Symposium article

Annals of Oncology 13 (Supplement 1): 75–78, 2002
DOI: 10.1093/annonc/mdf615

The disappearance of prognostic factors in Hodgkin's disease

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The purpose of this conceptual (and somewhat provocative) article is to analyse the reasons for the disappearance of prognostic factors in Hodgkin's disease (HD) and to explore the consequences for further research from a biometrical point of view. The very concept of prognostic factors is about to resolve in HD. Prognostic factors gradually loose their predictive power as treatment is successfully adapted to the disease burden. Freedom from treatment failure and overall survival curves of patients in early, intermediate and advanced stages of HD are superimposable with the best current treatment protocols of the German Hodgkin's Lymphoma Study Group. This disappearance of prognostic factors in HD necessitates a certain conceptual remodelling. It's time to think quantitatively and bivariately, and we need to (i) synthesise existing 'prognostic' factors into a quantitative measure of disease burden or severity; (ii) develop a quantitative measure of treatment strength and (iii) relate these two quantities in nomogram curves indicating how much treatment a patient with a given disease burden requires to have, say, a 85%, 90% and perhaps 95% expected chance of cure.

Key words: Hodgkin's disease, prognostic factors, risk-adapted therapy

Prognostic factors disappear in Hodgkin's disease

The ideal of risk-adapted therapy is to let prognostic differences disappear. The strategy is to give stronger treatment to patients with more advanced disease. Characteristics of more advanced disease would be observed as unfavourable prognostic factors as long as these patients are treated with similar therapeutic options as for limited stage disease. But if a sufficiently effective treatment for advanced stages is available, tolerable and employed, these characteristics of advanced disease are no longer prognostic for treatment failure. They become unobservable as prognostic factors.

The therapeutic situation in Hodgkin's disease (HD) is approaching this scenario. Figures 1 and 2 show freedom from treatment failure (FFTF) and overall survival (OS) curves with currently best treatment protocols of the German Hodgkin's Lymphoma Study Group (GHSG) in early, intermediate and advanced stages (courtesy of U. Paulus and V. Diehl for the GHSG).

Early stages in GHSG trials comprise Ann Arbor classification stage I/II without any unfavourable factors [large mediastinal mass, erythrocyte sedimentation rate (ESR) >50 or B stage and ESR >30, more than three lymph node areas involved, E stage, massive spleen involvement]. The data from the HD 7 trial of the GHSG [1] shown were obtained with two cycles of ABVD (doxurubicin, bleomycin, vinblastine and dacarbazine) plus extended-field irradiation 30 Gy + 10 Gy to the involved fields. (Most study groups have now abandoned extended-field irradiation. Similar data may be obtained with four cycles of ABVD + involved field and the ongoing HD 10 trial is intended to show that two cycles of ABVD + involved fields suffices.)

Advanced stages comprise all stages III and IV as well as selected stage IIB patients (with large mediastinal mass, E disease or massive spleen involvement). The data from the HD 9 trial of the GHSG [2] were obtained with eight cycles of dose-escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) (with additional radiotherapy to sites of bulky disease).

Intermediate stages comprise all patients that do not fall in the two other classes. The data from the HD 8 trial [3] were obtained with two double cycles of COPP/ABVD with involved field irradiation (40 Gy).

The curves are essentially superimposable. OS is ~90% at 5 years for all protocol groups. FFTF is >85% at 5 years. The worst outcome is observed in intermediate stages, although this difference is not statistically significant.

The criteria for treatment delineation employed were well-established prognostic factors at a time when radiotherapy was the main treatment modality in early and intermediate HD. They clearly measure the severity of the disease to a certain degree, but they evidently have now lost their predictive power with improved treatment options.

Prognostic scores lose predictive power with improved treatment

The international prognostic score (IPS) [4] was developed for advanced disease patients treated with the treatment options of

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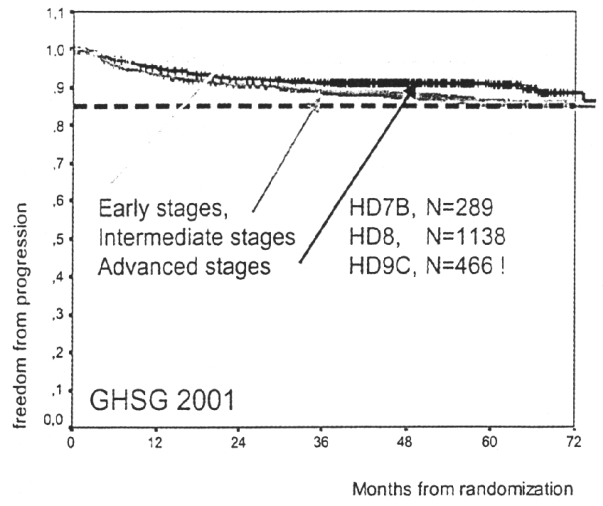

Figure 1. Freedom from progression curves in early, intermediate and advanced-stage HD with currently best treatment protocols of the GHSG (see text for details).

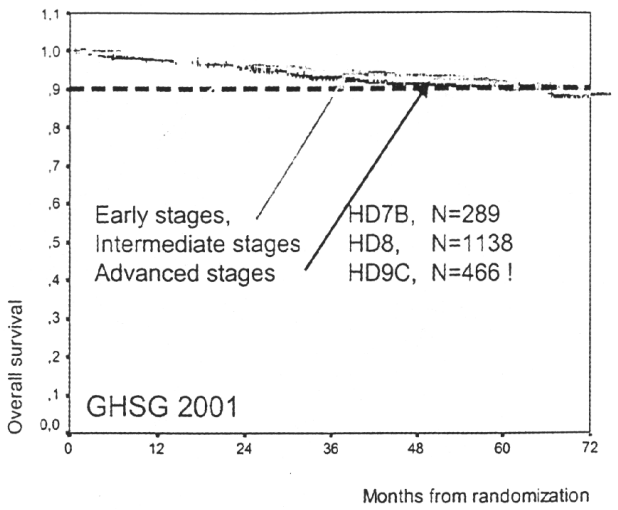

Figure 2. OS curves in early, intermediate and advanced-stage HD with currently best protocols of the GHSG (see text for details).

the MOPP (mechlorethamine, vincristine, procarbazine and prednisone)/ABVD and ABVD era. Figures 3–5 show the IPS with COPP/ABVD, BEACOPP and escalated BEACOPP in data from the HD 9 trial of the GHSG. While the IPS is moderately discriminative with COPP/ABVD as expected, with the increasingly more effective BEACOPP and dose-escalated BEACOPP regimens all curves move upwards and squeeze in the range of 80% to 100%. Again, improved therapy equalizes the outcome.

No events left to detect 'high risk' patients

Thus prognostic factors are disappearing with the availability of adequate therapeutic options. So do we need new prognostic factors? With >80% patients cured even in advanced stages we fortunately run out of events to be predicted.

With modern treatment strategies, prognostic factor studies will require huge patient numbers and their results will only apply on the unfavourable fringe of the prognostic spectrum within the respective treatment group. Thus 'high risk' patients so 'identified' typically will have a predicted cure rate of say 75% instead of 90%. These patients might profit from further fine-tuning of the allocation of patients to treatment groups.

A biological marker? Not much hope

Perhaps one can gain in specificity through biological markers? The HD 9 trial of the GHSG shows that the very early failure rate decreased from 12% with COPP/ABVD to 2% with escalated BEACOPP. Thus patients who formerly were thought to represent a qualitatively resistant subgroup turned out to simply require quantitatively stronger treatment. Thus biological studies might search in vain to characterize a qualitatively different, resistant subgroup of relevant size. Probably in HD things are as simple as that: a certain amount of disease burden has to be matched quantitatively by an adequate amount of treatment. It is important to carry out these biological studies, but the answer may well be 'no'.

Discrimination is difficult among routinely cured patients

On the other hand, many patients in advanced stages are clearly over-treated with, for example, escalated BEACOPP. Two-thirds of the patient population is already cured using COPP/ABVD-type therapy, and there are occasional cases of patients with advanced-stage who walk away after two to three cycles of therapy and remain in remission.

But how should we know? We are in an epistemological dilemma. As there are no observable events, there is no information discriminating among patients that are cured. Even if we had promising candidates for prognostic factors, we would need a study in which patients are intentionally exposed to the risk of under-treatment to gain prognostic information within the large spectrum of patients routinely cured with current approaches. There are obvious limits to such studies and thus we should recognize that it will be increasingly difficult to get more information beyond that already at hand from old studies.

Revised problem specification

Given that we want prognostic factors to disappear, we have to conceptually reformulate the research problem so that it fits the new task to develop an individualised treatment approach avoiding over-treatment. Let us not look for new prognostic factors, but think quantitatively and bivariately:

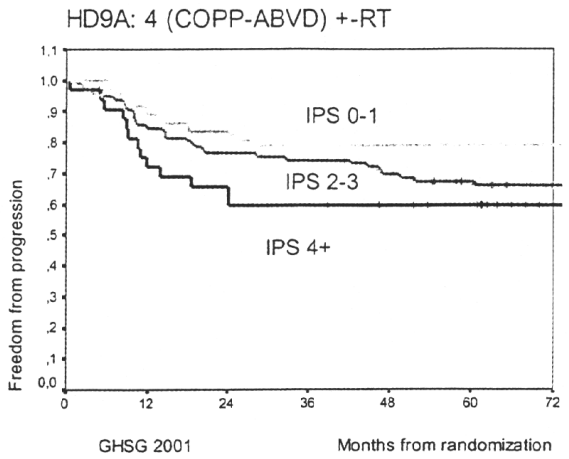

Figure 3. Prognostic discrimination of the IPS [4] with increasingly effective 4 (COPP/ABVD) ± RT chemotherapy. Data from the HD 9 trial [2] of the GHSG.

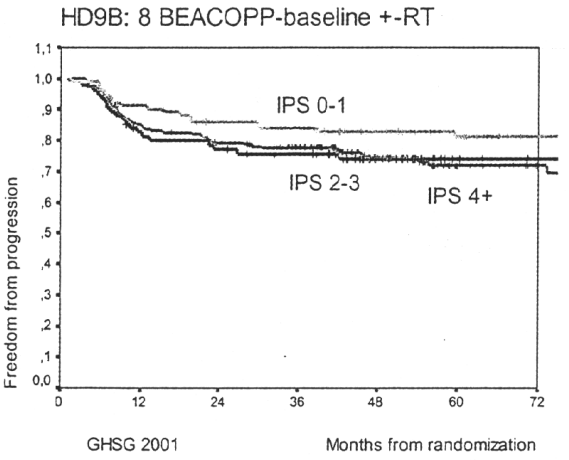

Figure 4. Prognostic discrimination of the IPS [4] with increasingly effective 8 BEACOPP-baseline ± RT chemotherapy. Data from the HD 9 trial [2] of the GHSG.

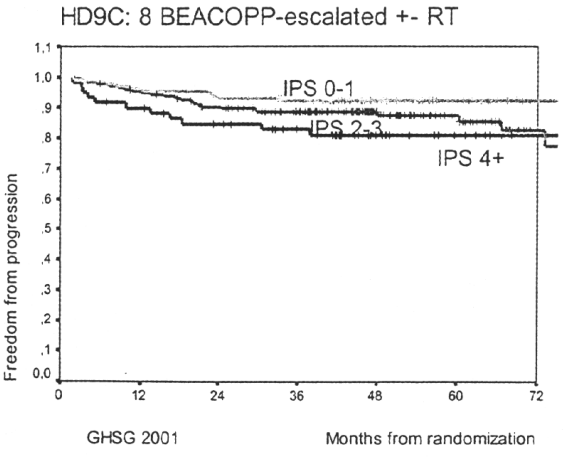

Figure 5. Prognostic discrimination of the IPS [4] with increasingly effective 8 dose-escalated BEACOPP ± RT chemotherapy. Data from the HD 9 trial [2] of the GHSG.

(a) synthesise former prognostic factors into a quantitative measure of severity or burden of disease;
(b) develop a quantitative measure of treatment strength; and
(c) relate these two quantities by nomogram curves indicating how much treatment a patient with a given disease burden requires in order to have an expected cure rate of, say, 85%, 90% and perhaps 95% with his first line of treatment (see Figure 6 for an illustration).

It is well known that 'prognostic' factors in HD are mainly crude direct measures of tumour burden and activity (stage, number of lymph node areas, bulk, B symptoms) or indirect surrogate measures of tumour burden and activity based on laboratory parameters (hemoglobin, s-albumin) [5, 6]. Recently Gobbi et al. [7], were able to quantify the tumour volume and showed good prognostic discrimination. This has been confirmed by the Scotland and Newcastle Group (abstract no. P163, this congress). It is possible that this approach is a way to define a workable measure of tumour burden and activity [task (i) above].

The concept of effective dose developed by Hasenclever et al. [8] provides an instrument to quantify chemotherapy strength [task (ii) above]. The effective dose of a treatment is calculated by a weighted sum of the doses of the cytostatic drugs given that is adjusted for treatment duration taking into account the disease-specific growth kinetics. The necessary weights may be roughly estimated by a model-based meta-analysis of all chemotherapy comparing randomised HD trials.

Task (iii) above, to establish nomogram curves for individualised treatment, is probably the most difficult one. It would certainly require modelling based on an individual data-based meta-analysis of randomised trials that compare strictly defined and delivered treatments in thoroughly and uniformly characterised patient populations.

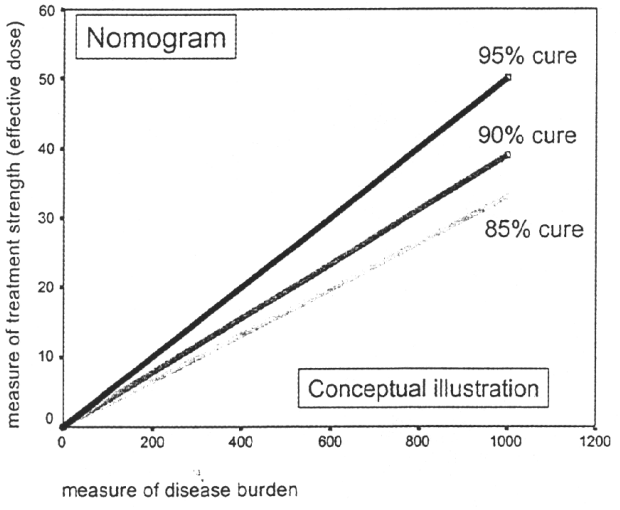

Figure 6. Illustration of the concept of a nomogram to represent the relationship between the individual disease burden and the required treatment strength to obtain a chosen (high) chance of cure.

In conclusion, prognostic factors are disappearing in HD because of successful adaptation of treatment strength to the individual disease burden of the patients. It is time to conceptually re-focus research from looking for prognostic factors to a direct representation of the relationship between the individual disease burden and the required treatment strength relationship to obtain a chosen (high) chance of cure.

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