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Is There a Rationale for High-Dose Chemotherapy as First Line Treatment of Advanced Hodgkin's Disease?

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Since the first report by Carella *et al.* (1991) several international meetings discussed high dose chemotherapy (HDCT) plus autologous stem cell transplantation (ASCT) as first line treatment for high risk patients with advanced stage Hodgkins's disease. Several aspects of this treatment option and of a trial design appropriate to determine its value are still controversial. In the first part of this paper we will present data of the GHSG to discuss possible choices of high risk groups to be included. In the second part we will pose some questions concerning the rationale of early HDCT and the possible benefit of this option.

How to select candidates for an early HDCT-strategy?

Since logistic and financial resources are limited and overtreatment is of major concern, a reliable identification of a particular high risk group is an essential issue in this discussion. The ongoing EBMT/Intergroup trial uses a high risk group definition of Straus *et al.* (1990). In planning a large multicenter trial concerning early HDCT it is important to validate the intergroup reproducibility of the high risk group selection criterion chosen and to quantitatively estimate the failure rates in the supposed high risk groups. Such validation can only be done using independent data.

We therefore have analyzed 599 patients in stage IIIB/IV Hodgkin's disease, aged under 60, who have been treated between 1983 and 1992 according to protocols of the GHSG and who responded within 4–6 months of modern multidrug regimen. Details of this analysis will be published elsewhere. Patients older than 60 years and early progressing patients have deliberately been excluded, since they are not potential candidates for early HDCT or would receive salvage treatment anyway.

We have tried to reproduce the analysis of Straus *et al.* (1990) in the GHSG data. Haemoglobin levels were used instead of hematocrit; this is admissible since these parameters are highly correlated. Of the six factors highlighted by Straus *et al.*: LDH > 400 U/L, age > 45, inguinal node involvement and bone marrow involvement show a slight trend in the expected direction, but are not univariantly significant in our rather large data set. Having a very large mediastinal mass (> 0.45 of the thoracic diameter) was borderline significant; as was having a large mediastinal mass (> 0.33). The only clearly significant parameter among the Straus factors in the GHSG data is a low haemoglobin level (♂ 12 g/dl; ♀ 10.5 g/dl). Multivariantly, low haemoglobin is the only independent single prognostic factor. The higher risk group selected by two or more of these factors (Straus criterion) has a Freedom From Treatment Failure (FFTF) rate of over 50% and an overall survival (SV) of 75% at 5 years. This is markedly higher than in the original publication. Using haemoglobin level as only criterion even leads to a slightly better discrimination.

Low haemoglobin (or haematocrit) has been described by several groups, Straus *et al.* (1990), Proctor *et al.* (1991), MacLennan *et al.* (1983), as an independent prognostic factor. Therefore, we think that a low haemoglobin

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level can be considered as an established and reproducible prognostic factor in advanced Hodgkin's Disease indicating an unfavorable prognosis.

We have tried to further complement low haemoglobin with other possible prognostic factors. The motivation is that, first, the prognosis of the low haemoglobin group is still rather favorable (FFTF: 45% at 5 yrs; SV: 74%) and, second, one would hesitate to use a single laboratory parameter alone to select a high risk group. Low haemoglobin in combination with either stage IVB or/and high alkaline phosphatase (> 230 U/l) defines a high risk group which has about 40% FFTF and 65% SV at 5 years. The relevance of stage IVB is not surprising. The relevance of alkaline phosphatase and the specific cutpoint at 230 U/l had already been published by our group in an analysis of the cohort of the first 137 patients reported here (Loeffler *et al.* 1988). This finding is now confirmed both with longer follow up in the original group and independently in the cohort of the 462 patients treated since then.

The intergroup validity of this new high risk group criterion should be confirmed by other large study groups. We will try to organize an international cooperation to validate various high risk group definitions and hope to report first results of this effort at the Third International Symposium on Hodgkin's Disease, Cologne, September 1995.

Using two or more of the Straus factors, 33% of all responding stage III/BIV patients would be selected as high risk. Our new criterion selects 21%. How many of these patients indeed would qualify for an early HDCT trial depends on when HDCT is integrated in the first line treatment. There are essentially 3 variants: (1) HDCT in addition after a full course of say 8 months of standard chemotherapy for patients that achieve a complete remission (CR) (2) HDCT after 4 cycles of standard chemotherapy for those patients that have responded (CR or PR) (3) HDCT after 4 cycles of standard chemotherapy exclusively for patients with a partial remission (PR) only. The ongoing EBMT/intergroup trial uses variant (2).

Our new criterion was developed on all patients responding to 4–6 cycles of standard chemotherapy using FFTF as endpoint; this is the analysis appropriate for variant (2). However our new criterion is also prognostic a) when restricted to patients that get into CR after full conventional treatment (FFTF 60% at 5 yrs), i.e. for variant (1), and b) when restricted to patients with early PR after 4–6 cycles, i.e for variant (3). High risk patients according to our criterion who only have a PR after 4–6 cycles of chemotherapy do particularly badly (FFTF: 27% at 5 yrs; but SV: 57% at 5 yrs). The problem with the latter group of patients is that a reliable and reproducible definition of PR is difficult especially in a multicenter setting. In addition this group is rather small (10% of all responding stage IIIB/IV patients).

It is noteworthy that our criterion is not prognostic once the relapse has occurred i.e for survival after treatment failure.

What is the rationale for early HDCT and what is the correct comparison to establish its value?

There is a considerable probability of cure with late HDCT (25–50%) after first relapse. Hodgkin's disease patients generally get a second chance. This has to be accounted for in the evaluation of early HDCT. On the other hand, the chance of cure after a failure of HDCT—whether in first line or as salvage treatment—appears to be minimal. Thus an early-HDCT-for-all-high-risk-patients strategy should be compared to a strategy with conventional chemotherapy and late HDCT offered to relapsing patients only.

Survival is the appropriate and decisive trial endpoint. In contrast, Freedom From First Treatment Failure is not fully appropriate in this setting. The argument is as follows: Early HDCT should at least cure all those patients that are currently cured by standard first line treatment plus those patients destined to relapse with conventional treatment but curable by late HDCT. Thus one should expect early HDCT to show a better Freedom From First Treatment Failure rate.

To illustrate this, assume a high risk group with 40% FFTF with conventional treatment. A reasonable estimate of the cure rate with late HDCT in relapsing patients might be 35%. Then you would expect 35% of the 60% relapsing patients to be cured by late HDCT and thus a fortiori to be cured by early HDCT. Therefore a difference of about 21% difference in long term FFTF between early HDCT and conventional treatment has to be expected if long term cure rates are to be the same. This assumes minimal chance of cure after a HDCT failure. Such a difference would not be surprising and thus FFTF as primary endpoint is questionable.

In order to preliminarily check the expectation that initial FFTF rates will be better with an early HDCT strategy we have proposed a cooperative EBMT/GHSG matched pair evaluation of those patients transplanted in CR after first line treatment and registered in the EBMT data base. They will be matched with comparable patients from the GHSG database who have not experienced relapse up to the day of their match's transplantation.

To achieve a survival benefit, early HDCT would have to show more than about a 21% difference in FFTF. Only patients destined to relapse with conventional treatment

and not curable with late HDCT might profit from early HDCT as concerns survival. Only these patients who make up only a fraction of all early HDCT candidates are truly informative in an appropriate trial.

An overall survival benefit with an early HDCT strategy—if there is any—will therefore probably be small. Patients currently cured with standard therapy might be overtreated. Early progressing patients will get salvage treatment anyway and will therefore not profit from this approach. On the other side, late and very late relapses are typically quite responsive to second line chemotherapy. Their results (e.g. Reece *et al.* 1994) with salvage treatment are such that some groups even wait with HDCT until the second relapse occurs. In patients not achieving CR or relapsing early with conventional chemotherapy, the results of late HDCT are not very encouraging. Such patients might have the best chance to profit from early HDCT. But in these patients the difference in timing between early or late HDCT is less than a year, so a dramatic difference in outcome seems improbable,—although it is an open question whether their drug resistance is biologically determined prior to therapy or develops during therapy and time to relapse.

Substantial patient numbers are thus needed for a trial to detect a small, but relevant difference in survival. A trial designed to really solve the question will be difficult to conduct. The ongoing EBMT/intergroup trial is designed to look primarily at FFTF and will hopefully succeed with this limited objective. But even if one is skeptical about the chance to detect a survival benefit with early HDCT, there might be considerable life planning, management or even toxicity benefits with an early HDCT strategy. Such benefits might be detected by other endpoints requiring less patients. These aspects need elaboration in order to further clarify the rationale of an early HDCT strategy.

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