A Systematic Overview of Chemotherapy Effects in Hodgkin's Disease

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A Systematic Overview of Chemotherapy Effects in Hodgkin’s Disease

Lars Brandt, Eva Kimby, Peter Nygren and Bengt Glimelius for the SBU-group

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A systematic review of chemotherapy trials in several tumour types was performed by The Swedish Council of Technology Assessment in Health Care (SBU). The procedures for the evaluation of the scientific literature are described separately (Acta Oncol 2001; 40: 155–65). This synthesis of the literature on chemotherapy for Hodgkin’s disease (HD) is based on 113 scientific reports including four meta-analyses, 44 randomised studies, 18 prospective studies and 40 retrospective studies. These studies involve 69,196 patients. The conclusions reached can be summarised into the following points:

- Chemotherapy is of utmost importance for the cure of HD.
- At early stages, extended field radiotherapy cures most patients. For the majority of patients with relapse after radiotherapy, chemotherapy is curative and the total proportion of cured early stage patients is 75–90%. Chemotherapy in addition to extended field radiotherapy reduces recurrences but does not improve long-term survival.
- In early stage HD with a large mediastinal mass and/or with systemic symptoms, combined treatment with chemotherapy and radiotherapy is recommended.
- It is likely that chemotherapy will play a greater role in the future in the treatment also of early stage patients in order to reduce late consequences from extended field radiotherapy. However, this conclusion remains to be better documented in the literature.
- At advanced stages, chemotherapy or a combination of chemotherapy and limited field radiotherapy are effective treatment options and, using the regimens available 10–20 years ago, 40–50% of the patients are cured. Based upon more favourable short-term (three to eight years) results of more recently developed regimens, it can be expected that today a higher proportion of the patients will become long-term survivors.
- Several chemotherapy regimens containing four to eight drugs are effective in HD. The best regimen considering both antitumour activity and acute and late side-effects is not known. The choice of regimen is probably best done after considering various pre-treatment factors such as the number of poor prognostic signs, concomitant diseases and individual preferences.
- The results of chemotherapy are more favourable in young than in elderly patients. The development of less toxic but still effective treatment programmes is therefore particularly important for the elderly.
- High dose chemotherapy with stem cell support is presently often used in patients who are chemotherapy induction failures, who relapse after a short initial remission or after a longer initial remission and treated initially with seven or eight drugs, or who have had multiple relapses. However, this use is based on data from uncontrolled or small controlled studies, not being fully convincing with respect to effect on survival.
- Persistent side-effects of treatment are common among long-term survivors, although most patients have an apparently normal life. The relative contributions of chemotherapy and radiotherapy to the persistent effects are not well documented.

1 Other members of the SBU-group were: Jonas Bergh, Radiumhemmet, Stockholm; Bengt Brorsson, SBU, Stockholm; Barbro Gunnars, Dept of Oncology, University Hospital, Lund; Larsolof Hafström, Dept of Surgery, University Hospital, Umeå; Ulf Haglund, Dept of Surgery, University Hospital, Uppsala; Thomas Högborg, Dept of Gynaecological Oncology, University Hospital, Linköping; Karl G. Janunger, Dept of Surgery, University Hospital, Umeå; Per-Ebbe Jönsson, Dept of Surgery, Helsingborgs lasarett; Helsingborg; Göran Karlsson, Handelshögskolan, Stockholm; Gunilla Lamnnevik, SBU, Stockholm; Sten Nilsson, Radiumhemmet, Stockholm; Johan Perment, Dept of Surgery, University Hospital, Huddinge; Peter Ragnhammar, Radiumhemmet, Stockholm; Sverre Sörenson, Dept of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway.
In Sweden, 172 cases of Hodgkin’s disease (HD) were diagnosed in 1997, corresponding to 0.4% of all newly diagnosed malignant tumours (1). Like in other countries, there is a biphasic age distribution with one peak around 20–30 years of age and another peak around the age of 70 years. Twenty-thirty % of the patients are older than 60 years at diagnosis.

Until the 1960s, HD was considered almost inevitably fatal but rapid advances in radiotherapy changed the outlook for many patients. Effective chemotherapy programmes were also introduced in the late 1960s and in later years the majority of patients with HD have been cured with radiotherapy, chemotherapy or a combination of these modalities. Population-based data support improvement in overall survival from the early 1970s when chemotherapy had been widely introduced to the 1990s (2, 3).

For the choice of treatment it is important to determine the stage of the disease (Table 1) (4). In Sweden, the following distribution has been described (Swedish National Care Programme, 1995) (Table 2).

Histologically, HD is classically divided into four major groups: Lymphocyte predominance (LP), Nodular sclerosis (NS), Mixed cellularity (MC) and Lymphocytic depletion (LD). A new group has recently been added, Lymphocyte-rich classical HD, separating LP from the others (5).

**LOCALISED DISEASE: STAGES I–II**

It is well documented that radiotherapy will induce complete remission (CR) in about 95% of the patients with HD stage I–II. About 15–35% relapse but most of them (75–90%) experience a new remission with chemotherapy or a combination of chemotherapy and radiotherapy. With radiotherapy as the initial treatment, about 75–90% are alive after 10–20 years. These results were reviewed and evaluated in SBU-report no. 129/12, 1996, pp. 185–202.

In order to further improve relapse-free and overall survival following initial radiotherapy in the early stages, a number of studies of combined radiotherapy-chemotherapy have been performed (6–15). According to these studies and two metaanalyses (16, 17), combined treatment results in an improved relapse-free survival after ten years being about 65% with radiotherapy and 85% with the combined treatment modality. However, overall long-term survival is comparable, approximately 80% after ten years, because most patients with a relapse after radiotherapy are cured with chemotherapy. In the most recently reported meta-analysis (17), individual patient data on 1 688 patients in 13 trials were analysed. Crude mortality data on 226 patients in two other trials were also reviewed. The addition of chemotherapy to radiotherapy halved the ten year risk of failure (15.8% vs 32.7%; p < 0.00001), with a small, non-significant improvement in survival (79.4% vs 76.5% alive; p = 0.7). The recurrences seen after radiotherapy were thus generally salvageable by re-treatment with chemotherapy.

In a small (n = 78) randomised trial in patients with favourable clinical stage I or II, comparable results after a median follow-up of four years were seen after radiotherapy alone (subtotal nodal irradiation) or two courses of a relatively mild chemotherapy regimen (VBM, vinblastine, methotrexate, bleomycin) followed by less extensive radiotherapy and four additional VBM courses (18). Two courses of the ABVD regimen (see below) prior to extended field radiotherapy resulted in a significantly superior freedom from treatment failure (96% vs 87% at 24 months) due to a reduced number of relapses (1 vs 17) when compared with the same radiotherapy alone (19). Survival rates were not different (97% vs 98%) in this German Hodgkin Study Group trial (GHSG HD 7 trial) including 640 patients in stage I and II without clinical risk factors.

Some patients with localized HD present with systemic symptoms, i.e. are in stages I–II B. For these, radiotherapy...
alone has been found to be insufficient. Following radiotherapy, most of them, or about 75%, will relapse within five years and chemotherapy as part of the primary treatment has therefore been recommended (6, 7, 20, 21). A combined treatment with chemotherapy and radiotherapy has been found to be effective, resulting in relapse-free and long-term survival for about 90% of the patients (22, 23).

In more than 50% of patients with HD, mediastinal lymph nodes are affected and sometimes a large mediastinal mass has developed, i.e. bulky mediastinum. Most investigators recommend a combined treatment in this situation. With radiotherapy alone 40–50% or more may relapse in the bulky area or in adjacent lung tissue (24–26). With initial chemotherapy followed by radiotherapy the local relapse rate is about 10% (2, 27–31).

The results thus indicate that only about 10% of the patients with early stage disease are expected to die of HD. Results from large co-operative groups after prolonged follow-up indicate, however, that long-term survival is not so favourable. There is an increased risk of late, sometimes fatal, complications, above all secondary malignancies (32, 33) and cardiac toxicity (34). The magnitude of these fatal complications is still poorly known. Most evidence indicates that the extended-field radiotherapy is responsible for a significant proportion of the late complications.

Two randomised trials have compared radiotherapy alone with combination chemotherapy as initial treatment for early stage HD. In an Italian trial, 89 patients with pathological stage I–IIA were randomly allocated to receive either radiotherapy with subtotal nodal irradiation or six courses of MOPP (see below) (35). With a median follow-up of eight years, the overall survival rate is higher in the radiotherapy than in the chemotherapy group (93% vs 56%; p = 0.001). In the second trial, 106 patients with pathological stage IB–IIIA:1 were randomised between total nodal irradiation and a minimum of six MOPP cycles (36). Patient inclusion started in 1978. In 1981 patients with bulky mediastinal disease, and in 1983, patients in stage IIIA were excluded from randomisation due to unexpectedly high recurrence rates after radiotherapy alone. The projective ten year overall survival for randomised patients tended to be higher for those randomised to chemotherapy compared with those randomised to radiotherapy (92% vs 76%; p = 0.05). When the randomised patients with bulky mediastinal disease or stage IIIA were excluded, the overall survival was not different (90% vs 85%; p-value not stated). These two studies, mainly recruiting patients during the 1980s thus reached different results. The overall conclusion was then that radiotherapy continued to be the preferred treatment to early stage HD except for subgroups with a high risk of recurrence. Combination chemotherapy could, however, be a relevant treatment in countries with limited radiotherapy facilities.

Even if the above mentioned two trials today mainly have historical interest, several international groups are exploring whether chemotherapy followed by limited field radiotherapy, or no radiotherapy at all, will result in the same high curability rates as extended field radiotherapy but with less late toxicity. Preliminary results from a randomised GHSG trial (HD 8) including 742 patients with early stage HD and unfavourable prognostic signs also indicate that, following two cycles of COPP/ABVD (see below), limited field radiotherapy results in the same high freedom from treatment failure as extended field radiotherapy (91% vs 94%, median follow-up 26 months) (37).

The literature shows that:

- At early stages of HD most patients are cured by extended field radiotherapy.
- For a majority of patients with relapse after radiotherapy chemotherapy is curative.
- Initial chemotherapy in addition to extended field radiotherapy reduces recurrence rates but does not increase overall survival.
- Patients presenting with a large mediastinal mass should be recommended an initial combined treatment with chemotherapy and radiotherapy since otherwise too many patients will suffer from a relapse. Chemotherapy should also be given to patients with B-symptoms.
- Efforts to minimize treatment without compromising the cure rate are important due to the risk of late and sometimes fatal treatment-related complications. These efforts will probably mean that chemotherapy will play an increased role in all early stage patients with a decreased relative importance of radiotherapy.

Chemotherapy of localised disease: Stages I–II:

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*The weight of scientific evidence for each publication was graded as described (Acta Oncol 2001; 40: 155–65). M = meta-analysis, C = controlled clinical trial, P = prospective trial, R = retrospective study, L = literature review and O = other studies. The classification of each publication is given in the reference list.
ADVANCED DISEASE: STAGE IIIA

Relapses five to ten years even after extended field radiotherapy have been reported in 50–75% of patients with HD stage IIIA (21, 38–41). Despite this high relapse rate, 65–95% of the patients are alive at ten years due to effective chemotherapy in the relapse situation. With combined chemotherapy and radiotherapy as primary treatment, the relapse rate may be reduced to about 15% and long-term survival is about 75–95% (38, 40, 42).

According to one controlled (21) and one retrospective study (43) comparable results may be obtained if radiotherapy alone or chemotherapy alone is the primary treatment. It has not been settled in randomised studies whether overall survival after primary combination therapy is better than after primary treatment with radiotherapy or chemotherapy alone. Since radiotherapy alone means that large tissue volumes must be irradiated, this treatment is no longer an accepted primary treatment because of a high risk of late adverse effects (32, 34). If radiotherapy is the primary treatment, a substantial proportion of the patients will first be treated with extended field radiotherapy and then with chemotherapy upon relapse.

The literature shows that:

- Relapse after radiotherapy alone of stage IIIA is common but chemotherapy is effective in this situation.
- Initial combination of radiotherapy and chemotherapy reduces the relapse rate but does not seem to increase long-term survival.
- Overall survival after initial chemotherapy is comparable with survival after initial radiotherapy.
- In the light of the most recent knowledge about long-term effects from particularly extended field radiotherapy, these patients should be treated with primary chemotherapy, and limited field radiotherapy should be provided to selected patients.

Chemotherapy of advanced disease: stage IIIA:

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ADVANCED DISEASE: STAGES IIIB–IV

Initial chemotherapy is standard treatment for these patients. CR may be obtained for 60–90% (21, 44–46) and 40–50% of the patients become long-term survivors (46). The prognosis is dependent upon a number of prognostic factors, among which age is one of the most important. Through the years several groups have developed prognostic indices for freedom from disease progression or overall survival. Recently, data from 25 centres and study groups on a total of 5141 patients treated with combination chemotherapy for advanced HD were used to create a prognostic score (47). Based upon the number of adverse prognostic factors, freedom from progression after five years ranged from 84% if no prognostic factor was present to 42% if five or more (maximum seven) were present. Five years overall survival ranged between 90% and 56%. In the total material it was 78%.

In order to achieve the overall results presented above, most centres have used eight cycles of chemotherapy, however, ranging from six to 12 cycles. Besides two early studies with a limited number of patients, showing that maintenance chemotherapy did not improve treatment results (48, 49), only one randomised study has addressed the importance of the number of cycles (50). Eighty-eight patients were randomised to either eight cycles (4 MOPP, 4 ABVD, see below) or to treatment until CR was reached. The predicted ten-year progression-free survival was 81% in the fixed group (mean number was 7.2 cycles) and 68% in the response-adapted group (mean 5.1 cycles) (p < 0.05).

Controlled studies have indicated that the addition of radiotherapy will not significantly improve relapse-free or overall survival (51). However, in one study, relapse-free survival at seven years was 45% with the combined treatment and 21% for those treated with chemotherapy alone (p = 0.002). Overall survival was not significantly different, 71% vs 58% (p = 0.15) (41). In a German study of patients in remission following chemotherapy, the addition of low-dose radiotherapy or a further consolidating course of chemotherapy yielded similar results in terms of relapse-free and overall survival (52). Data on 1 740 patients treated on 14 different trials have been analyzed in a meta-analysis (53). Eight comparisons were designed to evaluate whether radiotherapy in a combined modality setting could be substituted by chemotherapy using either more cycles of the same chemotherapy or regimens that contain additional drugs. Forty-five per cent of the patients had stage I–IIIA in these comparisons. Additional radiotherapy showed an 11% overall improvement in tumour control rate after 10 years (p = 0.0001). No difference could be detected with respect to overall survival (p = 0.6).

In the remaining trials, combined modality treatment was compared with chemotherapy alone. In these comparisons, more than 80% of the patients had stage IIIB–IV. No difference could be detected in tumour control rates (p = 0.4), but overall survival was significantly better after
10 years in the group that did not receive any radiotherapy (8% difference; p = 0.045). There were significantly fewer fatal events among patients in continuous CR if no radiotherapy was given (53). Similarly, the French group Groupe d’Etudes des Lymphomes de l’Adulte (GELA) randomised 418 patients in stages IIIB–IV in complete or good partial remission (PR) after six chemotherapy courses to either a further two consolidating chemotherapy courses or extended field radiotherapy without detecting any difference in event-free (70 and 72%) and overall (90 and 83%) survival, respectively (54). Like in the less advanced stages of HD, a large mediastinal mass is associated with a pronounced risk of relapse and for these patients radiotherapy is usually added to chemotherapy as primary treatment (55). In order to avoid relapse the addition of radiotherapy has also been recommended with bulky lesions located elsewhere (56, 57). Strong supportive evidence for these recommendations from randomised trials is not, however, available.

In elderly patients, the acute side-effects of chemotherapy are particularly obvious and often prevent conventional therapy in advanced stages resulting in a relatively poor outcome for patients > 60 years of age (58, 59). For the elderly patients, reduction of doses and the use of drugs with limited acute toxicity may permit more treatment courses. Preliminary data suggest that such a strategy may improve the outcome (59, 60). However, the treatment results of elderly patients with HD are not well documented in the literature.

The literature shows that:

- Initial chemotherapy is standard treatment for stage IIIB–IV and 40–50% of the patients become long-term survivors.
- The addition of radiotherapy does not improve relapse-free or overall survival in randomised trials.
- The outcome for elderly patients with current treatment is less favourable. The development of regimens causing less acute toxicity is particularly important for the elderly.

Chemotherapy of advanced disease: stage IIIB–IV:

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**RECOMMENDED CHEMOTHERAPY REGIMENS**

MOPP (mechlorethamine, vincristine, procarbazine, prednisone) is a well established, effective treatment of HD. In advanced stages CR rates range from 82–90% and long-term survival (cure) has been reported for 60–70% of the patients (61, 62). The original drug combination has been modified, with chlorambucil substituting mechlorethamine and vinblastine substituting vincristine, by several investigators in attempts to improve the efficacy and to reduce side-effects. These modifications failed to improve response rates and overall survival (63, 64) but reduced vomiting (63) and neurotoxicity (64).

ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) is another widely used effective drug combination. In a controlled study of advanced HD, the treatment results appeared better with ABVD than with MOPP (65). CR rates were 82% for ABVD and 67% for MOPP (relative risk 0.83; 95% CI 0.71–0.96). Survival at 5 years was 73 and 66%, respectively, a non-significant difference. However, the dose intensity of the MOPP therapy was lower than in the previous studies cited (61, 62) and it has been argued that the original MOPP regimen and ABVD give similar results (55, 66).

Treatment with MOPP alternating with ABVD did not improve the results compared with MOPP or ABVD in a controlled study (65) and, based upon this, it was concluded that there is no firm evidence that the use of seven- or eight-drug regimens is more effective than the standard four-drug regimens MOPP and ABVD (66). Several other randomised studies have, however, also addressed the question whether alternating regimens designed in accordance with the Goldie and Coldman hypothesis (67) are superior to single regimens. Alternating MOPP/CABS (CCNU, doxorubicin, bleomycin, streptozocin) was not found to be superior to MOPP alone in a small trial including 125 patients (68). Disease-free survival was 72% and 65%, respectively, and overall survival 68% and 66%, respectively, after ten years. Similarly, in 113 patients relapsing from a radiotherapy induced CR, 12 cycles of a MOPP-like regimen (CVPP), an ABVD-like regimen (ABOS) or CVPP alternating with ABOS all produced about 60% five-year survival (69).

A British group randomised 594 patients to either CHIVPP (chlorambucil, vincristine, procarbazine, prednisone) or CHIVPP alternating with a doxorubicin combination EVAP (etoposide, vinblastine, doxorubicin, prednisone). After initial chemotherapy, CR rates were 57% and 65%, respectively (not significant), but 65% and 75%, respectively, after the subsequent administration of radiotherapy to residual masses (p < 0.01). The relapse-free survival and overall survival at 5 years were superior in the alternating group (72% vs 52%; p < 0.001 and 75% vs 66%; p < 0.05, respectively) (70). A joint EORTC-French trial randomised, after two courses of MOPP, 192
patients to either six further courses of MOPP or to two courses of ABVD followed by two courses of MOPP and two courses of ABVD. They noted a longer failure-free survival in the MOPP/ABVD arm (60% vs 43% at six years; \( p = 0.03 \)). There was no statistically significant difference in overall survival (\( p = 0.13 \)) (71). A French group randomised 70 patients with stages IIIB and IV to either four cycles of MOPP or MOPP alternating with ABVD followed by extended field radiotherapy (STNi or TNi). No significant differences were seen in either response rates (overall 84%), eight-years disease-free survival (70%) or survival (65%) (72). Finally, in a randomised Norwegian study of 100 patients, one group was treated with a MOPP-derived regimen, and another group was treated with this regimen alternating with an ABVD-derived regimen. The results in terms of relapse-free and overall survival were almost identical (73). Taken together, some studies indicate that there is a slightly higher activity in alternating regimens than in conventional 4-drug regimens, but firm evidence is lacking.

So-called hybrid regimens, i.e. regimens containing drugs originating from both MOPP-like and ABVD-like programmes, have been introduced in recent years (74). In one study with a short follow-up (five years), survival following treatment with a MOPP/ABV-hybrid regimen was 81% and similar to the survival achieved with alternating MOPP and ABV (75). Also five-year failure-free survival was similar (71% and 57%; \( p = 0.87 \)). In another study of 427 patients, comparing a hybrid regimen with alternating MOPP and ABVD, survival at ten years was the same, or 74% and 72%, respectively, with the two regimens (76). In a large study of 691 patients (77), a hybrid regimen, MOPP/ABV, was compared with sequential treatment with six or eight courses of MOPP followed by three courses of ABVD. The eight-year survival was 79% with the hybrid and 71% with the sequential treatment (\( p = 0.02 \)). In another large US co-operative group trial, comparing ABVD with the MOPP/ABV-hybrid, no differences were seen in CR-rates, freedom from progression and survival (78). However, only preliminary results have been presented after a short follow-up. Improved progression-free survival was seen in a randomised trial comparing the ChlVPP/EVA (etoposide, vincristine, doxorubicin)-hybrid with MVPP (80% vs 66%; \( p = 0.005 \) at five years). There was no statistically significant difference in overall survival (80% vs 71%; \( p = 0.28 \) at five years) in this trial including 423 patients (79). The trial has been updated after a median follow-up of almost ten years. At eight years, freedom from progression remains superior for the hybrid regimen (78% vs 65%; \( p = 0.005 \)), whereas there is no overall survival benefit (74% vs 69%; \( p = 0.18 \)) (80). In a subsequent trial, so far only preliminarily reported (80), 282 patients were randomised between either six cycles of ChlVPP/ EVA or an 11-week cycle regimen, VAPEC-B (vincristine, doxorubicin, prednisolon, etoposide, cyclophosphamid and bleomycin). The ChlVPP/EVA regimen produced similar results in the two trials. It was superior to the VAPEC-B regimen in terms of both freedom from progression (80% vs 61%; \( p < 0.002 \) and survival (90% vs 77%; \( p < 0.03 \)) at a median follow-up of 3.5 years. The trial was prematurely interrupted when the inferior results of the short weekly regimen were noted.

Although long-term survival can be achieved for 70–80% of patients with advanced HD using current treatment programmes, the goal is to improve these results. Thus, several new regimens are currently under investigation. For example, an intensified treatment with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) was developed by the GHSG (81). A pilot study of 30 patients has been reported and 89% were in CR after a median follow-up time of 40 months (82).

In order to further improve treatment results, the same drugs at higher doses and with a shorter time-interval and with growth factor support (BEACOPP-escalated) have been tested in 60 patients (83). With a short follow-up (median 32 months), freedom from treatment failure and overall survival were 90 and 91%, respectively. The results were considered encouraging. However, only three patients were over 60 years (61–65) and the tolerance of elderly patients is unknown. Moreover, the potential for serious late complications might be high. With a short median observation period of less than three years, two patients have developed acute leukaemia.

The GHSG has randomised 1 200 patients with an alternating regimen, COPP/ABVD, the BEACOPP regimen at standard doses and BEACOPP-escalated. Eight cycles were given followed by irradiation of initial bulky and residual disease. The trial has so far only been preliminarily analysed and mainly presented at several scientific meetings (84–86). In the fourth interim analysis (85), BEACOPP is significantly superior to COPP/ABVD in all end-points, and BEACOPP-escalated is superior to BEA-COPP-standard in terms of progression-free survival. Acute toxicities were similar between COPP/ABVD and BEACOPP-standard, and increased, but manageable with BEACOPP-escalated. Leukaemogenicity remains a concern with five cases of acute myeloid leukaemia in the BEACOPP-escalated arm, one in BEACOPP-standard and none in the COPP/ABVD-arm. Non-Hodgkin’s lymphomas were, however, more commonly seen after COPP/ABVD and BEACOPP-standard.

In another German trial, 264 patients (data available for 211) were randomised between standard COPP/ABVD or dose-intensiﬁed COPP/ ABVD supported by GM-CSF (87). CRs were observed for 62 vs 77% (\( p = 0.02 \)). The data are preliminary and no information was given about survival.

Acute and late side-effects are different for MOPP-derived regimens and ABVD-like regimens. Neurotoxicity is more pronounced with MOPP, whereas vomiting is
more common with ABVD. Bone marrow depression is more pronounced with MOPP than with ABVD. There are also major differences in late toxicities. MOPP is associated with infertility in men and women. Recovery is uncertain and has been reported for only 14% of men (88). With ABVD the risk of infertility is considerably lower and a 100% recovery has been reported. Within the first 15 years there is an up to 10% risk of acute leukaemia or myelodysplastic syndrome in patients treated with MOPP-like regimens plus radiation therapy (88, 89). With ABVD and radiotherapy this risk is considerably lower, about 1%. Treatment with ABVD and radiotherapy may induce pulmonary fibrosis in about 60% of the patients (88) and cardiac disease may also result. It has been hypothesized that fatal pulmonary or cardiac disease will be similar in magnitude to the risk of leukaemia after MOPP but precise data are not available (66).

Because the patterns of late toxicity are quite different with MOPP- and ABVD-derived regimens it is not possible to recommend any of them for universal use in HD. It has been proposed that the choice depends on the toxicity profile the patient is willing to accept. In patients in whom fertility is an overriding concern, ABVD is the treatment of choice. For patients who are less concerned about fertility, MOPP or MOPP-derived regimens are reasonable choices, although concerns about secondary leukaemias and slightly inferior treatment results can be expressed. The alternating or hybrid regimens, in which lower total doses of MOPP- and ABVD-derived drugs are given, may provide advantages concerning late toxicity but firm evidence for this from clinical studies is not available. In one of the randomised studies mentioned above (77), 9/344 cases of acute myeloid leukaemia or myelodysplasia were reported after sequential six to eight courses of MOPP followed by three courses of ABVD as compared with 1/347 after MOPP/ABV-hybrid (8–12 cycles). Fewer secondary malignancies were seen with ABVD (two cases) than with MOPP/ABV-hybrid (12 cases) in a trial including 856 patients (78). In the British trials using the CHLPP/EVA hybrid with a median follow-up of almost ten years, 15/355 patients have developed a second malignancy (80).

The literature shows that:

- Several chemotherapy regimens, e.g. MOPP, ABVD, several alternating or so-called hybrid regimens and BEACOPP (standard and escalated) are effective in HD.
- MOPP and ABVD have been standard regimens and have also been used in combination.
- Regimens containing drugs originating from both MOPP-like and ABVD-like regimens (hybrid regimens) might be more effective than the original standard regimens, although superiority over ABVD has not been shown.

- It is possible that BEACOPP is the presently most active regimen, but this conclusion is based upon preliminary data from one large trial.
- Acute and late side-effects are different for the original regimens.

Chemotherapy regimens:

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*For abbreviations, see above.

HIGH-DOSE THERAPY AT RESISTANCE TO CONVENTIONAL TREATMENT

Patients who fail to achieve a CR to primary chemotherapy have a very poor prognosis, as have patients with relapse within 12 months after an initial chemotherapy-induced CR. These groups of patients are generally considered resistant to conventional combination chemotherapy because only about 10% of them will become long-term disease-free survivors to conventionally dose salvage chemotherapy (90–92). For patients with resistant HD, high-dose regimens with stem cell support have been proposed. The results of ten studies were summarized in 1994 (93). Treatment-related death rate was about 10–15%. An overall long-term, disease-free survival may be achieved in 20–30% of these patients. Similar results have been presented also in numerous other reports (94–103; only selected major recent trials have been reviewed). Two studies have recently reported results from transplanted patients who never achieved a CR to primary chemotherapy or who relapsed within 90 days. The patients have been reported to international transplantation registers (104, 105). Overall survival at five years was 35–40% in these studies. Although the results using high-dose therapy seem superior there is a possibility that selection bias is acting to make high-dose therapy appear more effective than conventional salvage chemotherapy.

A randomised study of 40 patients compared a dose-intensive regimen requiring stem cell support (BEAM; BCNU, etoposide, cytarabine, melphalan) with the same drugs used at doses not requiring stem cell support (mini-
At 3 years the progression-free survival was superior in the BEAM-arm (53% vs 10%; p = 0.025). There was no significant difference in total survival, but 4 patients randomised to mini-BEAM were transplanted after relapse. The GHSG and the European Bone Marrow Transplantation Group jointly randomised 161 patients less than 60 years with relapsed HD between 1993 and 1997. Patients who relapsed early (3–12 months after initial treatment), relapsed late (> 12 months and treated with seven or eight drugs) or patients with multiple relapses could be included. Treatment was either four courses of Dexa-BEAM (dexametason, BCNU, etoposide, ara-C and melphalan) or two courses of Dexa-BEAM followed by high-dose BEAM. Only patients with chemosensitive disease, i.e. CR or PR after two courses of Dexa-BEAM, continued treatment as randomised. The results have only been reported as an abstract (107). Among 142 evaluable patients, 115 were considered chemosensitive, i.e. proceeded to Dexa-BEAM three and four or high-dose therapy. Reasons for not proceeding were mainly toxic death, other life threatening toxicity or less than PR. Median follow-up is 33 months. When data were analysed based on intended treatment, time to treatment failure for all chemosensitive patients (p = 0.03) and for the subgroups with early or late relapse (p = 0.04 each) was significantly longer with high-dose treatment. Overall survival did not differ significantly (p = 0.3). Eight control patients have been transplanted after another relapse.

A French group (108) has performed a retrospective case-control study in 86 HD patients who underwent high-dose treatment after failure of the first chemotherapy regimen. Matching was done with 258 conventionally treated patients from international databases. In the grafted patients, the five-year event-free survival and overall survival after transplantation were 25% and 35%, respectively. The five-year overall survival rates of the grafted patients and the 258 matched conventionally-treated patients were 38% and 29%, respectively (p = 0.06). Median follow-up is short or 29 months (8–106 months) since the diagnosis of HD and 15 months (1–93 months) since the autologous stem cell transplantation. Toxicity was acceptable with seven (8%) procedure-related deaths.

Yet another retrospective case-control study was performed on primarily refractory HD patients (109). Event-free survival at four years was 52% in transplanted patients (n = 13) compared with 19% for those who received conventional-dose salvage therapy.

The literature shows that:

- The value of high-dose chemotherapy has not been documented in large controlled trials with long follow-up.
- The results of large uncontrolled single centre and multicentre studies, two case-control studies, and two small randomised studies show trends for improved survival from the use of high-dose chemotherapy in HD patients who are chemotherapy induction failures, who relapse after a short initial remission or after a longer initial remission and treated with a seven to eight drug combination or who have had multiple relapses. A recommendation of routine use of such treatment does not seem to be fully justified given the quality of data available and the observed effect on survival.

### High-dose chemotherapy:

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*For abbreviations, see above.

### QUALITY OF LIFE FOR LONG-TERM SURVIVORS

In a French study of 93 patients with a mean age of 32 years at diagnosis and free from relapse on an average ten years after treatment, late psychosocial sequelae were evaluated (110). The results were compared with a matched population-based control group. Radiation was given in 34% of patients, chemotherapy alone in 4% and 62% were treated with a combination of irradiation and chemotherapy. Compared with controls HD patients reported more physical impairments, e.g. dyspnoea (p < 0.001) and fatigue (p = 0.03). They were more often childless (p = 0.04). Psychologic, familial and professional status was not inferior among the former HD patients. The global health status was rated as equally good by patients and controls. Similar proportions of patients and controls worked, 74 and 72%, respectively. The sequelae of different treatment modalities were not analysed separately.

In a Norwegian study, 459 HD survivors aged 19–74 years treated at the Norwegian Radium Hospital 1971–1991 were approached in 1994 and compared with norms from 2 214 individuals approached in 1996. The mean time since diagnosis among the HD survivors was 12.2 years (range 3–23 years). Health-related quality of life (QoL) was assessed by the short form 36 (SF 36). Previous studies from the same group had demonstrated that the former HD patients reported high levels of anxiety and fatigue (111). Compared with the norms of the control group, being representative of the general Norwegian population, the HD survivors had lower scores, i.e. worse health state,
on all scales after adjustment for age, gender and educational levels. Statistically significant differences were thus found in general health, physical functioning, role limitations, social functioning, and in vitality. When analyzed according to previous treatment, no statistically significant differences were found. Patients treated with chemotherapy had, however, the highest scores on all scales, intermediate scores were found for those treated with chemotherapy and radiotherapy and the lowest scores for those treated with radiotherapy alone as primary treatment (112, 113).

When the psychosocial adaptation of 273 advanced stage HD survivors off treatment for one year or more (mean six years) was compared with that of 206 adult acute leukaemia survivors, HD survivors reported a distress score on the brief symptom inventory scale that was almost twice that found for the acute leukaemia survivors (p = 0.05) (114). HD survivors also reported more fatigue, conditioned nausea, greater impact of cancer on their family life and poorer sexual functioning than acute leukaemia survivors. All leukaemia patients had received chemotherapy only, whereas 20% of the Hodgkin disease survivors had received radiation therapy. The HD patients had relapsed more frequently than the leukaemia patients (29% vs 7%; p = 0.01). The relative contributions of these differences to the late problems are not known.

In a Swedish study (115), a questionnaire was sent to 110 HD patients surviving 4.6–19.3 (mean 10.3) years after treatment. The median age at diagnosis was 32 years and the former HD patients were asked about possible therapy-related side-effects. Ninety-nine (90%) responded. Thirty were treated with chemotherapy as the sole modality and this group was analysed separately. Shortness of breath and a reduced physical condition were the most common complaints (19 patients, 63%). Sixteen (53%) reported numbness in hands/feet. Muscle weakness was experienced by 14 (47%). Mouth dryness was reported by 12 (40%), and 13 (43%) had problems with teeth. Ten out of the 30 patients treated with chemotherapy were involuntarily childless. In the total material of 99 former patients, 17% experienced a reduced capacity for work. The results of this study were not compared with any control material.

The health-related QoL findings reflect the treatment practices of the 1970s and 1980s and the consequences of giving either chemotherapy, radiotherapy or both. Since advances have been made in the treatment, as well as in the treatment of side-effects, it is possible that the results might be quite different from those treatments used today. The relative contributions of chemotherapy and radiotherapy on the late effects are not known, although it may be suspected that the extended field radiotherapy, used more previously, is more responsible for some late effects than the chemotherapy.

This assumption is supported by a study of late sequelae after mantle field irradiation for supradiaphragmatic HD in 221 Norwegian patients (116). The patients were studied more than three years (mean 12 years) after treatment. Respiratory symptoms, cardiac disease and dental complications were compared with a group of 201 former HD patients treated with chemotherapy only for advanced-stage disease and followed for a comparable period. Dyspnoea on exertion was reported by 30% of the irradiated patients and 9% in the chemotherapy group (p = 0.0001). Myocardial infarction was about equally common in the two groups, 4% and 3%, respectively, but valvular disease was reported by 11% and 0%, respectively. Increased expenses for dental care were reported by 48% of the irradiated patients and 21% of patients treated with chemotherapy only (p = 0.0001). Moreover, the impact of chemotherapy in addition to irradiation could be evaluated for the respiratory and dental sequelae. The addition of chemotherapy did not cause an increase in these complications.

The literature shows:

- Persistent side-effects of treatment are common among long-term survivors. For some of these side-effects, radiotherapy contributes more than chemotherapy.
- Social and professional status are not impaired.
- 75–85% of former HD patients have a preserved capacity for work.

Quality of life for long-term survivors:

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LITERATURE

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REFERENCES


