Hodgkin' s lymphoma: new treatment ideas for an old disease

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The treatment of Hodgkin' s lymphoma remains a research interest for clinicians as progress is made in basic cancer biology, chemotherapy, radiotherapy, nuclear radio-imaging and stem cell transplantation. The tumour cells of Hodgkin' s lymphoma (HL), Reed/Sternberg cells, are derived from mature B-cells that have lost the expression of most B-cell lineage specific genes. Apart from the causal effect of Epstein Barr virus infection in some HL cases, the transforming events involved in the pathogenesis of HL are still largely unknown and only few oncogenes have been identified so far.

Prognostic factors

The choice of modern treatment strategies for each patient will rely on effective prognoses to indicate the adequate amount of chemotherapy and radiotherapy. Radiotherapy should however, to be kept to a minimum.

The prognosis of localised Hodgkin' s lymphoma patients can be assessed by different scoring systems (EORTC, GHSG and Canadian-ECOG). Several acceptable prognostic factors are still determined by dividing clinical stage (CS) I and II localised HL patients into favourable and intermediate/unfavourable subgroups. The specific criteria used differ in different centres, but a reasonable goal for a favourable category is the identification by clinical characteristics of individuals with a 80% relapse-free survival at 10 years. These prognostic factors have been established for a long time since radiotherapy was used alone or in association with MOPP chemotherapy. However, some patients in CS I and II have been identified with a 10-year relapse-free survival in the 50% range when treated with extended field irradiation only. Several clinical criteria will help identify these individuals. More recently an International Prognostic score (IPS) has been developed for clinical stage III and IV with parameters somewhat different from those utilised in localised stage. Although many similar characteristics have been identified, these scoring systems are not easy to relate to advanced stage HL. We recently aimed to refine the assessment of risks using the published scoring systems in favourable and unfavourable HL patients treated with modern treatment and combined modalities, and their correlation with the International Prognostic Score (IPS) for advanced HL (1–2). A population of 1156 patients with localised stage HL, Stage 1: 25%; stage 2: 75%, were treated prospectively within GELA centres in H8 (518 patients) and H9 (638 patients) protocols. According to scoring systems 70% of the patients had 0–1 EORTC factors; 60% 0–1 GHSG factors and 82% 0–1 Canadian factors. The International prognostic score for advanced stages was available only in H9 study with 64% of the patients with 0–1 factor. Survival curves according to each of the different scoring systems could significantly discriminate the subgroup populations. When a multivariate Cox analysis was performed for overall survival including all the scoring system variables: age >45yr, sex male, haemoglobin <10.5 g/dl, lymphocytes <600/μL, B symptoms with elevated ESR, extra nodal sites did retain an independent significant value. The probability of overall survival was 99%, 98%, 92%, 82%, 73% for patients with 1, 2, 3, 4, 5 factors respectively P <0.0001. In fact, all the patients with 1, 2, 3 factors, who represent 90% of the population, have a very favourable outcome and only the two other groups may need a more effective therapy. It is remarkable that these factors are similar for most of them with those described in the IPS when stages 3–4 are replaced by extra nodal (E) localisation. This new score should be validated in other prospective trials as it will simplify the Hodgkin prognostic scoring systems for localised and advanced stages.

Treatment of localised stages

Many of the ongoing or completed studies were developed in an attempt to reduce long-term complications of treatment without increasing mortality from HL. These include evaluation of radiation dose or field size, identification of the optimal chemotherapy. Two

recent studies are providing information in the same direction.

The first one is the recently reported EORTC and GELA H9 study [3]. From October 1998 to May 2004, 1591 patients with stage I–II HL were enrolled into two trials based on four prognostic factors: age, symptoms, number of involved areas, and MT-ratio. The H9-F trial compared 36 Gy involved field radiotherapy (IF-RT) *vs* 20 Gy IF-RT *vs* no radiotherapy (RT) in patients in complete remission (CR(u)) after 6 cycles of EBVP. The H9-U trial compared 6 cycles of ABVD *vs* 4 cycles of ABVD *vs* 4 cycles of BEACOPP baseline, followed by 30 Gy IF-RT in all arms, in patients with unfavourable clinical features. In the H9-F trial, of the 783 patients enrolled, 619 (79%) achieved a CR(u) and were randomised. Inclusion of patients in the no-RT arm was stopped in May 2002, because stopping rules were met (i.e. >20% of events). Inclusion in the other two arms continued until May 2004. After a median follow-up of 33 months, the 4-year EFS rates were 87% in the 36 Gy and 84% in the 20 Gy arm; it was 70% in the 0 Gy arm ($P < 0.001$). The 4-year overall survival (OS) rate was 98% in all 3 arms. Until September 2002, 808 patients were randomised in the H9-U trial. The 4-year EFS rates were 94%, 89% and 91% in the 3 arms, respectively ($P = 0.23$) and the 4-year OS rates 96%, 95% and 93% ($P = 0.89$). Chemotherapy-related toxicity (measured by antibiotics, transfusions, hospitalisation, S.A.E.) was higher with BEACOPP compared to ABVD. In favourable HL patients who achieved CR(u) after 6 cycles of EBVP, omission of IF-RT lead to an unacceptable failure rate; in contrast, an IF-RT dose reduced to 20 Gy provides equivalent early results as an IF-RT dose of 36 Gy. In unfavourable HL patients, similar early EFS rates are observed when the number of ABVD cycles is reduced from 6 to 4 and BEACOPP is not more efficient but more toxic.

In the second study, similar results were obtained in the HD11 study from the GHSG where 1043 patients with intermediate stage HL were randomised between 4 ABVD + 30 Gy, 4 ABVD + 20 Gy, 4 BEACOPP + 30 Gy and 4 BEACOPP + 20 Gy. Overall survival was 97% and freedom from treatment failure was 89%. There was no sequential significant difference either between ABVD and BEACOPP arms ort between 30 Gy and 20 Gy involved field-radiotherapy arms.

One can conclude that ABVD remains the best and less toxic chemotherapy regimen for localised stage. Second, limited radiotherapy at 20 Gy seems to as good as 30 Gy in Cr(u) patients. The results of the H9 study demonstrated that chemotherapy alone such as EBVPP was deleterious.

Is more effective chemotherapy alone with ABVD possible in a selected population of good prognosis patients? Two studies are supporting this approach; however, it seems that the local recurrence rate is slightly increased. With the evolution of modern radiotherapy, it is possible by using imaging of both computerised scan and PET scan to further restrict the field of irradiation to involved nodes only. This approach will need to be evaluated with strong cooperation between hematologists, radiotherapists and the department of nuclear medicine.

PET-scan

Tailoring the intensity of the treatment to the individual patient has become very topical. Achievement of complete response after chemotherapy needs a precise evaluation which is not easy to make with conventional CT-scan. Approximately two-thirds of patients with HL will have a residual mass at the end of treatment, but only 20% of these patients will eventually relapse. A high negative predictive value of FDG-PET has been consistently reported by most studies, clearly showing the ability of PET to identify patients with excellent prognosis [4]. Definition of complete remission (CR) will now involve PET negativity. The prognostic value of early FDG reduction probably reflects initial chemosensitivity of the tumour whereas results of later evaluations are more related to the detection of resistant clones. Several studies have correlated PET response during treatment with final outcome and allowed risk adapted treatment. Pet scan will be part of the armamentarium of staging and evaluation in future studies.

Treatment of advanced stages

Several attempts have been made to improve the results obtained with ABVD and the GHSG designed BEACOPP regimen which has been used since 1992 to treat several thousands of HL patients in randomised studies [5]. The comparison of standard BEACOPP, escalated BEACOPP and COPP/ABVD was reported with a median follow up of five years on 1201 patients [6]. There was a significant superiority over the COPP/ABV arm from freedom from treatment failure with 87% for escalated BEACOPP versus BEACOPP baseline with 76% and COPP/ABVD with 69% at 5 years. A major difference was observed in the rate of primary progressive disease during the initial therapy that was significantly lower with escalated BEACOPP (2%) versus (8%) for baseline and COPP/ABV (12%). The survival differences

where highly significant for BEACOPP. Despite more toxic events in the BEACOPP arms, the death rates at 5 years including all acute and late causes of deaths were for the COPP/ABV arm 18%, for BEACOPP baseline 13% and for escalated BEACOPP 8.6%. Using the IPS, the early progression rate were also inferior for the patients with 0–2 factors and the 3–7 factors if one compared patients treated with COPP/ABV and with escalated BEACOPP.

This regimen with hematotoxicity obviously introduces a different clinical management from the easy classical ABVD and confirmatory studies are on going with a comparison of escalated BEACOPP to ABVD within GELA-EORTC.

Treatment of relapse and refractory Hodgkin lymphoma

Most patients with Hodgkin' s lymphoma can be cured with chemotherapy alone or combined with radiotherapy. Depending on the initial treatment, different treatment options are available for patients who relapse after achieving CR, including radiotherapy for localised disease and conventional salvage chemotherapy. However, patients who fail to achieve an initial CR, and those who relapse within the first year after CR have a poor outcome. Salvage chemotherapy regimens with HDT and ASCT are associated with higher response rates and longer progression-free survival when compared to Dexa-BEAM (dexamethasone and carmustine, etoposide, cytarabine and melphalan) combination chemotherapy. Several studies have attempted to better characterise prognostic factors at relapse and to facilitate the choice of treatment. Relapse within the first year, disseminated stages, B symptoms, anaemia and age are the main prognostic factors described. The 4-year probability of survival ranged from 83% for patients without any unfavourable factor to 27% for patients with three risk factors. Consequently, patients without risk factors with late localised relapse in a non-irradiated area can be treated with combined chemoradiotherapy. Administration of salvage therapy prior to transplant aimed at achieving maximum tumour reduction and mobilising peripheral blood progenitors for ASCT. Salvage regimens can be followed either with conventional HDT with ASCT or with new approaches such as sequential high-dose chemotherapy with first two cycles of DHAP then followed by high dose chemotherapy with cyclophosphamide, methotrexate and etoposide with a final myeloablative course with BEAM and ASCT [7]. With a median follow up of 30 months FF2F and OS were 59% and 78% for all the 102 patients included in the Cologne study. FF2F and OS was 41% and 48% for those with progressive disease at time of inclusion.

Despite these improvements observed with high-dose therapy and ASCT some patients who failed to achieve complete remission or early and disseminated relapse with B symptoms have a poor outcome with five-year survival rates under 40%. In this population new approaches are warranted and more intensive regimen with tandem transplant can be studied [8]. A prospective multicenter study has been developed within GELA. Ninety-nine patients were included in the study with induction failure (n=49) or very unfavourable relapse (n=50). They planned to receive two courses of Ifosfamide, VP16 and Adriamycin with GSCF and blood stem-cell collection. In case of prior exposure to Adriamycin, patients received the MINE regimen. First ASCT1 was conditioned with CBV-mitoxantrone (30 mg/m^2) and second ASCT2 with (cytarabine 6 g/m^2); melphalan 140 mg/m^2 and total body irradiation at 12 Gy or busulfan (12–16 mg/kg). Median age was 33 years, initial stage III–IV 55%, bulky disease 50%, B symptoms 46% and extranodal sites 50%. After two cycles of salvage chemotherapy, response >50% was observed in 65% of the patients with unfavourable relapse and in 50% of induction failure. Seventeen patients were not submitted to ASCT for disease progression and one for insufficient stem cells collection, consequently eighty one patients received ASCT1. Seventy-one patients received the second ASCT. Hematologic recovery was within the usual time after ASCT1 but delayed platelet recovery was observed after ASCT2 with busulfan in the conditioning regimen. On an intent-to-treat analysis, 2-year event free survival was 45% and 70% for the patients having received the two autotransplants. The main reason for not completing the whole program was disease progression in 23% of the patients. Tandem ASCT is feasible in very unfavourable relapse from HD and may lead to some prolonged remission. However, salvage of early failure remains a difficult challenge.

Allogeneic stem cell transplantation with reduced intensity regimen

The most extensive experience of RIC allo-SCT comes from the EBMT registry data on 311 patients after a median of two lines of prior therapy and 45% had failed prior ASCT [9]. At transplantation, 158 had chemo sensitive disease, 100 had chemo resistant

disease and 53 untested relapse. With a median follow up of 1 year, 59% of patients remained alive. The treatment related mortality was still high 24% but half of what is observed with conventional SCT. The two year progression free survival was 26% and the OS 37%. The outcome depends mainly upon the chemosensitivity at transplant and the crucial question is whether or not there is a truly GVL effects and how strong it can be. In this sense all these patients should be included within prospective trials.

New tools are now present to improve the treatment of HL in reducing late toxicity or to overcome the few patients who still have a resistant disease.

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