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ORIGINAL ARTICLE

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Low acute hematological toxicity during chemotherapy predicts reduced disease control in advanced Hodgkin's disease

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Abstract Chemotherapy-treated patients with advanced Hodgkin's disease (HD) differ considerably in acute hematotoxicity. Hematotoxicity may be indicative of pharmacological and metabolic heterogeneity. We hypothesized that low hematotoxicity might correlate with reduced systemic dose and thus reduced disease control. A total of 266 patients with advanced HD treated with cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, and dacarbazine (COPP-ABVD) were analyzed (HD6 trial of the German Hodgkin's Lymphoma Study Group). The reported WHO grade of leukocytopenia was averaged over chemotherapy cycles given and weighted with the reciprocal dose intensity of the corresponding cycle. The low and high toxicity groups were defined in retrospect as having had an averaged WHO grade of leukocytopenia $\leq$2.1 and >2.1, respectively. The independent impact of low hematological toxicity on freedom from treatment failure (FFTF) was assessed multivariately adjusting for the international prognostic score for advanced HD. The results were validated in two independent cohorts [181 patients treated with COPP-ABVD (HD9-trial) and 250 patients treated with COPP-ABV-ifosfamide, methotrexate, etoposide, and prednisone (IMEP) (HD6 trial)]. The 5-year FFTF rates were 68% for patients with high toxicity vs 47% for patients with low toxicity [multivariate relative risk (RR) 2.0, 95% confidence interval (CI) 1.4–3.0, p=0.0002]. Patients with low toxicity received significantly higher nominal dose (p=0.02) and dose intensity (p<0.0001). This finding was confirmed in both validation cohorts (multivariate RR 2.1, 95% CI 1.2–3.8, p=0.01 and RR 1.5, 95% CI 1.01–2.26, p=0.04, respectively). Patients with low hematotoxicity have significantly higher failure rates despite higher doses and dose intensity. Hematotoxicity is an independent prognostic factor for treatment outcome. This observation suggests a strategy of individualized dosing adapted to hematotoxicity.

Keywords Hematotoxicity · Advanced Hodgkin's disease · German Hodgkin's Lymphoma Study Group

Introduction

Acute hematological toxicity (leukocytopenia, thrombocytopenia, anemia) is a serious and often dose-limiting side effect of a combination chemotherapy regimen in the treatment of advanced Hodgkin's disease [1, 2]. However, patients treated with the same chemotherapy regimen largely differ in the severity of acute hematotoxicity experienced during therapy. The analysis of two dose escalation trials of conventional chemotherapy conducted by the German Hodgkin's Lymphoma Study Group (GHSG)—bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) for first-line therapy [3, 4], and dexamethasone, carmustine, etoposide, aracytine, and melphalan (DexaBEAM) for second-line therapy [5]—revealed considerable heterogeneity in the degree of acute hematotoxicity between patients treated at the same dose level.

Wide inter-patient variability in the pharmacokinetic parameters of most cytotoxic drugs has been described, e.g., for doxorubicin, etoposide, ifosfamide, and others [6]. This variability is probably caused by differences in metabolic reactions and in elimination capability between patients due to genetic polymorphisms in drug metabolizing enzymes [7] as well as to impaired liver and/or kidney function [8].

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Variance in the degree of hematological toxicity may reflect the known differences in pharmacokinetic response between patients, and thus may correlate with the systemic dose of chemotherapeutic drugs a patient receives [9]. Assuming a dose outcome relationship, we suspected that low hematotoxicity might correlate with reduced disease control. The present study was undertaken to investigate this hypothesis.

Patients and methods

Patients

Three cohorts of patients with advanced Hodgkin's disease, treated from 1988 to 1996 within two subsequent trials of the German Hodgkin's Lymphoma Study Group (GHSG), were analyzed. The two trials were conducted in accordance with the Guidelines of Good Clinical Practice and the Declaration of Helsinki after approval by local ethics committees. All patients gave their informed consent. Only patients with complete information on details of the therapy given and on acute hematotoxicity were entered in the present analysis (89.7% of all patients).

The first cohort consisted of 266 patients treated with four double cycles of cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, and dacarbazine (COPP-ABVD) (for details see Table 1) from 1988 to 1993 within the HD6 trial (standard arm) [10]. This cohort was used to explore the association between low toxicity and disease control. The second cohort consisted of 181 patients treated with the same chemotherapy (four double cycles COPP-ABVD) as standard arm of the subsequent HD9 trial [11]. This cohort was used for independent validation of the results found in the first cohort in identically treated patients. Finally, the third cohort analyzed consisted of 250 patients from the experimental arm of the HD6 trial. These patients were treated with four cycles of COPP-ABV-ifosfamide, methotrexate, etoposide, and prednisone (IMEP) (see Table 1). The third cohort was used to validate the results in patients treated with a more hematotoxic regimen. In all three cohorts, adjuvant irradiation of residual tumor masses and of sites of initial bulk was performed after chemotherapy. Initial patient characteristics and outcome in the three cohorts are shown in Table 2.

Table 1 Chemotherapy regimen. In case of postponement of therapy due to myelopoietic toxicity, the dose of myelotoxic drugs was to be reduced in the subsequent corresponding subcycle by 25% (delay of 1–2 weeks) or 50% (delay of more than 2 weeks), respectively

COPP-ABVD (repeat day 57)			
Cyclophosphamide	650	mg/m^2 i.v.	Day 1 + day 8
Vincristine	1.4	mg/m^2 i.v.	Day 1 + day 8
Procarbazine	100	mg/m^2 p.o.	Day 1–day 14
Prednisone	40	mg/m^2 p.o.	Day 1–day 14
Doxorubicin	25	mg/m^2 i.v.	Day 29 + day 43
Bleomycin	10	mg/m^2 i.v.	Day 29 + day 43
Vinblastine	6	mg/m^2 i.v.	Day 29 + day 43
DTIC	375	mg/m^2 i.v.	Day 29 + day 43
COPP-ABV-IMEP (repeat day 43)			
Cyclophosphamide	800	mg/m^2 i.v.	Day 1
Vincristine	1.4	mg/m^2 i.v.	Day 1
Procarbazine	100	mg/m^2 p.o.	Day 1–day 10
Prednisone	40	mg/m^2 p.o.	Day 1–day 15
Doxorubicin	40	mg/m^2 i.v.	Day 15
Bleomycin	10	mg/m^2 i.v.	Day 15
Vinblastine	6	mg/m^2 i.v.	Day 15
Ifosfamide	1000	mg/m^2 i.v.	Day 29–day 33
Methotrexate	30	mg/m^2 i.v.	Day 31
Etoposide	100	mg/m^2 i.v.	Day 29–day 31
Prednisone	40	mg/m^2 p.o.	Day 29–day 35

A score for measuring acute hematological toxicity

Acute hematological toxicity during chemotherapy was documented according to the WHO criteria [12]. Considerable leukocytopenia (WHO grade 3 or 4) occurred in 53% of all patients in at least one cycle. Thrombocytopenia and anemia of WHO grade 3 or 4 occurred in only 1.6% and 1.5% of all patients, respectively. Since thrombocytopenia and anemia are not major side effects of the chemotherapy regimens considered, only acute white blood toxicity was analyzed.

There was substantial variation between patients in relative dose given, defined as amount of drug administered divided by the amount of drug planned per unit body surface area, averaged over all drugs and all cycles given, and relative duration of therapy, defined as actual duration divided by originally scheduled duration.

Table 2 Patient characteristics and outcome. *FFTF* freedom from treatment failure, *SV* survival

	COPP-ABVD (HD6) *n*=266	COPP-ABVD (HD9) *n*=181	COPP-ABV-IMEP *n*=250
Gender			
Male	160 (60%)	103 (57%)	141 (56%)
Female	106 (40%)	78 (43%)	109 (44%)
Stage (%)			
IIB/IIIA	-	71 (39%)	-
IIIB	133 (50%)	58 (32%)	123 (49%)
V	133 (50%)	52 (29%)	126 (51%)
Median age (range)	33 (15–72)	33 (16–74)	35 (15–73)
Treatment outcome			
Complete remission	75.9%	81.9%	78.0%
Progress	17.3%	12.2%	16.0%
FFTF			
2 years	69.6%	74.9%	68.5%
5 years	59.4%	-	58.8%
SV			
2 years	87.1%	88.9%	89.5%
5 years	78.7%	-	80.8%

The relative dose intensity (relative dose divided by relative duration, averaged over all cycles given) ranged from about 0.5 to 1.1, with a median at 0.84 (25% quartile 0.76, 75% quartile 0.91).

An aggregate toxicity score for a given patient was constructed by averaging the WHO grades of leukocytopenia over all cycles administered. To adjust for variation in relative dose intensity between patients due to dose reduction strategies, the WHO grades were weighted with the reciprocal relative dose intensity of the cycle. Thus, toxicity experienced despite dose reduction and/or delay of therapy had a higher weight than the same toxicity experienced under unmodified treatment.

The toxicity score used for each patient is given by the formula

$$\frac{1}{\text{given cycles}} \sum_{\text{given cycles}} \left(\frac{\text{WHO grade leukotoxicity} + 1}{\text{relative dose intensity of the cycle}} - 1 \right)$$

The toxicity score is interpretable as averaged WHO grade for acute hematological toxicity and has been constructed as an analytic tool to quantify the toxicity burden of an individual patient. It can only be obtained in retrospect after the treatment was applied.

Endpoints

The main endpoint used in the analysis was time to treatment failure (FFTF), defined as occurrence of either progression during treatment, no complete remission at the end of treatment, relapse, or death of any cause (whichever occurs first). Overall survival, defined as time to death of any cause, was the second endpoint used. Both endpoints were measured since the start of treatment.

Statistical methods

Kaplan-Meier estimates together with the log-rank test were used to obtain univariate results for survival time data. For the purpose of multivariate analysis, proportional hazard models were fitted. In order to adjust for known prognostic factors for advanced Hodgkin's disease, the score resulting from the International Prognostic Factors Project [13] was incorporated into the model. This prognostic score is defined by counting the number of adverse prognostic factors found to be relevant (albumin <4 g/dl, hemoglobin <10.5 g/dl, male gender, age $\geq$ 45 years, stage IV, leukocytosis $\geq 15\times10^9$/l, and lymphocytopenia $<0.6\times10^9$/l or <8% of leukocytes or both).

Mann-Whitney U test and χ^2 test were used when appropriate. Finally, for prediction of low hematological toxicity, a logistic regression analysis was performed.

Results

Distribution of the toxicity score

The distribution of the toxicity score for the three different cohorts is shown in Fig. 1. In all three cohorts, there is a remarkable heterogeneity between patients concerning their average white blood toxicity experienced during chemotherapy, ranging from almost no toxicity (WHO grade 0) to white blood toxicity of WHO grade 4 in every chemotherapy cycle given.

The two cohorts treated with COPP-ABVD have a similar distribution of the toxicity score. The COPP-ABV-IMEP regimen, however, induced a more pronounced acute leukotoxicity, mainly due to the addition of ifosfamide, methotrexate, and etoposide. The median is here 2.97, and 38% of the patients have a toxicity score

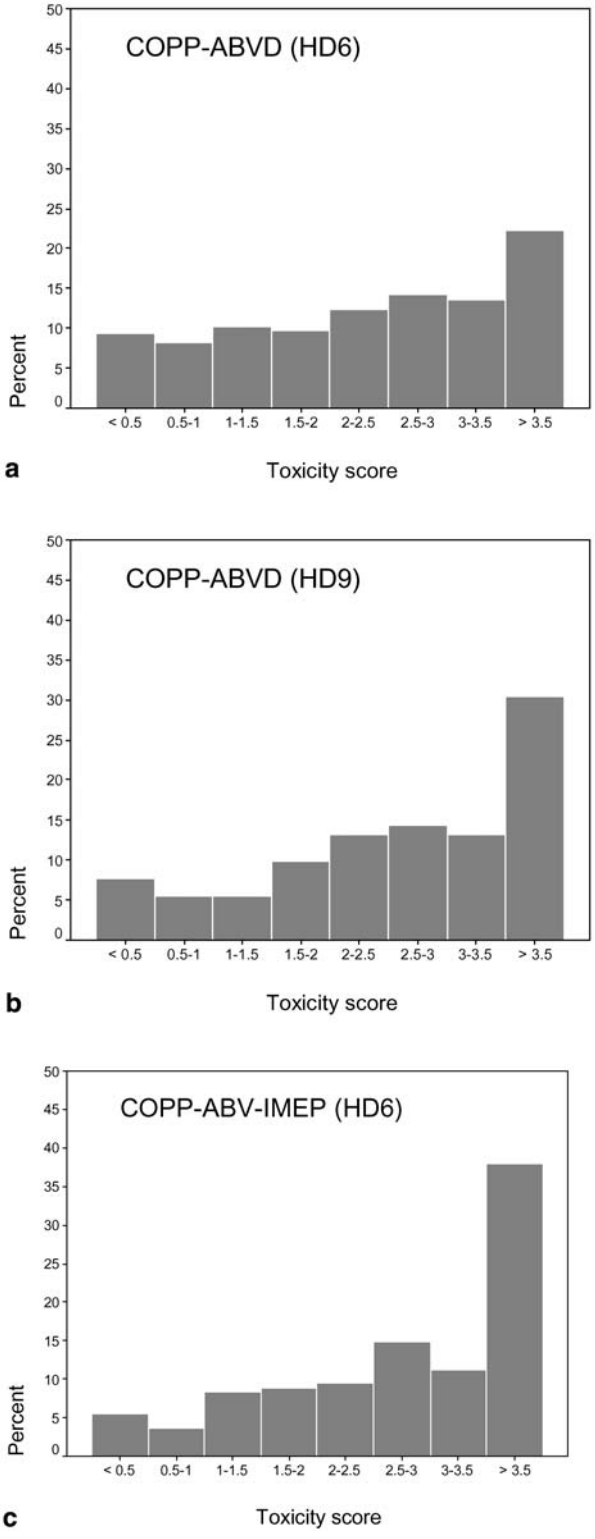

Fig. 1a–c Distribution of the toxicity score. **a** COPP-ABVD cohort (HD6): median 2.5, quartiles (1.4; 3.4); **b** COPP-ABVD cohort (HD9): median 2.7, quartiles (1.7; 3.7); **c** COPP-ABV-IMEP cohort (HD6): median 3.0, quartiles (1.9; 4.0)

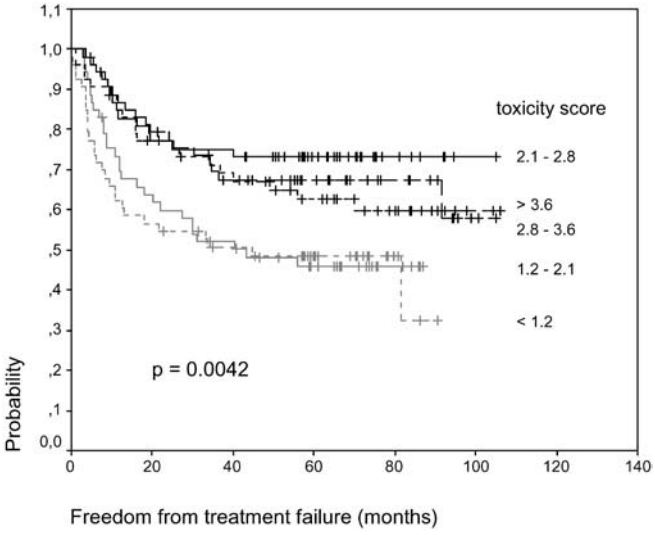

Fig. 2 Time to treatment failure (FFTF) in the HD6 COPP-ABVD cohort according to hematological toxicity

over 3.5, whereas only about 25% of the patients belong to this group if treated with COPP-ABVD.

Acute hematological toxicity is cumulative, i.e., the toxicity score of the last cycle of chemotherapy is higher than that of the first cycle. This effect is quantitatively small, but highly significant in all three cohorts. In the COPP-ABVD (HD6) cohort, the median toxicity score in the first cycle is 2.2, in the last cycle 2.7 ($p<0.0001$). Similar results hold true for the other two cohorts.

Results in the HD6 COPP-ABVD cohort

To explore the association between toxicity score and treatment outcome, the cohort was split up into five groups of equal size. Figure 2 shows the time to treatment failure (FFTF) of the five groups. The figure reveals that the toxicity score is associated with disease control, patients with low toxicity having a reduced prognosis.

The association is not linear in the toxicity score, rather there seems to be a threshold dividing the cohort into two prognostic groups. Hence a low and a high toxicity group were defined, using as cutoff point a value of 2.1 of the toxicity score. With this cutoff point, 40% of the patients belong to the low toxicity group.

Patients belonging to the low toxicity group had significantly higher relative dose (0.96±0.06 vs 0.94± 0.07, $p=0.02$) and relative dose intensity (0.90± 0.09 vs 0.78±0.1, $p<0.0001$) given compared with patients with high toxicity.

The univariate analysis of time to treatment failure (Fig. 3a) shows a highly significant difference between patients with low and high toxicity scores, respectively (FFTF at 5 years 47% vs 68%, $p=0.0001$). A multivariate analysis adjusting for the international prognostic score was performed yielding a relative risk for low toxicity of 2.04 (95% CI 1.40–3.00, $p=0.0002$).

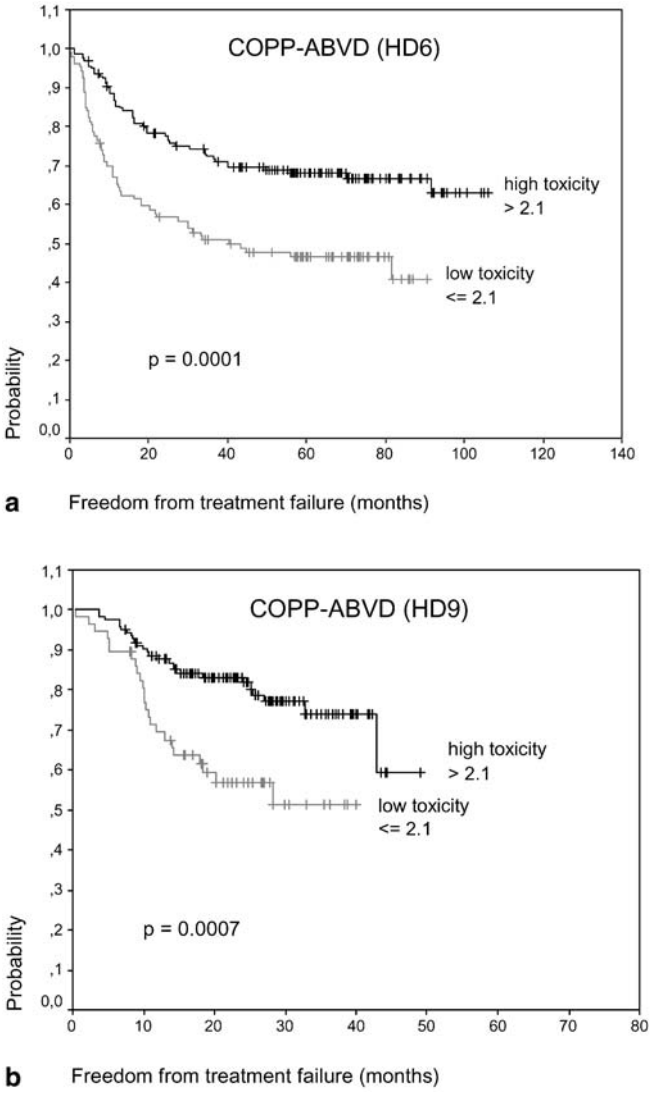

Fig. 3a–c Time to treatment failure (FFTF) according to hematological toxicity. **a** HD6: COPP-ABVD cohort; **b** HD9: COPP-ABVD cohort; **c** HD6: COPP-ABV-IMEP cohort

In order to exclude a potential source of bias due to patients not receiving the full number of chemotherapy cycles (e.g., early deaths and progressions) and thus not subject to cumulative toxicity, a second multivariate analysis was performed, restricted to those patients who received all four double cycles of chemotherapy planned ($n=224$). This results in a relative risk of 1.7 (95% CI 1.05–2.63, $p=0.03$) after multivariate adjustment.

Validation in the HD9 COPP-ABVD cohort

A second cohort of patients, treated with the same regimen (COPP-ABVD), was used to validate these results. It had a similar distribution of the toxicity score (Fig. 1b). The cutpoint of 2.1 for the toxicity score separates 37% of the patients into the low toxicity group.

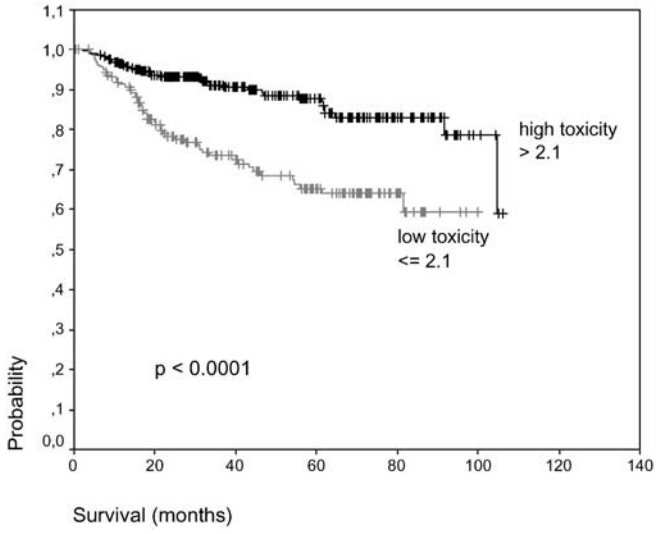

Fig. 4 Survival (SV) according to hematological toxicity in the two COPP-ABVD cohorts

Figure 3b shows the time to treatment failure for the low and the high toxicity group. Patients with low toxicity have a significantly lower FFTF rate (57% vs 82% at 2 years, p=0.0007). The multivariate analysis leads to an adjusted relative risk estimate for low toxicity of 2.1 (95% CI 1.2–3.8, p=0.01). Restriction of the multivariate analysis to patients with full chemotherapy (n=164) leads to an adjusted relative risk estimate of 2.5 (95% CI 1.3–5.1, p=0.008).

In this cohort, the relative dose given was similar in the two toxicity groups (0.95±0.07 vs 0.95±0.08, p=0.51), while the relative dose intensity was significantly higher in the low toxicity group (0.91±0.09 vs 0.82±0.12, p<0.0001).

Survival analysis

Survival analysis of both COPP-ABVD cohorts pooled shows that low toxicity is associated with a significantly reduced overall survival (Fig. 4; survival rates at 5 years 65% vs 88%, p<0.0001). The effect is present also in patients who received full chemotherapy (78% vs 92%, p=0.003).

Validation in the HD6 COPP-ABV-IMEP cohort

The third cohort of patients was treated with a chemotherapy regimen inducing more leukocytopenia. There are two ways to translate the established cutoff point for the toxicity score for validation in a differently treated cohort: as a relative cut at 40% of the toxicity score distribution or as an absolute cutoff point at a value of 2.1 of the toxicity score.

Using a relative cut at 40% of the toxicity score distribution, there is a nonsignificant trend (FFTF rates at 5 years 54% vs 62%, univariate comparison p=0.17) towards a reduced disease control with low toxicity. After multivariate adjustment, there is no difference between the two groups (relative risk 1.1, 95% CI 0.8–1.7, p=0.5).

Definition of the lower toxicity group according to the absolute cutoff point at 2.1 of the toxicity score (which corresponds here to 27% of the patients) leads to a significant difference between the two groups (Fig. 3c, FFTF rates at 5 years 49% vs 62%, p=0.01). This effect persists after multivariate adjustment (relative risk 1.5, 95% CI 1.01–2.26, p=0.04) and restriction of the analysis to patients who received full chemotherapy (n=232, relative risk 1.5, 95% CI 1.0–2.4, p=0.048).

In this cohort, patients with low toxicity had significantly higher relative dose (0.98±0.05 vs 0.96±0.06, p=0.045) and relative dose intensity (0.87±0.1 vs 0.75±0.1, p<0.0001) given.

Prediction of low toxicity

Using the established cutoff point at 2.1 of the toxicity score, the association between initial parameters and low toxicity was investigated. For this analysis, data of the three cohorts were pooled (n=697).

Univariately, gender (male 44% low toxicity vs female 19%, p<0.00001), large body surface (p=0.006) weight, height, and splenectomy (splenectomized patients 56% low toxicity vs no splenectomy 31%, p=0.00005) were associated with low toxicity, while no association could be found for age, stage, B symptoms, histology, Karnofsky performance status, and bone marrow involvement.

From the laboratory parameters, high hemoglobin levels (median 12.4 g/dl for low vs 11.9 g/dl for high toxicity, p=0.005), high initial white blood counts (median 12.1×10^9/l for low vs 9.8×10^9/l for high toxicity, p<0.0001), high initial lymphocyte, high thrombocyte counts, and a higher level of creatinine (median 0.9 mg/dl for low vs0.8 mg/dl for high toxicity, p=0.008) were associated with low toxicity. Erythrocyte sedimentation rate (ESR), lactic dehydrogenase (LDH), albumin, AP, and cholesterol were not correlated with toxicity.

In multivariate logistic regression analysis involving all univariately significant parameters, only gender (p<0.0001), splenectomy (p=0.0002), and initial white blood count (p<0.0001) remained significant. The predictive power of this model was poor, with an area under the curve (ROC-AUC) of the corresponding ROC curve of 0.74 (95% CI 0.70–0.78).

After inclusion of the leukocytotoxicity (WHO grade) experienced during the first cycle of chemotherapy into the multivariate model, the ROC-AUC increased, but the prediction is still not satisfactory (0.89, 95% CI 0.87–0.92).

Discussion

The severity of acute hematotoxicity varies considerably among advanced Hodgkin's disease patients treated with the same chemotherapy. Our analysis shows that patients with low acute hematotoxicity during chemotherapy have significantly higher failure rates, in the magnitude of 20% after 5 years. The effect found in the exploratory analysis of the first cohort was confirmed in two independent validation cohorts, and persisted after multivariate adjustment involving the international prognostic score. Moreover, the reduced tumor control rates led to significantly reduced overall survival in the low toxicity group.

It is important to stress that low toxicity cannot be explained by reduced relative dose or relative dose intensity. In contrast, our analysis shows that patients with low toxicity had received significantly higher relative dose and dose intensity than patients with high toxicity. Low-toxicity patients were those who received the chemotherapy regimen as planned, while in high-toxicity patients dose reductions and/or therapy delays were undertaken to manage toxicity, leading to reduced relative dose and relative dose intensity.

Acute hematological toxicity is cumulative, although the size of the effect is rather small in our data. However, the reduced prognosis for patients with a low overall toxicity score cannot be explained by early progressions or deaths not exposed to cumulative toxicity. Restriction of the analysis to patients who received all chemotherapy cycles planned shows no difference in the magnitude of the multivariately estimated relative risk as compared to analysis of the full data set, although the power of the restricted analysis is lower, due to fewer events.

Similar observations concerning the association between low acute hematotoxicity and outcome have been reported for other chemosensitive malignancies, e.g., breast cancer [14, 15, 16], osteosarcoma [17], and multiple myeloma [18].

A possible explanation for the observed association between low hematotoxicity and treatment outcome is based on the following three general observations, as previously discussed by Gurney [6]:

1. There is wide variability in pharmacokinetic parameters for many cytostatic drugs (including several of the drugs used in this study) administered at the same dose per body surface area, reflecting the range of metabolism and elimination capability of individuals [19, 20, 21, 22, 23].
2. Variability in the area under the time-concentration curve (AUC) of hematotoxic drugs is often correlated with hematotoxicity [19, 21, 24, 25, 26].
3. Variability of AUC is reported to be correlated with treatment efficacy in several chemosensitive malignancies [27, 28, 29].

Patients who experience increased hematotoxicity probably do so because they achieve higher concentrations of the cytostatic drugs due to their individual metabolic disposition. With higher concentrations of the cytostatic drugs, better disease control may be expected, given that in Hodgkin's disease there is a rather steep dose-outcome relationship [30, 31].

Our results suggest to investigate a strategy of dosing chemotherapy based on the hematotoxicity observed. In what clinical situation does such an approach make sense?

If outcome is generally unsatisfactory (as in the COPP-ABVD data for advanced HD presented here), and if one believes in the existence of a clear dose-outcome relationship, an upfront dose escalation for all patients is the natural approach.

Dose escalation for all patients may become feasible giving growth factor support. With such a strategy there is no longer a low toxicity group. Patients experiencing overly high hematotoxicity in their first cycles are managed with adaptive dose reductions. In advanced HD such an approach was successfully implemented by the GHSG and led to a marked survival benefit of BEACOPP escalated over COPP-ABVD, accepting a higher but manageable level of acute toxicity [11, 30, 31].

Individualized dose escalation starting with a standard dose regimen with which there is a low toxicity group of relevant size only makes sense if

1. A high proportion of patients (say FFTF ~80%, SV ~90%) is already cured with standard chemotherapy
2. The clinical intention is to improve the fate of those rare patients in whom treatment fails, but
3. A general dose escalation for all patients is considered unacceptable as it would increase the toxicity burden of the vast majority of patients and
4. One suspects a correlation of low toxicity and inferior outcome due to metabolic differences

Such a situation may exist in intermediate stage (stage I, II with unfavorable risk factors) Hodgkin's disease.

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