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Prognostic Factors in Hodgkin's Disease

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The clinical course of patients with Hodgkin's disease (HD) is highly variable. On the extremely favorable end of the prognostic spectrum, the disease may remain localized for several years even without therapy. On the unfavorable end, the disease rapidly disseminates and aggressively progresses despite full state-of-the-art treatment.

How, then, can the clinician deal with this enormous heterogeneity of the disease course and delineate appropriate treatment strategies? Reliable prognostic tools are needed to predict outcome of patients based on their clinical characteristics. Unfortunately, the development of such tools is not an easy task. Despite the achievements of the last 30 years, the ability to predict the course of HD for a specific patient remains limited.

A major historic step toward prognostication of outcome was the adoption of the staging classification established by a consensus workshop situated in Ann Arbor in 1971.[1] Stage is based on the anatomic extent of involvement: stage I—involvement of a single lymph node region; stage II—involvement of two or more lymph node regions on the same side of the diaphragm; stage III—involvement of lymph nodes on both sides of the diaphragm; stage IV—any visceral involvement that is not contiguous or proximal to a known nodal site (ie, not an E stage only). This is in line with the concept that the spread of HD from an initially involved lymph node through the lymphatic system is associated with a progressively worsening prognosis.

In addition, the staging system codes for absence ("A") or presence ("B") of systemic symptoms (unexplained fever, weight loss, or night sweats). In 1988, a meeting in the Cotswolds area of England proposed a modification to the Ann Arbor system[2] incorporating number of involved sites and extent of bulky disease. However, these recommendations have not been universally adopted. Figure 22–1 shows overall survival curves by stage and systemic symptoms in 14,291 patients from the International Database on Hodgkin's Disease (IDHD).[3]

Although tumor stage remains the backbone of clinical evaluation of HD, a plethora of other prognostic factors (PFs) have been investigated and combined in various prognostic scores or numerical indexes to improve prognostication.

PROGNOSTICATION

The understanding of a few general conceptual points regarding PFs is essential to understanding an HD specific discussion: Prognostic factors are

- clinical features or variables measured in a patient;
- at or up to a certain **reference time point** (eg, time of diagnosis or relapse);
- used to predict the probability of a specific future event (eg, death, relapse, toxicity, diagnostic finding); and
- applied assuming that the patient is diagnosed and treated **within** a certain **broadly defined clinical strategy**.

It is important that PFs be documented before the time point at which the outcome is predicted. Predictions based on yet unknown future events repre-

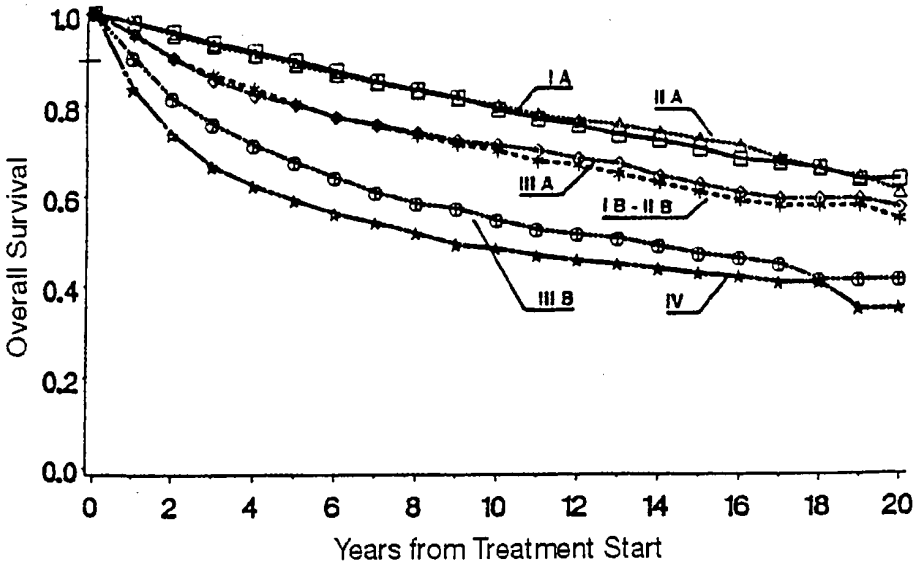

Figure 22–1. Overall survival by clinical stage and presence or absence of systemic symptoms from the International Database on Hodgkin's Disease. Stage IA: 2,707 patients; stage IIA: 4,406 patients; stage IB–IIB: 1,974 patients; stage IIIA: 1,558 patients; stage IIIB: 1,779 patients: stage IV: 1,860 patients. (Reproduced with permission from Henry-Amar M, Aeppli DM, Anderson J, et al. Workshop statistical report. In: Somers R, Henry-Amar M, Meewaldt JH, Carde P, editors. Colloque INSERM. Vol. 196. London: John Libbey Eurotext Ltd.; 1990. p. 169–418.)

sent bad intellectual practice. Thus, instead of recognizing relapse as a bad prognostic factor for survival, it is better to search PFs for survival after relapse in a separate analysis.

From a statistical point of view, prognosis defines the probability of a certain event in a (sufficiently large) group of patients with common clinical characteristics. Thus, PFs and prognostic scores are pertinent mainly to the delineation of general treatment strategies or trial inclusion criteria. Application of the prognosis to individual patients is accurate only if the particular patient is seen as a typical member of its group and thereby sufficiently characterized just by the PFs considered.

INTERACTIONS OF PROGNOSTIC FACTORS AND TREATMENT STRATEGIES

The outcome of patients with HD obviously does not depend on PFs alone but also on the therapy employed. In the discussion of PFs, the dependence of results on treatment choices is intentionally disregarded. This decision is based on the experience that prognostic differences are influenced only marginally by minor treatment variations. In addition, prognostic scores typically are developed in large data sets pooling outcome results of heterogeneously treated patients from several study groups to provide adequate statistical power. Propositions concerning PFs are intended to apply to an "average" state-of-the-art treatment.

Nevertheless, in HD, PFs for freedom from progression depend, to some extent, on treatment modality (radiotherapy alone or chemotherapy with or without additional radiotherapy) and the diagnostic strategy (diagnostic laparotomy or not). In patients with localized disease treated with radiotherapy alone, occult involvement outside of the radiation field that would have been targeted by systemic treatment may be left untreated. Thus, factors that predict positive laparotomy findings, or that are correlated with the spread of disease through the lymphatic system, tend to be more important with radiotherapy alone than with chemotherapy-based treatment when freedom from treatment failure is the end point considered. A recent meta-analysis[4] shows that combined modality treatment reduces the risk of relapse but does not improve overall survival in early-stage HD. The following discussion concentrates on the end points of freedom from progression and survival and points out interactions with treatment modalities as appropriate.

SOURCES OF EVIDENCE

In HD, prognostic differences described by clinical features typically are of moderate size (eg, 8 to 10% difference in plateau). In addition, the problem is not only to estimate the prognostic impact of individual features but also to select among correlated parameters and identify factors that carry independent prognostic information.

There is a huge amount of literature on prognostic factors in HD (see Specht and colleagues' articles[5,6] for extensive references). Most papers are based on conclusions drawn from a few dozen to a few hundred patients and provide valuable information in the context of specific treatment strategies or clinical situations. In addition, there are two very large international data sets that pool data from many leading study groups: the IDHD and the International Prognostic Factors Project on Advanced Hodgkin's Disease (IPFP).

In 1989, the IDHD was established, coordinated by the European Organization for Research and Treatment of Cancer (EORTC). The IDHD combines data from more than 14,000 patients in all stages from 20 study groups between the 1960s to the mid-1980s (typically the era of radiotherapy and MOPP [nitrogen mustard, vincristine, procarbazine, and prednisone]-type chemotherapy). The workshop report on this data set,[3] compiled and analyzed mainly by Michel Henry-Amar, and further papers based on these data[7–12] remain the major source on PFs in HD.

The second international cooperation, the IPFP, collected the trial data in advanced disease (N > 5,000) from the 1980s (mainly treated with doxorubicin-containing regimens) to construct an international prognostic score in advanced HD.[13]

TYPES

Prognostic factors may be grouped into patient-related and tumor-related PFs. Tumor-related PFs describe the type of tumor, pattern and size of involvement, growth kinetics, and consequences of tumor-released cytokines. Patient-related PFs describe the ability of the patient to undergo treatment and include mainly age, performance status, and, to a certain extent, gender. Both types of PF contribute to overall prognosis, but it is useful to keep them distinct. Risk of disease progression and the patient's reserve to tolerate treatment and its sequelae are aspects to be considered separately when choosing a treatment strategy.

Patient-Related Prognostic Factors

Older age has frequently been reported as being associated with poor survival[14–16] and independently contributes to most published prognostic scores.[11,13,17–22] Figure 22–2 shows the relation of age groups to overall survival in the IDHD data.[3]

Discussing age as a PF is complicated since there are several possible pathways through which higher age can become an unfavorable prognostic feature for overall survival. It is difficult to entangle the relative impacts of these different effects:

- Higher acute toxicity of therapy, either fatal by itself or leading to major dose reductions associated with inferior disease control
- Higher rate of late toxicity, sequelae of treatment, or second malignancies in relapse-free patients
- Natural age-related mortality
- Reduced ability to undergo salvage treatment in the event of relapse
- Higher rate of abdominal involvement (age is a PF for positive laparotomy findings and thus higher stage[3])
- More aggressive disease biology

The combined impact of higher acute and late toxicity can be illustrated from the IPFP data (Figure 22–3). The estimated 7-year rate of death in continuous complete remission was 3 percent in patients aged up to 44 years, 9 percent in the age group 45 to 54 years, and 15 percent in the age group 55 to 65 years. Thus, mortality begins to increase even in middle-aged populations.

In HD, the reduced ability with age to undergo second-line treatment is particularly important since young patients who relapse from HD do have a second chance of cure. Figure 22–4 shows unpublished data on survival after relapse in 1,490 chemotherapy pretreated patients from the IPFP. Young patients have about a 40 percent chance to survive 5 years after relapse; this chance approaches zero with higher age.

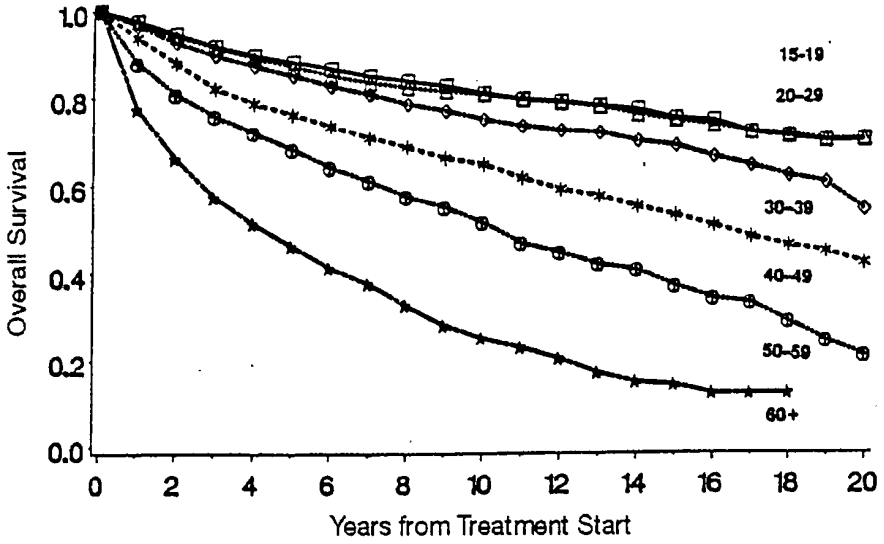

Figure 22–2. Overall survival by age at diagnosis from the International Database on Hodgkin's Disease. Age 15–19 years: 1,684 patients; 20–29 years: 5,026 patients; 30–39 years: 3,254 patients; 40–49 years: 1,837 patients; 50–59 years: 1,292 patients; 60+ years: 1,198 patients. (Reproduced with permission from Henry-Amar M, Aeppli DM, Anderson J, et al. Workshop statistical report. In: Somers R, Henry-Amar M, Meewaldt JH, Carde P, editors. Colloque INSERM. Vol. 196. London: John Libbey Eurotext Ltd.; 1990. p. 169–418.)

In summary, age is a dominant PF for overall survival. Its impact on freedom from first progression is quantitatively much less pronounced, and this remaining impact may rather be explained by treatment reductions due to toxicity rather than by a more aggressive biology.

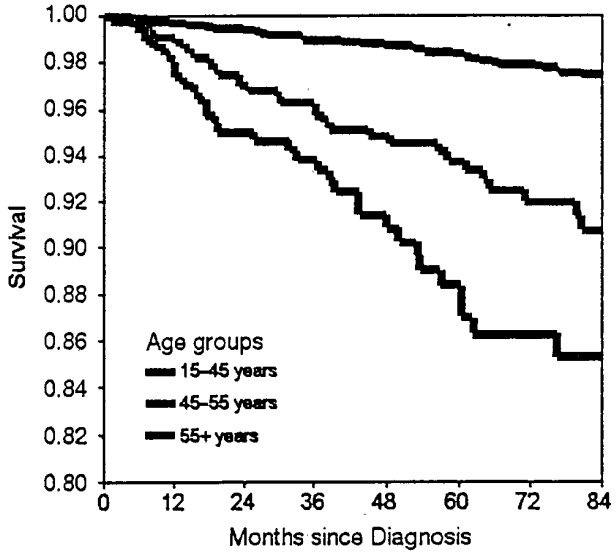

Figure 22–3. Freedom from death in continuous complete remission (time to death, censoring patients at relapse or last information) in 4,695 patients by age groups. (Unpublished data from the International Prognostic Factor Project on Advanced Hodgkin's Disease.)

Male gender repeatedly has been reported as unfavorably prognostic. Male gender is correlated with disease stage, and about two-thirds of advanced-stage patients are men.[3,13] Correspondingly, male gender is a PF for positive laparotomy results.[3,23] However, even after accounting for stage, a small independent prognostic impact of gender remains in most multivariate analyses.[13,17,19,20,24–26] Race does not appear to have independent prognostic impact,[27] although data are sparse.

Tumor-Related Prognostic Factors

Histology

In 1965, a consensus on the histopathologic classification of HD was established at the Rye conference.[28–28b] Four subtypes were distinguished: lymphocyte depletion, lymphocyte predominance, nodular sclerosis (NS), and mixed cellularity (MC).

Lymphocyte depletion is rare (< 3%) and diagnosed less frequently in recent years, probably due to shifts in diagnostic criteria[3,29] toward classifying these cases as non-Hodgkin's lymphoma. It is associated with more aggressive disease.[3]

The former category of lymphocyte predominance type (5 to 10%) was split in 1996 by the

Revised European-American Lymphoma (REAL) classification[30] based on immunohistochemistry. Lymphocyte-rich classic HD is CD30 and/or CD15 positive but CD20 negative, and can thus be distinguished from lymphocyte predominance HD, which is CD20 positive. Paraffin blocks and data on clinical presentation and course of 426 lymphocyte-predominant cases were collected and analyzed by the European Task Force on Lymphoma project on lymphocyte predominance HD.[31,32] Both subtypes show a male preponderance and typically present in early stages. With standard HD treatment, their clinical course is similar to that of stage-comparable classic HD patients. These patients may have a tendency for multiple late relapses. There are some reports of long-term survival with a "watch-and-wait" strategy in young patients with early-stage or misdiagnosed lymphocyte-predominant disease.[30,31]

Most HD cases present with the other two subtypes: 60 to 70 percent of all cases have the NS type and 25 to 30 percent present with MC subtype. Age-specific incidence of NS peaks in young adults; it is more frequent in women and is often associated with mediastinal involvement. Incidence of MC is rather uniform with age; MC thus occurs relatively more frequent in the elderly and in men and is less frequently associated with mediastinal involvement.[3]

Mixed cellularity subtype is a PF for positive laparotomy findings. This probably explains why MC has been reported as an unfavorable PF in clinically staged I–II patients treated with radiotherapy alone.[3,33,34] Localized therapy can leave undetected abdominal disease outside the irradiation field untreated. In chemotherapy-treated patients, there is no relevant prognostic difference between NS and MC after adjusting for stage.[13]

Because of the large proportion of NS cases, attempts have been made to subdivide this group further. The British National Lymphoma Investigation proposed a subdivision into grade 1 and grade 2 NS,[35,36] based on the cellular composition of the involved nodules, and reported this to be moderately prognostic in a large data set. Several studies, some with limited patient numbers, attempted to reproduce this finding and reported conflicting results.[37–44] As in the case of MC, NS grade 2 appears to have a moderately unfavorable prognostic impact. This is especially true in patients treated with radiotherapy alone, but is less apparent in patients receiving full chemotherapy treatment.[43,44]

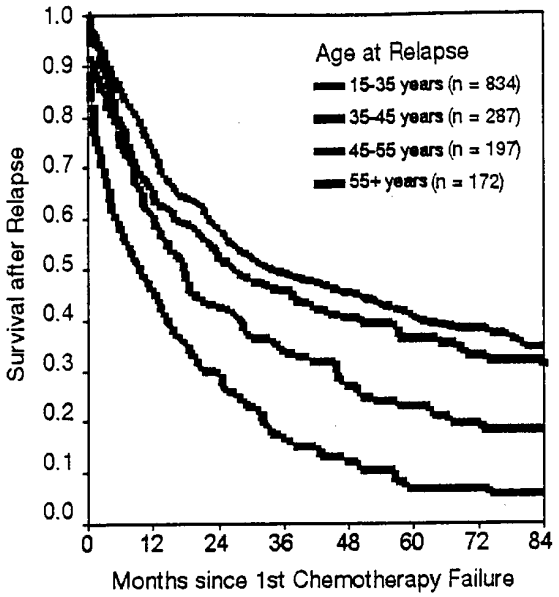

Figure 22–4. Survival after relapse by age at time of progression in 1,490 patients initially treated with chemotherapy. (Unpublished data from the International Prognostic Factor Project on Advanced Hodgkin's Disease.)

Although the diagnosis of HD is generally confirmed after expert panel review (in about 95% of cases), reclassification rates among subtypes may be substantial (40% of cases). In summary, histologic subtypes are not important PFs in HD and should not play a major role in therapeutic decisions.

Tumor Burden

The tumor burden is the major determinant of prognosis in HD. The higher the tumor burden, the worse the prognosis. This observation has been highlighted in a series of papers by Lena Specht.[26,45–47] Specht developed a scoring system based on the number and size of all involved lymph nodes measured on radiographs. She demonstrated that the tumor burden so defined is a major PF in NS stage I–III HD, in particular, when patients are treated with radiotherapy alone, and relapse-free survival is the end point considered.

Unfortunately, quantification of tumor burden is difficult and labor intense. Other routinely considered PFs may be viewed as more practical but are

less precise direct or indirect surrogate measures for tumor burden. Although certain blood parameters correlate indirectly with tumor burden, both stage and, within stage II and III, the number of involved lymph node areas are obvious direct surrogates for tumor burden.

Prognosis in stage I–II worsens with an increasing number of involved sites or lymph node areas.[3,33,48–52] Again, the prognostic impact is most pronounced with radiotherapy alone, probably since the number of lymph node areas involved is prognostic for positive laparotomy results.[3,23,53–55] The number of involved sites or lymph node areas is used by several study groups to discriminate stage I–II patients with favorable or unfavorable prognoses.[33,56,57] Patients with favorable prognoses may profit from less toxic treatment strategies, whereas patients with unfavorable features probably need full systemic treatment.

The number of involved areas[47,58] or stage III substage[59–61] (stage III_1 disease includes involvement of spleen, or splenic, celiac, or portal nodes, or any combination of these; stage III_2 disease includes involvement of para-aortic, iliac, or mesenteric nodes, with or without upper abdominal involvement) continues to carry prognostic information in stage III. This is particularly true in patients treated with radiotherapy only.

In most study groups, laparotomy now is used only in selected cases, so precise substage information rarely is available. However, inguinal involvement is considered a negative PF[13,18] since it probably indicates completed spread of the disease through the lymphatic system and correlates with the maximal number of involved lymph node areas.

Specific Patterns of Involvement

About 50 percent of all HD patients present with mediastinal involvement. Large masses are not uncommon, and about one-third of patients with mediastinal involvement present with "bulky" disease.[3] Several methods are used to quantify mediastinal mass (eg, the absolute width of the involvement on radiographs, or the width divided by the thoracic aperture, or measures derived from computed tomograms), none of which is clearly superior to the others in discriminating prognosis.[62] A large mediastinal mass (eg, > 33% of the thoracic aperture on a radiograph) is reported to be an unfavorable PF for relapse-free survival in patients treated with radiotherapy alone.[50,63,64] However, if systemic treatment with or without radiotherapy is given, large mediastinal masses lose most of their independent prognostic impact,[3,13] except possibly in the small group (< 5%) of patients with very large masses (eg, > 45% of the thoracic aperture on radiograph or > 10 cm).[13,18,22]

Other patterns of involvement are specifically relevant within particular stage groups. Involvement confined to upper cervical nodes is a favorable PF in clinically staged I–II patients because abdominal involvement detected by laparotomy is rare in such patients.[54]

Primarily infradiaphragmatic clinical stage I–II disease is infrequent (about 3 to 10% of cases). Patients with this disease presentation tend to be older and male and to have less frequent NS histologic subtype. Primary subdiaphragmatic disease is not associated with a difference in prognosis.[3,51,65–78]

An important question is whether any dissemination outside the lymphatic system represents an unfavorable PF. Stage IV disease (visceral involvement) is recognized as a bad PF.[3,13] E stage is defined as "extra-nodal involvement by contiguity, encompassable in the nodal radiation field."[1,2] There is substantial uncertainty and variation in distinguishing between extranodal disease and stage IV disease.[79,80] It is controversial whether E stage is an unfavorable sign. E stage was included in the Ann Arbor system because early studies showed that patients with localized extralymphatic lesions have a prognosis similar to that of patients with exclusively nodal involvement of the corresponding stages. Later studies essentially confirm this,[3,63,81] although E disease within the intermediate stage (IIB–IIIA) was reported recently to be unfavorable in a large data set.[82]

Within stage IV, liver, lung, and bone marrow are the most frequent sites of disseminated disease, with a proportion of about one-third each. None of them appears to have a particularly unfavorable additional prognostic impact within stage IV for time to treatment failure, although liver involvement may be related to worse overall survival.[13] Multiple organ involvement occurs infrequently but is a poor prog-

nostic sign within stage IV, especially for overall survival.[13] In summary, the quantity of tumor (and not so much specific pattern, types, or locations of involvement) is the major determinant of the prognosis.

Systemic Symptoms and Related Blood Parameters

Many patients with HD present with nonspecific systemic symptoms. Stage B is documented if there is at least one of the following: unexplained fever > 38°C, drenching sweats, or unexplained weight loss greater than 10 percent of body weight in 6 months. The probability of systemic symptoms strongly increases with stage (stage I, 9%; stage II, 28%; stage III, 53%, stage IV, 78%, in the IDHD data[3]). The presence of B symptoms was incorporated into the classic Ann Arbor staging system and is a stage-independent unfavorable PF (see Figure 22–1).

Several hematologic and biochemical laboratory parameters carry prognostic information and are related to the presence of systemic symptoms. These variables form a cluster of interrelated prognostic factors that mirror both tumor burden and inflammatory processes. Decreased levels of serum albumin[13,82–86] and hemoglobin[3,13,21,87–89] (or hematocrit[18]) and elevated erythrocyte sedimentation rates (ESR),[3,24,83,90] and to a lesser degree elevated alkaline phospatase levels,[17,91,92] correlate[3] with increased stage, the presence of systemic symptoms, and, accordingly, prognosis.

Serum albumin and hemoglobin levels show a remarkably consistent and linear relation to prognosis over their full range of variation.[13] In contrast to ESR, which undergoes short-term changes, hemoglobin and albumin levels change over weeks and are more reliable biometrically. Figures 22–5 and 22–6 show the striking correlation of hemoglobin and albumin with freedom from progression in the IPFP data.[13] When hemoglobin and albumin levels are defined, the other members of the cluster of systemic symptoms lose their independent prognostic impact.[13]

White Blood Counts and Other Serum Parameters

White blood and lymphocyte counts form a second cluster of laboratory parameters, nearly independent from the first. Analysis of the joint distribution of

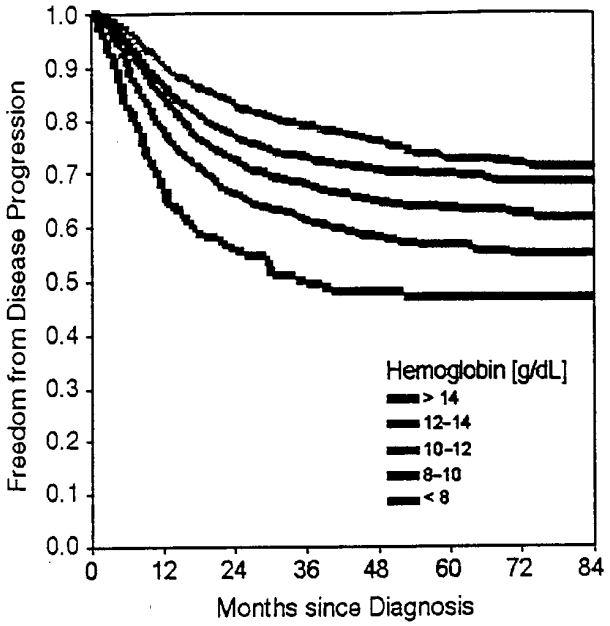

Figure 22–5. Freedom from progression by level of hemoglobin at diagnosis in 4,314 patients. (Modified from Hasenclever D, Diehl V, for the International Prognostic Factor Project on Advanced Hodgkin's Disease. A prognostic score for advanced Hodgkin's disease. N Engl J Med 1998;339:1506–14.)

leukocyte and lymphocyte counts in the advanced stage IPFP data[13] reveals a simultaneous shift away from the normal pattern toward both leukocytosis and lymphocytopenia. This shift may indirectly cap-

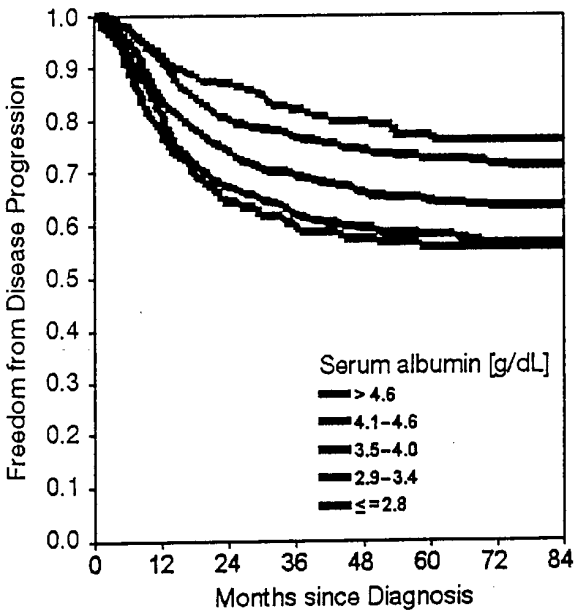

Figure 22–6. Freedom from progression by level of serum albumin at diagnosis in 2,238 patients. (Modified from Hasenclever D, Diehl V, for the International Prognostic Factor Project on Advanced Hodgkin's Disease. A prognostic score for advanced Hodgkin's disease. N Engl J Med 1998;339:1506–14.)

ture dysregulation of hematopoiesis caused by cytokine release from the HD cells. Both pronounced leukocytosis and/or pronounced lymphocytopenia[17,21,46,87,93] carry independent adverse prognostic information, but they are relatively rare and are mainly found in advanced-stage cases.

Elevated serum lactic dehydrogenase (LDH) plays an important role in aggressive non-Hodgkin's lymphoma.[94] In HD, some groups[18,87] report LDH to have independent prognostic impact, but this was not confirmed in the large data sets of the IDHD[3] and the IPFP.[13] This may be related to data quality problems in varied normal ranges for LDH. Elevated β_2-microglobulin is not generally documented but also was reported to be prognostic.[95]

Biologically Specific Factors

The general clinical features and routine laboratory parameters discussed so far are relatively nonspecific.[96] The malignant HD cell is known to produce various cytokines and to express several antigens. Soluble forms of membrane-derived antigens and increased levels of certain cytokines have been detected in the serum of HD patients. These biologic parameters are thought to be correlated with both the number and the activity of HD cells. The CD30 surface molecule is expressed consistently by HD and Reed-Sternberg cells. The soluble form of CD30 is released by the cells and is detectable in practically all untreated HD patients.[97,98] Soluble CD30 correlates with stage and may have additional prognostic impact.[99] It will be important to accumulate more extensive data on soluble CD30 and other specific biologic markers.[100–102]

PROGNOSTIC INDEXES OR SCORES

Prognostic indexes or scores are constructed to synthesize the information given by the many univariate PFs. They may be clinically important in identifying both patients who may be overtreated with full systemic treatment and those in whom standard treatment has an increased probability of failure and who may therefore be candidates for experimental approaches.

Several groups have developed prognostic indexes or scores for overall survival based on a few hundred cases. Wagstaff and colleagues[17] used a score based on age above 45 years, male gender, absolute lymphocyte counts below 0.75×10^9/L, and stage IV disease. Straus and colleagues[18] proposed a five-factor score based on age above 45 years, elevated LDH (above upper normal), low hematocrit (< 38% for males or < 34% for females), inguinal involvement, and a mediastinal mass larger than 0.45 of the thoracic aperture. Gobbi and colleagues[19,20] proposed a predictive equation based on age, gender, stage, histology, B symptoms, mediastinal mass, ESR, hemoglobin, and serum albumin. Proctor and colleagues[21,22] developed and validated a numerical index on age (linear and squared), stage, hemoglobin level, absolute lymphocyte counts, and tumor bulk (> 10 cm). These scores and others have been compared by Fermé and colleagues.[87] All prognostic models could be reproduced but all failed to identify a high-risk group with a 3-year survival rate of less than 50 percent.

Gobbi and colleagues[11] proposed an alternative parametric model to derive numeric estimates of expected survival in all stages based on the IDHD data (N = 5,023). The equation incorporates seven factors: stage, age, histology, B symptoms, serum albumin, sex, and distribution of involved areas (infradiaphragmatic disease or more than three supradiaphragmatic areas). Patients in the IDHD were rather heterogeneously treated with radiotherapy alone or mainly MOPP chemotherapy with or without radiotherapy. These models all have overall survival as the main end point.

In contrast, the IPFP[13] used the end point freedom from progression (censoring deaths not preceded by progression) to focus on the outcome after state-of-the-art first-line chemotherapy (mostly doxorubicin-containing regimens) with and without radiotherapy. Data on 5,141 patients with advanced HD (requiring full systemic treatment) from 23 centers or study groups were collected. Besides the course of the disease, 19 generally documented clinical features at diagnosis were collected. An international prognostic index (IPI) was developed from these data in patients up to 65 years of age. The IPI is constructed from seven binary adverse PFs (Table 22–1) that have approximately similar prognostic impact on freedom from progression. Expected 5-year freedom-from-progression rates

(Figure 22–7) range from 80 percent or more with IPI = 0 to about 45 percent with IPI = 5. Each additional factor reduces the prognosis by about 8 to 9 percent. The score also is predictive for overall survival (Figure 22–8).

This IPI was developed from the combined experience of most major study groups from the 1980s. More than 75 percent of the patients were treated with doxorubicin-containing regimens. Until biologically more specific markers become available, the IPI may be useful to delineate study populations for future therapeutic trials in advanced HD.

A major motivation of the IPFP was the desire to identify a very-high-risk group based on routinely documented features. In particular, the question was whether a group of patients could be selected as candidates for early high-dose chemotherapy with autologous stem cell transplantation. These patients can achieve a complete remission with conventional treatment but nevertheless have a high risk of relapse. The answer to this question is essentially negative. Freedom-from-progression rates at 5 years in patients that achieve a complete remission are higher than those in unselected patients: 73 percent, 70 percent, and 65 percent in the IPI = 2, 3, 4+ subgroups, respectively. Thus, two-thirds of those higher-risk patients who achieve a complete remission are already cured by conventional treatment.

The IPI was developed from data of patients thought to have advanced disease (stage III–IV and selected stage I/II patients with additional risk factors) and who were treated accordingly. Does it also apply to early-stage patients? From the IDS factor

Table 22–1. UNFAVORABLE FACTOR IN THE INTERNATIONAL PROGNOSTIC SCORE*†

Age of 45 years or older
Male gender
Stage IV disease
Serum albumin level < 4.0 g/dL
Hemoglobin level < 10.5 g/dL
Leukocytosis (white blood count ≥ 15 × 10^9/L)
Lymphocytopenia (lymphocyte count < 0.6 × 10^9/L or < 8% of leukocytes or both)

*For freedom from progression (FFP) in advanced Hodgkin's disease.
†Each factor present reduces the expected 5-year FFP rates by about 8 to 9 percent.
Listed from Hasenclever D, Diehl V, for the International Prognostic Factors Project on Advanced Hodgkin's Disease. A prognostic score for advanced Hodgkin's disease. N Engl J Med 1998;339:1506–14.

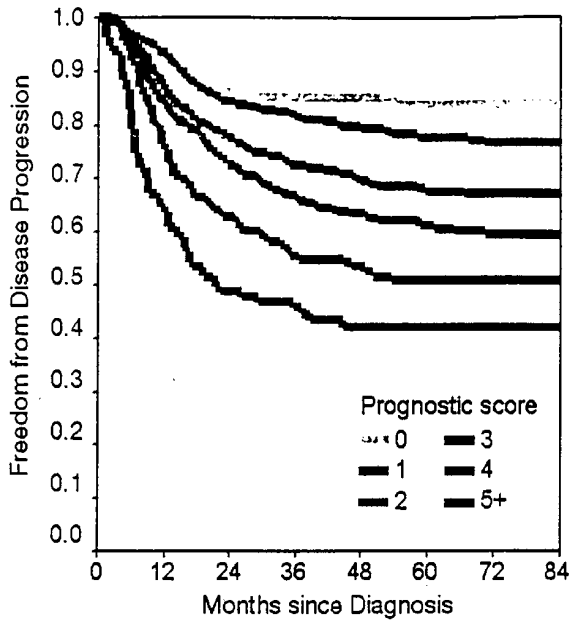

Figure 22–7. Freedom from progression by the number of adverse prognostic factors (see Table 22–1) for 1,618 patients with advanced Hodgkin's disease. Number and percentage of patients with each score: score 0, n = 115 (7%); score 1, n = 360 (22%); score 2, n = 464 (29%); score 3, n = 378 (23%); score 4, n = 190 (12%); score 5 or higher, n = 111 (7%). (Modified from Hasenclever D, Diehl V, for the International Prognostic Factor Project on Advanced Hodgkin's Disease. A prognostic score for advanced Hodgkin's disease. N Engl J Med 1998;339:1506–14.)

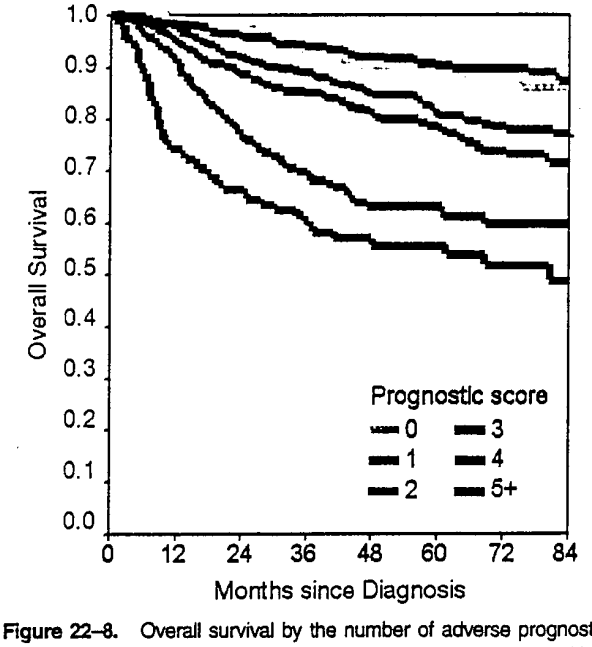

Figure 22–8. Overall survival by the number of adverse prognostic factors (see Table 22–1) for 1,618 patients with advanced Hodgkin's disease. Number and percentage of patients with each score: score 0, n = 115 (7%); score 1, n = 360 (22%); score 2, n = 464 (29%); score 3, n = 378 (23%); score 4, n = 190 (12%); score 5 or higher, n = 111 (7%). (Modified from Hasenclever D, Diehl V, for the International Prognostic Factor Project on Advanced Hodgkin's Disease. A prognostic score for advanced Hodgkin's disease. N Engl J Med 1998;339:1506–14.)

marked anemia, leukocytosis, and lymphocytopenia are infrequent even in advanced disease (< 20% of patients) and are not useful PFs in early stages. However, a recent analysis of 1,424 German patients[82] suggested that the IPI may be useful in early stages, with serum albumin < 4.0 g/dL being the most informative component. The suggestion also has been made that the factor "stage IV," which a priori would not apply to early-stage disease, should be replaced with "E stage" when the IPI is applied to patients in stage IIB–IIIA. However, this proposal requires further validation.

PROGNOSTIC FACTORS AT PROGRESSION OR RELAPSE

When the reference time point of prognostication shifts to the time of progression or relapse after first-line (or further) treatment, a new type of PF emerges. Prognostic factors from treatment history become available and important, in addition to patient-related and tumor-related PFs characterizing disease status at relapse. Treatment history–based PFs include response and duration of response to prior therapy, type of prior therapy, and the number of lines of therapy.

Prognostic factors are only meaningful within a certain broadly defined clinical strategy. Accordingly, one distinguishes the following predictive contexts:

- Patients relapsing after radiotherapy alone who are now being treated with conventional chemotherapy similar to that of initial advanced-stage cases
- Patients relapsing after chemotherapy who are now being treated with salvage chemotherapy with or without high-dose chemotherapy with autologous stem cell transplantation
- A small group of patients with localized relapse after initial chemotherapy that may now be treated with salvage radiotherapy

Prognostic Factors at Relapse after First-Line Radiotherapy

After radiotherapy alone, about 30 percent of the patients relapse. However, most of these patients respond well to conventional chemotherapy, and long-term remissions may be achieved in about 60 percent. This is the main reason why the reduction of risk of relapse seen with combined modality treatment as compared with radiotherapy alone in early-stage patients does not translate into a survival benefit as shown in a recent meta-analysis of such trials.[4]

Extent of the disease at relapse is an important PF for outcome after failure of radiotherapy alone. This is reported either as the impact of stage at relapse[103] or as the type of relapse (ie, nodal involvement only versus extranodal disease with or without nodal involvement).[9,10]

In contrast to the situation in untreated patients, unfavorable histology (eg, MC) is prognostic after radiotherapy relapse.[9,10,104] Mixed cellularity is correlated with older age, which is related to unfavorable prognosis after relapse.[9,10] As discussed above, it remains unclear whether this unfavorable prognosis is related to a biologic difference or to reduced tolerance to treatment in the elderly. The time to failure and remission duration are not related to the prognosis after radiation failure.[9]

Prognostic Factors at Relapse after First-Line Chemotherapy

Patients with progression or relapse after chemotherapy generally have a worse prognosis than patients who relapse after radiotherapy alone. They may be retreated with a first-line regimen in late relapse cases,[105] but long-term remission is rare (eg, 20 percent survival at 10 years[106]). At present, patients who relapse after chemotherapy typically are treated with intensified salvage chemotherapy[107,108] with or without high-dose chemotherapy with autologous stem cell transplantation. Emerging evidence indicates that high-dose chemotherapy with autologous stem cell rescue at least prolongs time to second failure.[109,110] Selected cases with localized relapse may receive radiotherapy.

There is no evidence that PFs differ whether or not the general treatment strategy in relapse includes high doses. However, there are two differences to keep in mind when comparing respective studies of PFs. First, it is important to note that studies of PFs in transplanted patients only concern a patient population that is favorably selected. The age of transplanted patients is typically limited, such that the

prognostic impact of age is less pronounced and is rarely investigated. Second, patients receive transplants only after undergoing debulking with conventional salvage chemotherapy. Thus, only patients responding to salvage therapy and who tolerate its toxicity proceed to transplantation. A French study with MINE initrogua?????, ifostamide, vinorelbine, etoposide salvage therapy[107] reported that only 72 percent of the initial relapse patient population eventually underwent transplantation. This selection bias is the reason why survival curves of transplanted patients generally look much more impressive than those from unselected series of patients.

In addition, studies of PFs in transplanted patients have a somewhat different reference time point of prognostication. At time of transplantation, the response to salvage chemotherapy prior to transplantation may be available as important prognostic information.

Achievement of second long-term remissions depends mainly on age at relapse, the time to first chemotherapy failure, and disease stage at relapse. Young patients with a remission duration of more than 18 months have a fair chance of second long-term remission of 30 to 50 percent. In contrast, refractory disease or early relapse and age over 55 years considerably reduces the outcome (< 10%).

The dramatic impact of age on survival after relapse has been discussed above (see Figure 22–4). Figure 22–9 illustrates the well-known impact of time to chemotherapy failure (often alternatively documented as primarily refractory disease versus relapse and remission duration in relapsed patients) on survival.[105,108,111–113] The plot exhibits a striking correlation between time to chemotherapy failure and time to death. Note that it is the time scale, and not so much the plateau, that is different. Time to first failure reflects the aggressiveness of tumor regrowth and determines a specific time scale for the patient's disease. This implies that long-term outcome in patients with late first relapse may be overestimated unless follow-up time is longer than time to first relapse.

In addition to age and time to first failure, disease status at relapse (or at time of transplantation) has prognostic impact. Advanced relapse stage, extranodal relapse, multiple relapse sites, bulky disease, and B symptoms are unfavorably prognostic.[112–116]

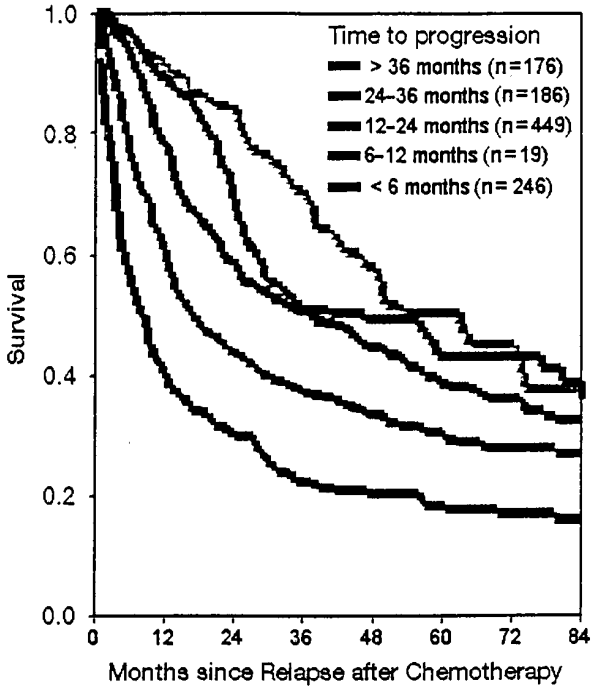

Figure 22–9. Survival after relapse by time to first chemotherapy failure in 1,476 patients. (Unpublished data from the International Prognostic Factor Project on Advanced Hodgkin's Disease.)

Patients in whom multiple lines of therapy have failed form a heterogeneous group of patients. Whereas most such patients have a dismal prognosis, some patients with multiple (late) relapses may survive for a considerable time with relatively chronic disease.

CONCLUSION

A plethora of PFs have been investigated and reported in HD. Many of them are correlated and may at least partially substitute for one another. Although the detailed picture is bewildering, it has certain general traits. Among patient-related PFs, age is the most important. It determines patients' ability to tolerate short- and long-term side effects of the treatment and their ability to tolerate and respond to subsequent therapy in the event of relapse.

The major tumor-related determinant of outcome is tumor burden. This may be quantified either directly (eg, stage or number of involved areas) or indirectly through the effect of the tumor cell activity on blood parameters or symptoms (eg, serum albumin, hemoglobin, CD30, or B symptoms). In the setting of relapse, time to first chemotherapy

failure defines an individual time scale for the patient, that is, the specific aggressiveness and regrowth velocity of disease.

Prognostic differences in untreated patients that may be captured by currently available parameters are of moderate size, and they discriminate 5-year freedom-from-progression rates between about 45 and 95 percent. Due to excellent treatment results, even those HD patients of the highest risk still have a 50 percent chance of achieving long-term remission. Thus, insight into PFs is useful to allocate patients to risk-adapted treatment strategies, but predictability of the individual course of disease remains weak, except in the most favorable cases.

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