Review

The case for and against high-dose therapy with stem cell rescue for early poor prognosis Hodgkin's disease in first remission

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Summary

After 10 years we are still not clear whether dose escalation with stem cell transplantation is relevant for some patients with poor prognosis Hodgkin's disease in first remission. Some of the problems relating to the controversy relate to the fact that the definition of high risk Hodgkin's disease in terms of prognostic factors is only now in 1998 being delineated properly. It is also possible that some of the dose escalation in lymphoma has taken place without an adequate amount of conventional therapy beforehand. It may be possible that dose escalation should be added to an adequate amount of conventional chemotherapy not integrated in a conventional regimen thus shortening it. Newer studies from the German Hodgkin's Disease Study Group, i.e. HD9, may be suggesting that conventional chemotherapy is producing good results in poor prognosis patients and thus negating the need for dose escalation and stem cell transplantation.

Key words: first remission, Hodgkin's disease, stem cell transplant

Introduction

The fact that such therapy has been considered for over 10 years now without a clear consensus indicates what a difficult area this still is in order to make a clinical judgement as to what is appropriate. A considerable number of questions remain in relation to the topic.

(1) Can one define high risk Hodgkin's disease? Are there prognostic factors which can be identified at diagnosis which when the patient has achieved first remission will ultimately determine what is good and what is poor prognosis? Will these factors remain the same in the remission patient from those determining the prognosis of an untreated patient?

(2) If high dose therapy is used should one add it as additional therapy to a complete course of conventional front line chemotherapy or on the other hand integrate it into conventional chemotherapy giving a less than optimal total number of conventional treatments and complete treatment with high-dose therapy?

(3) Can conventional therapy be dose escalated to produce as good a result as potentially high-dose therapy following on conventional therapy? In other words, is there a dose response relationship with conventional chemotherapy?

(4) What is the price of dose escalation with high-dose therapy and stem cell transplantation? What is the price in terms of the overall economic cost of adding a so called transplant to conventional therapy? What is the toxicity of such dose escalation with stem cell rescue? Are patients lost who would otherwise survive conventional therapy or dose intensified conventional therapy? Does the clinical toxicity of high-dose therapy and later complications such as second neoplasms outweigh any potential survival benefit by shortening the patient's life due to the second neoplasm?

A considerable series of attempts have been carried out to define high-risk Hodgkin's disease and consider the usefulness of early dose escalation with stem cell rescue, and at least one randomised trial is underway using prognostic factors defined in the centre at Genoa and used by the EBMT.

The definition of high-risk Hodgkin's disease

David Strauss and his group at the Memorial Sloan Kettering [1] defined a poor risk group of Hodgkin's patients at diagnosis. High-risk patients had two or more of the following factors: (a) aged over 45, (b) LDH over 400 at diagnosis, (c) haematocrit less than 38% for males and less than 34% for females, (d) mediastinal mass greater than 0.45 in diameter vs. the whole mediastinum, (e) involvement with inguinal lymph nodes, (f) involvement by Hodgkin's disease in the bone marrow. Low-risk patients had only 0 or 1 of these factors. When this index was used to apply to the data of other groups it was found difficult if not impossible to identify a group of patients who had a long-term survival of less than 55% or so. This thus made progress in applying such a rationale to the transplantation of some patients difficult.

Proctor at Newcastle, UK [2], in 1992 defined a
numerical prognostic index for identification of poor risk HD at diagnosis. Proctor's index took account of the patient's age, stage, lymphocyte count, hemoglobin, and an additional factor for bulk disease. Proctor used his index in an on-going local trial in which patients with the appropriate index less than 55 years and reaching CR or VGPR were randomised to either two further courses of conventional treatment to ABMT using marrow at that time and an ablative regimen of melphalan and TBI. Clearcut superiority for transplantation or indeed for one arm over another has never emerged from this study despite regular updates.

The GELA group using their own data defined six prognostic factors and considered high-risk patients to have three or more of these. They include (a) LDH > 100% of normal value, (b) an anemia with a hemoglobin of <12 g/dl for males and <10 g/dl for females, (c) mediastinal diameter of disease > 0.45 of the diameter of the whole chest, (d) inguinal involvement, (e) bone marrow involvement and (f) two or more extra-nodal sites of disease. Carella's group [3] in Genoa have already transplanted in a single-line pilot study 24 patients with a median age of 31 years with what they call high-risk disease. Their inclusion criteria have at least two of the following features: (a) high serum LDH, (b) large mediastinal mass (> 0.45), (c) two or more extra-nodal sites, (d) inguinal node involvement, (e) hematocrit below normal, (f) bone marrow involvement. Carella has also been responsible for chairing the EBMT HD01 protocol in which patients with two or more of those prognostic factors are given four courses of ABVD or ABVD-like regimens and if they respond and go into CR or PR they are harvested with a stem cell harvest and are randomised between four further courses of ABVD or ABVD-like regimens or an autologous stem cell transplant after only the first four courses of ABVD. As of March 1998 both the EBMT and GELA were entering patients into this study and a total of 129 patients had been accrued of whom 81 had been randomised. Hasenclever and others [4] have now gathered together details on 5141 patients from 22 centres to produce a national prognostic score for advanced Hodgkin's disease in which patients with 0 adverse prognostic factors have somewhere between 85% and 90% prospect of tumor control at seven years whereas those patients with more than five adverse prognostic factors have around 40% tumor control at seven years. The final model of a Cox regression analysis from the International Group incorporates seven binary factors: (1) albumin < 4 g/l, (2) Hb < 10.5 g/dl, (3) male gender, (4) age > 45, (5) stage IV, (6) leucocytosis > 15 g/l, (7) lymphocytopenia.

Additive or integrative high-dose chemotherapy?

The Carella EMBT study illustrates the problem of additive high-dose chemotherapy post conventional chemotherapy vs. integrative. In the first instance one must consider what the issues are in relation to high-dose chemotherapy being given additively post conventional chemotherapy vs. high-dose chemotherapy as it is presently given after relapse. If one considered those patients receiving high-dose chemotherapy after relapse then 60% of patients are cured first time around by conventional chemotherapy and that means 40% relapse. Of those 40% relapsing 40% of those are cured by high-dose chemotherapy, i.e., an extra 16%. Therefore the total number of patients cured first and second time around is 60% plus 16%, i.e., 76%. When additive high-dose chemotherapy is given post conventional therapy, for these patients there is no genuine possibility of high-dose chemotherapy after relapse so that in being cured first time around these patients will include that 60% cured by conventional chemotherapy without the transplant so a further 16% at least must be cured by the high-dose chemotherapy to reach an overall cure of 76%. This assumes that of those patients receiving additive high-dose chemotherapy post conventional chemotherapy first time around, there is no possibility of a further treatment which will cure them at relapse. Cure for these patients at relapse is highly unlikely with conventional salvage chemotherapy but may be possible with a second high-dose chemotherapy and autologous transplantation assuming the first remission is reasonably long or rarely it may be possible to allograft these patients with a matched sibling and cure some of them at that point.

There is a basic problem which relates to trials which use so called additive high-dose chemotherapy in addition to fully conventional chemotherapy vs. those trials which integrate the high-dose chemotherapy such as the Carella Hodgkin's study after giving the patient only four rather than eight courses of conventional chemotherapy. Hasenclever, Loeffler and others have done some work looking at the anti tumor 'value', 'rating' or 'score' of various chemotherapy agents, conventional regimens and high-dose regimens. It is certainly possible that in some studies which substitute high-dose chemotherapy for the later courses of conventional chemotherapy that in total an inadequate amount of chemotherapy may be given, i.e., that which is in fact less than that achieved by the usual full number of courses of conventional chemotherapy. I suspect that this may be applicable both in Hodgkin's disease and non-Hodgkin's lymphoma and might be an explanation for some of the anomalous results seen particularly in some of the non-Hodgkin's lymphoma randomised studies when early high-dose therapy has been given after three or four courses only of CHOP chemotherapy. The Carella HD01 Hodgkin's poor risk study is at risk from this phenomenon and we will have to see in due course what the outcome is. The BNL1/UKLG/EBMT study in poor risk adult high-grade non-Hodgkin's lymphoma is also at risk for this problem, giving as it does high-dose chemotherapy with BEAM after only three courses of CHOP, in the transplant arm.
Can conventional chemotherapy be intensified and thus preclude the need for high-dose chemotherapy?

The early results of the German HD Study Group, HD9, presented in 1998 using a new drug regimen called the BEACOPP grasps the principle of dose escalation of conventional chemotherapy and begins to look at possibilities to improve the outcome of poor risk patients by intensifying conventional chemotherapy. It addresses this by rearranging cytotoxic drugs and reducing the time interval between two cycles from 28 to 21 days. G-CSF is applied to prevent prolonged neutropenia and the three cytotoxic drugs which are most significantly escalated are adriamycin, cyclophosphamide and epoposide. The German group has randomised their patients into three groups. Group A receives four conventional COPP/ABVD alternating courses. Group B receives eight baseline BEACOPP chemotherapies and group C receive eight escalated BEACOPP chemotherapies. In each of these three groups radiotherapy can be given to initial bulk and residual tumour. In relation to early results with baseline COPP and ABVD 13% of patients progress. With baseline BEACOPP every 21 days 10% progress and with escalated BEACOPP only 2% progress. In escalated BEACOPP cyclophosphamide is increased from 650 mgs/msq to 1250, adriamycin from 25 mgs/msq to 35, and VP16 from 100 mgs/msq to 200. This is accompanied by a CR rate of 83% with baseline COPP/ABVD, 88% with baseline BEACOPP and 95% with escalated BEACOPP. In general terms the freedom from treatment failure is better with BEACOPP at either baseline or escalated than COPP/ABVD survival, although this is an early stage of the analysis, shows a trend in favor of BEACOPP. In addition to that the change at escalation of chemotherapy has an influence on the outcome of patients with poor prognosis. Patients with 0–4 adverse prognostic factors when given COPP/ABVD have a superior result in response and outcome to those with 5–7 prognostic factors. With BEACOPP the 0–4 factor patients have a super-imposable result with the 5–7 factor patients and therefore BEACOPP improves the outcome for the high-risk patient and it may well be that the use of BEACOPP and escalated BEACOPP is addressing the same constituency of patients that Carella is addressing with his intercalated high-dose chemotherapy after four courses of ABVD. At the early stages of analysis of the outcome of HD9 it appears that BEACOPP produces better disease control with less progression and probably improved survival. The relevance of prognostic factors is also reduced under BEACOPP. BEACOPP escalated shows that worthwhile escalation is possible and although there is considerable acute toxicity it is manageable. The leukemigenicity of BEACOPP and escalated BEACOPP is still uncertain and there are certainly some case produced on these regimens of MDS and perhaps ultimately AML. It will need three to five years of further follow up to view the outcome of the Carella study and whether it produces better or even indeed worse results than conventional chemotherapy and also of the HD9 study to consider the long-term effects of BEACOPP and its toxicity.

The most sensible approach today (1998) in terms of high-dose therapy for patients at diagnosis may be to follow the outcomes of these two studies, i.e. Carella’s randomised EBMT trial and the German HD9 and not initiate a new study. Other possibilities to consider will include shortening the number of courses of escalated BEACOPP and using transplant as integrated rather than added therapy and randomising this complex against conventional BEACOPP and escalated BEACOPP. Another possibility is to look at short BEACOPP plus transplant against conventional ABVD. There is a variety of possibilities but there is a strong argument for not initiating a new transplant study until we know the outcome of the HD9 chemotherapy studies and the Carella EBMT randomised study.

References


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