial HD 12 has a 2 × 2 factorial design in order to make two comparisons: (i) eight cycles of escalated BEACOPP (as in HD9) are compared with four escalated cycles followed by four at baseline dose; (ii) the use of additional local radiotherapy to initial bulky disease and residual disease after chemotherapy is compared with chemotherapy alone, except where radiotherapy was prescribed by a central diagnostic panel. Eligible are patients aged 16–65 years with newly diagnosed HL of stage IIB with risk factors or stage III/IV. The EORTC multicentre trial 20012 randomises patients with HL stage III/IV to either eight cycles of ABVD or eight cycles of BEACOPP (four escalated + four baseline).

Results: The first interim analysis (January 2001) of HD 12 with 221 evaluable patients indicated continuation of recruitment. Recruitment will end in 2002 and the final data analysis will appear in 2006.

Conclusions: The BEACOPP regimen is highly effective, and moderate dose escalation makes a further worthwhile improvement in tumour control. Current trials will measure BEACOPP against the international standard and show whether the amount of chemotherapy and/or radiotherapy can be reduced.

Key words: advanced-stage, BEACOPP, chemotherapy, dose escalation, Hodgkin’s lymphoma, randomised controlled trial

The development of BEACOPP

Treatment of advanced-stage Hodgkin’s disease (HD) had, around 1990, not increased in effectiveness compared with the MOPP (mechlorethamine, vincristine, procarbazine, prednisone) and ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine)-based chemotherapy regimens that had been the standard over the previous two decades. Despite the still unsatisfactory levels of overall and failure-free survival in this group of patients, most efforts were devoted to reducing treatment toxicity by exchange of drugs and elimination of additional radiotherapy. Attempts to improve effectiveness by rapid alternation of drugs using so-called hybrid regimens did not, in general, succeed. Investigation of the use of high-dose chemotherapy with haematological stem-cell transplantation was beginning, but no group of patients with a sufficiently poor prognosis to justify this highly toxic intervention could be prospectively identified [1].

Moderate dose escalation of conventional chemotherapy was made possible by the development of haematological stem-cell growth factors. The potential of such increased doses to improve tumour control had been suggested by both animal experiments and retrospective analyses of clinical data [2–5]. The German Hodgkin Lymphoma Study Group (GHSG) therefore designed a new regimen based on the standard chemotherapy of the group, cyclophosphamide–vincristine–procarbazine–prednisone (COPP)/ABVD. The new regimen, bleomycin–etoposide–doxorubicin–cyclophosphamide–vincristine–procarbazine–prednisone (BEACOPP), should be amenable to dose escalation of the most important haematotoxic drugs, namely cyclophosphamide and doxorubicin together with the recently developed etoposide, and to the administration of granulocyte colony-stimulating factor (G-CSF) following the haematotoxic drugs within each cycle. Further improvement potential was incorporated by shorten-
ing the cycle duration from 4 to 3 weeks, thereby increasing dose intensity. Initially, the use of additional local radiation for all initially bulky sites and those showing residual disease after chemotherapy was retained.

A pilot study with 30 patients proved the feasibility of the BEACOPP regimen at standard doses (similar to COPP/ABVD and referred to as ‘baseline’ dose) without G-CSF [6]. A subsequent dose-finding trial intensively monitored toxicity during stepwise escalation from the baseline up to the estimated maximum tolerable dose, in which cyclophosphamide, etoposide and doxorubicin were administrated at 190, 200 and 140% of baseline, respectively (referred to as ‘escalated’ dose) [7]. Both these trials demonstrated promising short-term treatment results. This result formed the basis for the first randomised trial, HD 9, in which both baseline and escalated BEACOPP were compared with COPP/ABVD (all eight cycles plus radiation as described above). At the first interim analysis in 1996, recruitment to the COPP/ABVD arm was stopped because the failure-free survival in this arm was dramatically worse than that of the pooled BEACOPP arms [8]. The most recent interim analysis in June 2000 with 1180 patients showed, through comparing the two BEACOPP arms, that dose escalation significantly and markedly reduces the early progression rate and improves failure free survival [9]. Overall survival with escalated BEACOPP was significantly superior to that with COPP/ABVD, although a significant improvement in overall survival due to dose escalation alone could not be shown (Table 1). All prognostic groups within the advanced stages profited from BEACOPP and dose escalation to a similar extent.

The acute toxicity of escalated BEACOPP was severe but manageable [10]. Almost all patients suffered WHO grade III/IV leukopenia in at least one cycle; grade III/IV thrombopenia and anaemia are also frequent. The acute toxic death rate did not increase compared with COPP/ABVD. On the other hand, dose-limiting toxicities led to a progressive reduction in given dose during the later cycles. Furthermore, an increased incidence of acute leukaemia was observed with the escalated regimen, estimated as 2.5% at 5 years after the beginning of treatment.

### HD 12 trial

Whilst the excellent effectiveness of dose escalated BEACOPP cannot be doubted, its acceptance by study groups outside Germany has been hampered by the increased acute toxicity, the perceived difficulties when administered by the ‘typical’ physician, the increased and still imprecisely measured second leukaemia rate, and possibly also the increased cost of G-CSF and extended in-patient stays [11]. Following completion of HD 9, the GHSG recruited advanced-stage HD patients into the successor trial HD 12, which aims to reduce treatment intensity, and thereby also toxicity and cost, without impairing tumour control.

First, HD 12 investigates the use of four cycles of escalated BEACOPP followed by four cycles at baseline dose. This strategy is motivated by the conjecture that an early intensive onslaught combats the tumour most effectively, while later cycles are less critical. Furthermore, the observation that the actually given BEACOPP doses decrease markedly during later cycles due to dose-limiting toxicities suggests that such a strategy could reduce toxicity without greatly decreasing the total dose actually administered. Therefore, half the HD 12 patients will receive eight escalated cycles and half will reduce to baseline dose after the fourth cycle.

Secondly, radiation is omitted as far as possible for half the HD 12 patients, the other half receiving local radiation to initial bulky and residual disease sites as in HD 9. A central radiology panel reviews all chemotherapy images from staging examinations and restaging after four and eight BEACOPP cycles and determines whether radiation is absolutely necessary, according to predefined criteria, or whether it could be omitted according to randomisation arm (to which the panel is blinded). The elimination of additional radiotherapy is supported by a meta-analysis of randomised HD trials [12] and by recent results of the European Organisation for Research and Treatment of Cancer (EORTC) trial 20884 [13]. It is hoped in particular to reduce thereby the incidence of secondary solid tumours, which are one of the most serious and frequent late effects of HD treatment.

In order to investigate both the above aspects simultaneously, a $2 \times 2$ factorial design was chosen. The four randomisation arms are as follows:

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### Table 1. Treatment results and 3-year survival rates in HD 9 arms A, B and C (interim analysis June 2000)

<table>
<thead>
<tr>
<th></th>
<th>COPP/ABVD (%)</th>
<th>Baseline BEACOPP (%)</th>
<th>Escalated BEACOPP (%)</th>
<th>Significant differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>84 (n = 263)</td>
<td>88 (n = 457)</td>
<td>96 (n = 460)</td>
<td>A &lt; C, B &lt; C</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12</td>
<td>8</td>
<td>2</td>
<td>A &gt; C, B &gt; C</td>
</tr>
<tr>
<td>Failure-free survival (3 years)</td>
<td>70</td>
<td>79</td>
<td>89</td>
<td>A &lt; B &lt; C</td>
</tr>
<tr>
<td>Disease-free survival (3 years)</td>
<td>72</td>
<td>80</td>
<td>92</td>
<td>A &lt; B &lt; C</td>
</tr>
<tr>
<td>Overall survival (3 years)</td>
<td>86</td>
<td>91</td>
<td>92</td>
<td>A &lt; B, A &lt; C</td>
</tr>
</tbody>
</table>

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Arm A: BEACOPP (eight escalated) + 30 Gy radiotherapy (bulk + residual)
Arm B: BEACOPP (eight escalated)
Arm C: BEACOPP (four escalated + four baseline) + 30 Gy radiotherapy (bulk + residual)
Arm D: BEACOPP (four escalated + four baseline)

Similar to HD 9, the trial recruits patients aged 16–65 years with newly diagnosed, untreated HD of Ann Arbor stage IIb with large mediastinal mass and/or extranodal lesions, stage III or stage IV. The planned drug dosages and dose reduction schedules in the event of dose-limiting toxicities are retained from HD 9.

At least 1200 patients are needed to answer with adequate precision the questions investigated by the trial. They will be recruited from over 300 centres in Germany, Switzerland, Austria and the Czech Republic. Formally, the analysis will test for equivalence of the two chemotherapy dosage schemes and for equivalence of treatment with and without radiotherapy. ‘Without radiotherapy’ means radiotherapy only in those cases defined by the central review panel as requiring it. With the planned sample size, equivalence to within a 5% to 9% difference in failure-free survival will be demonstrable, depending on the true failure-free rates in the four arms. Annual interim analyses will be performed in order to detect early arm differences or other grounds for modifying or stopping the trial, according to a prespecified sequential trial scheme. The final analysis is planned for 2006 or once 80% of expected events have been documented.

The first interim analysis of HD 12 in January 2000 with 221 evaluable patients and a median follow-up interval of 17 months did not detect any arm differences that would justify stopping or modifying the trial. The overall results were compatible with those of HD 9. The recruitment rate was higher than in HD 9: by December 2001, 1119 patients had been randomised, so that the target size had almost been attained.

**EORTC 20012 trial**

To date, the BEACOPP phenomenon has been regarded with much interest by researchers outside Germany, but there has also been some scepticism and reluctance to adopt this regimen for the reasons listed above. Since the ABVD regimen is widely recognised as the current standard for advanced HD because of its effectiveness (at least as good as any other non-dose-escalated regimen), its low acute toxicity and its low rate of late effects such as infertility and secondary leukaemia, a direct randomised comparison between BEACOPP and ABVD will clarify the value of BEACOPP internationally. The EORTC Lymphoma Group in collaboration with study groups in Australia, Belgium, Canada, France, Scandinavia, Spain and the UK will begin recruitment early in 2002 into a multicentre randomised trial of BEACOPP (four cycles escalated followed by four cycles baseline) versus ABVD (eight cycles). No radiation is planned. Only patients aged 16–60 years with stage III/IV disease and an international prognostic factor score of at least 3 [1] are eligible. Recruitment of ~500 patients (~5 years) is planned, allowing an arm difference of 10% in the 3-year freedom from treatment failure rate to be detected.

**Current prospects**

Further observation of HD 9 patients will shed light on long-term overall survival with escalated and baseline BEACOPP and thus allow the benefit due to moderate dose escalation to be measured more precisely. Second neoplasias will also continue to be monitored closely, and the second leukaemia risk after escalated (and baseline) BEACOPP will become more accurately known. The contribution of salvage therapy following early progression or relapse to the overall risk of second leukaemia, which (due to the reduced failure rate) is expected to tilt the balance in favour of BEACOPP, will with longer follow-up become increasingly influential.

HD 12 results will in the next few years indicate where the optimum amount of BEACOPP and additional radiotherapy lies. Hopefully, a sequence of four escalated and four baseline cycles will suffice, with irradiation only in a small minority of cases (as in arm D), but this will not be known before about 2006.

The EORTC 20012 trial will soon provide evidence on the feasibility and toxicity of escalated BEACOPP in a new multicentre setting. The effectiveness of BEACOPP in randomised comparison with ABVD will not be revealed before recruitment ends (in 2005 or 2006).

**References**


