Biologically Effective Dose in Total-Body Irradiation and Hematopoietic Stem Cell Transplantation

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Background and Purpose: Total-body irradiation (TBI) is an important part of the conditioning regimen for hematopoietic stem cell transplantation (HSCT) in patients with hematologic malignancies. The results after treatment with various TBI regimens were compared, and dose-effect relationships for the endpoints relapse incidence, disease-free survival, treatment-related mortality, and overall survival were derived. The aim was to define requirements for an optimal treatment schedule with respect to leukemic cell kill and late normal-tissue morbidity.

Material and Methods: A literature search was performed. Three randomized studies, four studies comparing results of two or three TBI regimens, and nine reports with results of one specific TBI regimen were identified. Biologically effective doses (BEDs) were calculated. The results of the randomized studies and the studies comparing results of two or three TBI regimens were pooled, and the pooled relative risk (RR) was calculated for the treatments with high BED values versus treatments with a low BED. BED-effect relationships were obtained.

Results: RRs for the high BED treatments were significantly lower for relapse incidence, not significantly different for disease-free survival and treatment-related mortality, and significantly higher for overall survival. BED-effect relationships indicate a decrease in relapse incidence and treatment-related mortality and an increase in disease-free and overall survival with higher BED values.

Conclusion: "More dose is better", provided that a TBI setting is used limiting the BEDs of lungs, kidneys, and eye lenses.

Key Words: Allogeneic HSCT · BED · Leukemia · Organ shielding · TBI

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Biologisch wirksame Dosis bei Ganzkörperbestrahlung und hämatopoetischer Stammzelltransplantation

Hintergrund und Ziel: Die Ganzkörperbestrahlung ist eine wichtige Komponente bei der Konditionierung des Patienten vor einer hämatopoetischen Stammzelltransplantation bei hämatologischen Malignomen. Die Therapieergebnisse verschiedener Ganzkörperbestrahlungs-Regime wurden verglichen und Dosis-Wirkungs-Beziehungen für die Endpunkte Rückfallinzidenz, krankheitsfreies Überleben, behandlungsbezogene Letalität und Gesamtüberleben abgeleitet. Ziel war, die Bedingungen eines auf Elimination von Leukämiezellen und Spätschäden von Normalgewebe optimierten Behandlungsplans zu definieren.

Material und Methoden: Es wurde eine Literaturrecherche durchgeführt. Drei randomisierte Studien, vier Studien zum Vergleich von zwei oder drei Ganzkörperbestrahlungs-Regimen und neun Berichte über Ergebnisse eines spezifischen Ganzkörperstrahlungs-Regimes wurden gefunden. Es wurden die biologisch effektiven Dosen (BEDs) berechnet. Die Ergebnisse der randomisierten und der Studien, die zwei oder drei Ganzkörperbestrahlungs-Regime miteinander verglichen, wurden zusammengefasst und das gepoolte relative Risiko (RR) berechnet für Behandlungen mit hohen BED-Werten im Vergleich mit Behandlungen mit niedriger BED. Man erhielt BED-Wirkungs-Beziehungen.

Ergebnisse: Die RR-Werte für Behandlungsformen mit hoher BED waren signifikant niedriger für die Rückfallinzidenz, nicht signifikant unterschiedlich hinsichtlich des krankheitsfreien Überlebens und der behandlungsbezogenen Letalität und signifikant höher, bezogen auf Gesamtüberleben. Die BED-Wirkungs-Relationen zeigen eine Abnahme der Rückfallinzidenz und der behandlungsbezogenen Letalität und eine Zunahme von krankheitsfreiem Überleben und Gesamtüberleben bei höheren BED-Werten.

Schlussfolgerung: „Mehr Bestrahlung ist besser" – eine Ganzkörperbestrahlung vorausgesetzt, die die BEDs an Lungen, Nieren und Linsen begrenzt.

Schlüsselwörter: Allogene hämatopoetische Stammzelltransplantation · Biologisch effektive Dosis · Leukämie · Organabschirmung · Ganzkörperbestrahlung

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Introduction

Total-body irradiation (TBI) is an important part of the conditioning regimen for hematopoietic stem cell transplantation (HSCT) (e.g., [4, 7, 10, 11, 14, 20, 22, 28, 36, 41]). Several authors tried to find a relationship between the total doses of TBI and treatment outcome. Some reported a higher overall survival with increasing TBI dose [28, 36], others found opposite results [4, 7]. Vriesendorp et al. [45] stated that the important issues in any analysis of TBI results are dose, fraction size and endpoint selection and that different TBI procedures could not be compared without radiobiological "normalization". This normalization will also be different for different endpoints.

We reviewed the results of 16 publications describing 14 different TBI regimens and applied, for normalization, the linear-quadratic (LQ) concept, which allows converting each TBI schedule into a single biologically effective dose (BED) [2].

The aim is to evaluate relationships between BEDs and the endpoints: relapse incidence, disease-free survival, treatment-related mortality, and overall survival. The ultimate aim is to derive a treatment regimen that could be recommended, taking a high efficacy and a low toxicity profile into account.

Material and Methods

Literature Search

We searched PubMed from 1986 up to 2005 using the search terms TBI, acute leukemia (AL), allogeneic, and bone marrow transplantation. Studies were included when the follow-up time was at least 3 years. Results on autologous-transplanted patients were excluded because, in general, results concerning relapse rate and treatment-related mortality differ from those after allogeneic transplantation (e.g., no graft-versus-host disease). In only a few instances, also data of some patients treated for chronic myeloid leukemia, non-Hodgkin's lymphoma, and multiple myeloma were included. Many factors determine the outcome of HSCT, amongst all, status of the disease at transplantation and conditioning regimen. We assumed that these factors are not very different per center, just as the donor type and the percentage of patients who had graft-versus-host disease after transplantation.

Linear-Quadratic and Biologically Effective Dose (LQ-BED) Concept

The occurrence of a biological effect E depends on the dose in a linear and a quadratic fashion:

$$E = n\,(\alpha d + \beta d^2) \quad (1),$$

where n is the number of fractions, d is the dose per fraction at a high dose rate, α (indicative of intrinsic radiosensitivity) and β (indicative of repair capacity) are constants. From equation (1), the BED can be derived [2]:

$$BED = nd\,[1 + d/(\alpha/\beta)] \quad (2).$$

For fractionated low-dose-rate irradiation:

$$BED = nRT\,[1 + kR/(\alpha/\beta)] \quad (3),$$

where R is the dose rate, T the treatment time of a dose fraction, and $k = 2[1–\{1–\exp(–\mu T)\}/(\mu T)]/\mu$ [12]. The μ is related to the half-time for repair of sublethal damage T½, where $T½ = \ln 2/\mu$.

For the leukemia-related endpoints we applied $\alpha/\beta = 10$ Gy and $\mu = 1.4$/h [40, 42]. For the endpoints transplant-related mortality and overall survival we applied the same values; transplant-related mortality is related to the chemoradiotherapy used for conditioning: early toxicity, and to the infusion of donor marrow: bone marrow aplasia, graft failure/rejection, acute graft-versus-host disease, and lung toxicity.

For the TBI regimens the overall treatment times ranged from < 1 h (single dose) to 6 days (e.g., seven daily fractions of 2.25 Gy). Due to the relatively short overall treatment time, long cell-cycle time [9, 34] and potential doubling time [40], a correction for overall treatment time was not applied.

Dose-Effect Relationships, Relative Risks

Linear regression of the dose-effect relations weighted by the number of patients was applied using SPSS 9.0 Statistical Package. The relative risks (RRs) of a high-BED versus a low-BED treatment were calculated. An RR of 1 indicates no difference in endpoints for a high-BED versus a low-BED treatment. Subsequently, we calculated the pooled RR. RRs, pooled RR, and 95% confidence intervals were calculated using STATA 8.0. When a 95% confidence interval did not include the value 1, we considered the RR significantly different from 1.

Late Normal-Tissue Morbidity

As a theoretical exercise we evaluated the effect of the TBI regimens on some late responding tissues, and calculated the corresponding BED values for eye lenses, lungs, and kidneys, supposing that no shielding of the organs was applied.

For late responding tissues the BED value can be calculated using the appropriate α/β and μ values. Earlier, we derived an $\alpha/\beta = 0.75$ Gy and $\mu = 0.65$/h for cataract development [44]. For lung and kidney we applied α/β values of 3.5 Gy and 2.5 Gy, respectively, and for μ the value of 0.46/h [40, 42].

Results

Literature Search

Three randomized studies were identified [7, 14, 20], and four studies in which results of two or three TBI regimens were compared [4, 11, 28, 36] (Table 1). Nine papers were found with results of one specific TBI scheme [1, 3, 10, 14, 18, 21, 30, 33, 41] (Table 1). Several studies could not be included because of obscurity of dose rate or number of fractions, abundance of autologous-transplanted patients, or because of a too short follow-up period [6, 13, 15–17, 35, 37, 38, 43].

Biologically Effective Doses, Relative Risk

Table 1 also shows the calculated BED values for leukemic cell kill and organs at risk, as well as the percentages of the four treatment endpoints.

Table 1. Summary of publications with number of patients, TBI fractionation scheme, dose rate, calculated BED for leukemic cells, lung, eye lens, and kidney, relapse incidence, disease-free survival, treatment-related mortality and overall survival. ALL: acute lymphoblastic leukemia; ANLL: acute nonlymphoblastic leukemia; BED: biologically effective dose; TBI: total-body irradiation.

Tabelle 1. Zusammenstellung von Publikationen, jeweils mit Patientenzahl, Fraktionierungsschema der Ganzkörperbestrahlung, Dosisrate, berechneter BED für Leukämiezellen, Lunge, Linsen und Nieren, Rückfallinzidenz, krankheitsfreiem Überleben, behandlungsbezogener Letalität und Gesamtüberleben. ALL: akute lymphoblastische Leukämie; ANLL: akute nicht-lymphoblastische Leukämie; BED: biologisch effektive Dosis; TBI (total-body irradiation): Ganzkörperbestrahlung.

Reference	Patients (n)	TBI scheme	Dose rate (Gy/h)	BED leukemia (Gy)	Relapse incidence (%)	Disease-free survival (%)	Treatment-related mortality (%)	Overall survival (%)	BED[a] lung; lens; kidney (Gy)
Randomized trials:									
[7]	34	6 × 2 Gy	3.9	13.9	35	58	12	65	18.3; 40.5; 20.8
[7]	36	7 × 2.25 Gy	3.9	18.5	12	59	32	59	25.1; 57.2; 28.7
[14]	27	1 × 10 Gy	3.0	13.4	22.2		55.6	33	28.2; 82.8; 35.5
[14]	26	6 × 2 Gy	3.0	13.8	11.5		30.8	54	18.2; 39.8; 20.7
[20]	73	1 × 10 Gy	2.7	13.1	27		33	38	27.4; 78.9; 34.4
[20]	74	11 × 1.35 Gy	15	16.8	15		35	45	20.5; 41.1; 22.8
Studies comparing two or three TBI schemes:									
[4]	24	6 × 1.67 Gy	9.6	11.6	25	42	21	62	14.7; 31.5; 16.5
[4]	66	6 × 2 Gy	9.6	14.2	15	50	29	56	18.7; 42.8; 21.4
[4]	26	6 × 2.25 Gy	9.6	16.2	38	38	19	46	21.9; 52.0; 25.2
[11]	53	3 × 3.3 Gy	3.6	12.1	31		41	51	18.1; 46.1; 21.3
[11]	46	6 × 2 Gy	3.6	13.9	13		31	68	18.3; 40.5; 20.8
[28]	36	1 × 7.5 Gy	15.6	12.0	19	56	30.5	58	21.9; 71.7; 27.6
[28]	48	8 × 1.65 Gy	6.0	15.1	10	69	23	77	19.1; 40.1; 21.4
[36]	65	1 × 10 Gy	2.34	12.8	29	43	38	45	26.3; 73.6; 32.9
[36]	106	6 × 2 Gy	3.96	13.9	26	56	24	64	18.3; 40.8; 20.9
Studies reporting results of one TBI scheme or from which results were combined:									
[1]	57	5 × 2.2 Gy	3.6	12.9		47		53	17.3; 39.3; 19.8
[3]	104, ANLL	1 × 10 Gy and 6 × 2 Gy	4.2	14.1[b]	31.3	49.5	27.5	51	30.6; 95.1; 38.8
[3]	84, ALL	1 × 10 Gy and 6 × 2 Gy	4.2	14.1[b]	53.2	33.2	26	34.6	18.4; 41.1; 21.0
[10]	65	6 × 2 Gy	3.6	13.9		65	23	45	18.3; 40.5; 20.8
[14]	22	1 × 9.2 Gy	3.0	12.2	13.6		36.4	54	25.1; 73.4; 31.5
[18]	166	1 × 5 Gy	34.8	7.34	44	29		31.9	12.0; 37.4; 14.8
[21]	39, ANLL	1 × 9 Gy	2.4	11.5	23		26	47	23.0; 64.4; 28.7
[21]	46, ALL	1 × 9 Gy	2.4	11.5	31		14	46	23.0; 64.4; 28.7
[30]	67	11 × 1.2 Gy	10.2	14.7	30	42	13.4	45	17.7; 34.2; 19.5
[33]	100	6 × 2 Gy	1.3 and 1.6	13.4[b]	34	57.9		53.3	17.5; 35.5; 19.7
[41]	184	1 × 10 Gy	2.18	12.6	22.9	48.4	36.4		25.8; 71.0; 32.1

[a] assuming no shielding of organs; [b] mean value of two regimens

In Table 2, the total number of patients and responders for the low- and higher-BED treatments are presented. The RRs with 95% confidence limits are shown as well. The RRs of the randomized trials [7, 14, 20] were not significantly different from 1, except for relapse incidence in one study [7]. We therefore decided to pool the results of the three randomized studies with those of studies in which two or three TBI regimens were compared [4, 11, 28, 36]. For all but one study, the relapse incidence was lower for the high-BED treatments (RR < 1). For the pooled data, the relapse incidence was significantly lower for the high-BED treatments compared with low-BED treatments.

Disease-free survival was increased for all the regimens with the high-BED treatments, except for one. The pooled data show that for the high-BED treatments the disease-free survival was not significantly higher than for the low-BED treatments.

Treatment-related mortality was higher for the high-BED treatments in three studies [4, 7, 20] and lower in five studies [4, 11, 14, 28, 36]. For the pooled data, the treatment-related mortality was not significantly lower for the high-BED regimens than for the low-BED schemes.

Overall survival was increased in five studies [11, 14, 20, 28, 36] and decreased in two studies [4, 7]. The pooled overall survival was significantly higher for the high-BED schemes. Figure 1 summarizes the above findings.

Dose-Effect Relationships

Dose-effect relationships were constructed for the four endpoints, using the dataset of Table 1. In Figure 2a, the relapse

Table 2. Relapse incidence, disease-free survival, treatment-related mortality, and overall survival in the three randomized trials [7, 14, 20] and four studies [4, 11, 28, 36] comparing two or three TBI schemes at low and high BED, relative risks, and pooled relative risk. BED: biologically effective dose; N: total number of patients; n: number of responders; NS: nonsignificant (95% CI includes value 1), RR (95% CI): relative risk and 95% confidence limits; S: significant; TBI: total-body irradiation. The low-BED group numbers in the study of Bieri et al. [4] contributed once to the pooled values.

Tabelle 2. Rückfallinzidenz, krankheitsfreies Überleben, behandlungsbezogene Letalität und Gesamtüberleben in den drei randomisierten Studien [7, 14, 20] und vier Studien [4, 11, 28, 36], die zum Vergleich von zwei oder drei Ganzkörperbestrahlungsregimen jeweils mit niedriger und hoher BED durchgeführt wurden, relative Risiken und gepoolter RR-Wert. BED: biologisch effektive Dosis; N: Gesamtzahl der Pateinten; n: Anzahl der Responder; NS: nicht signifikant (Wert 1 liegt im 95%-CI), RR (95% CI): relatives Risiko und Grenzen des 95%-Konfidenzintervalls; S: signifikant; TBI (total-body irradiation.): Ganzkörperbestrahlung. Die Zahlen der niedrigen BED-Gruppe aus der Studie von Bieri et al. [4] gingen nur einmal in die gepoolten Werte ein .

Reference	BED (Gy) low	n/N low	BED (Gy) high	n/N high	RR (95% CI)	Significance
A. Relapse incidence						
[4]	11.6	6/24	14.2	10/66	0.61 (0.25–1.49)	NS
[4]	11.6	6/24	16.2	10/26	1.54 (0.66–3.59)	NS
[7]	13.9	12/34	18.5	4/37	0.31 (0.11–0.86)	S
[11]	12.1	16/53	13.9	6/46	0.43 (0.18–1.01)	NS
[14]	13.4	6/27	13.8	3/26	0.52 (0.14–1.86)	NS
[20]	13.1	20/73	16.8	11/74	0.54 (0.28–1.05)	NS
[28]	12.0	7/36	15.1	5/48	0.54 (0.19–1.55)	NS
[36]	12.8	19/65	13.9	28/106	0.90 (0.56–1.48)	NS
Pooled values		86/312 (28%)		77/429 (18%)	0.65 (0.50–0.85)	S
B. Disease-free survival						
[4]	11.6	10/24	14.2	33/66	1.20 (0.71–2.04)	NS
[4]	11.6	10/24	16.2	10/26	0.92 (0.47–1.82)	NS
[7]	13.9	20/34	18.5	22/37	1.01 (0.69–1.49)	NS
[28]	12.0	20/36	15.1	33/48	1.24 (0.87–1.75)	NS
[36]	12.8	28/65	13.9	59/106	1.29 (093–1.79)	NS
Pooled values		78/159 (49%)		157/283(55%)	1.13 (0.94–1.37)	NS
C. Treatment-related mortality						
[4]	11.6	5/24	14.2	19/66	1.38 (0.58–3.29)	NS
[4]	11.6	5/24	16.2	5/26	0.92 (0.30–2.80)	NS
[7]	13.9	4/34	18.5	12/37	2.76 (0.98–7.73)	NS
[11]	12.1	22/53	13.9	14/46	0.73 (0.43–1.26)	NS
[14]	13.4	15/27	13.8	8/26	0.55 (0.28–1.08)	NS
[20]	13.1	24/73	16.8	26/74	1.07 (0.68–1.68)	NS
[28]	12.0	11/36	15.1	11/48	0.75 (0.37–1.53)	NS
[36]	12.8	25/65	13.9	25/106	0.61 (0.39–0.97)	S
Pooled values		106/312 (34%)		120/429 (28%)	0.82 (0.66–1.02)	NS
D. Overall survival						
[4]	11.6	15/24	14.2	37/66	0.90 (0.62–1.31)	NS
[4]	11.6	15/24	16.2	12/26	0.74 (0.44–1.24)	NS
[7]	13.9	22/34	18.5	22/37	0.92 (0.64–1.32)	NS
[11]	12.1	27/53	13.9	31/46	1.32 (0.95–1.84)	NS
[14]	13.4	8/27	13.8	14/26	1.74 (0.91–3.32)	NS
[20]	13.1	28/73	16.8	33/74	1.16 (0.79–1.71)	NS
[28]	12.0	21/36	15.1	37/48	1.32 (0.96–1.81)	NS
[36]	12.8	29/65	13.9	68/106	1.44 (1.06–1.95)	S
Pooled values		150/312 (48%)		254/429 (59%)	1.23 (1.07–1.42)	S

incidence decreases with increasing BED values. The slope of the curve, weighted for the number of patients per study, is significantly different from 0 ($p = 0.035$).

In Figure 2b, the slope of the disease-free survival curve, weighted for the number of patients per study, is significantly different from 1 ($p = 0.02$); disease-free survival increases with increasing BED.

In Figures 2c and 2d, the treatment-related mortality rates and overall survival as function of BED are shown. No significant difference in treatment-related mortality as function of the BED is observed. The slope of the overall survival curve, weighted for the number of patients per study, is significantly different from 1 ($p = 0.03$); overall survival increases with increasing BED.

Late Normal-Tissue Morbidity

The BED values of the regimens in Table 1 for eye lens, lung, and kidney, supposing no shielding, are shown in Figure 3. In

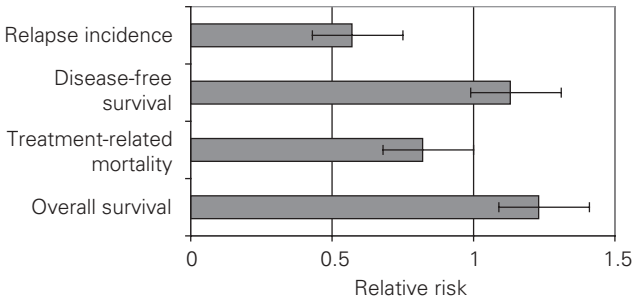
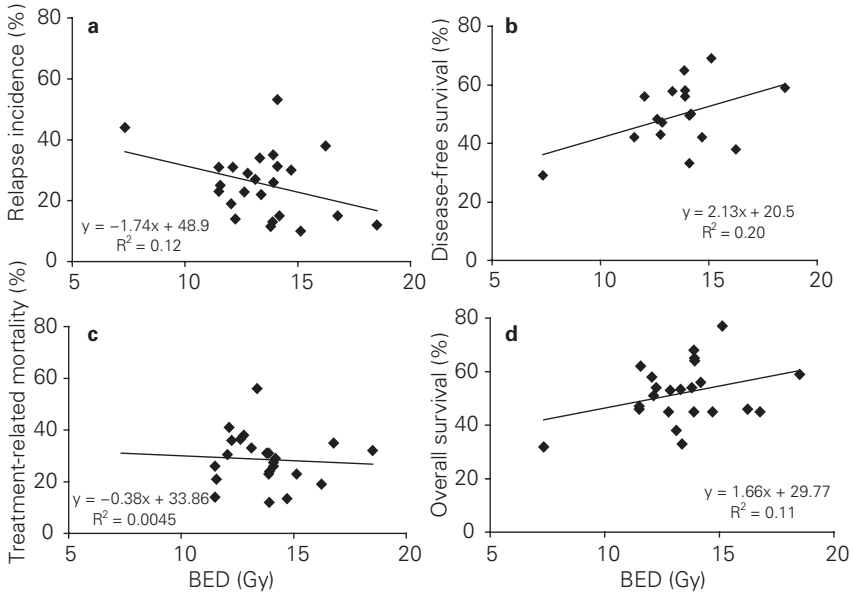


Figure 1 – Abbildung 1

Figure 1. Pooled relative risks for relapse incidence, disease-free survival, treatment-related mortality, and overall survival at high biologically effective dose (BED) as compared to low BED of the three randomized trials and four studies comparing two or three TBI schemes.

Abbildung 1. Gepooltes relatives Risiko, bezogen auf Rückfallinzidenz, krankheitsfreies Überleben, behandlungsbezogene Letalität und Gesamtüberleben bei hoher biologisch effektiver Dosis (BED), verglichen mit niedriger BED in drei randomisierten Studien und vier Studien zum Vergleich von zwei oder drei Ganzkörperbestrahlungs-Regimen.



Figures 2a to 2d. Relapse incidence (a), disease-free survival (b), treatment-related mortality (c), and overall survival rate (d) as function of the biologically effective dose (α/β = 10 Gy and μ = 1.4/h).

Abbildungen 2a bis 2d. Rückfallinzidenz (a), krankheitsfreies Überleben (b), behandlungsbezogene Letalität (c) und Gesamtüberleben (d) als Funktion der biologisch effektiven Dosis (α/β = 10 Gy und μ = 1.4/h).

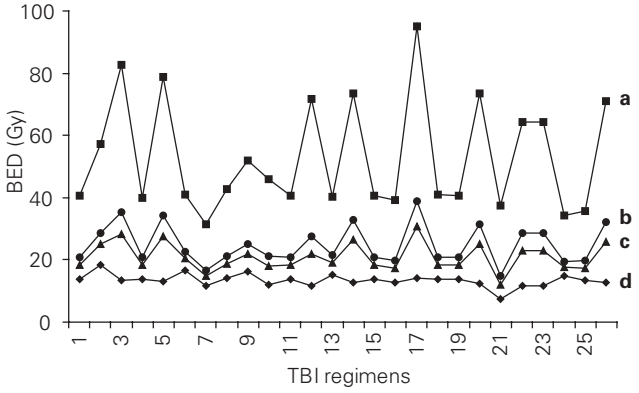


Figure 3 – Abbildung 3

addition, the BED values for leukemia are shown. The TBI regimen numbers in Figure 3 correspond with the ranking in Table 1.

Discussion

The role of high-dose TBI is still under debate. Gale et al. [19] stated that different TBI schemes all had the same results. Some authors reported a higher overall survival with increasing TBI dose [28, 36], others found opposite results [4, 7]. Recently, totally different low-intensity conditioning regimens with low-dose TBI have extended the benefit of graft-versus-tumor effect to patients who are not candidates for fully ablative stem cell transplantations by virtue of their age or existing comorbidities [32, 39]. TBI schemes used, e.g., 1 × 2 Gy, are easy to apply, as shielding is not necessary and toxicity is low. In terms of leukemic cell kill they are, however, very suboptimal.

Vriesendorp et al. [45] stated that different TBI procedures could not be compared without radiobiological "normalization". We performed "normalization" according to the LQ-BED model.

Figure 3. Biologically effective doses (BED) for various TBI regimens calculated for eye lens, kidney, lung, and leukemic cells with appropriate α/β and μ values. The order in the TBI regimens on the horizontal axis is identical with the ranking in Table 1. a (squares): eye lens; b (circles): kidney; c (triangles): lung; d (diamonds): leukemic cells.

Abbildung 3. Biologisch effektive Dosen (BED) verschiedener Ganzkörperbestrahlungs-Regime, berechnet für Linse, Niere, Lunge und Leukämiezellen mit geeigneten α/β- und μ-Werten. Die Reihenfolge der Ganzkörperbgestrahlungs-Regime auf der x-Achse ist identisch mit der in Tabelle 1. a (Quadrate): Linse; b (Kreise): Niere; c (Dreiecke): Lunge; d (Rauten): Leukämiezellen.

Table 3. Summary of TBI regimens with requirements for minimum BED values for leukemia and maximum BED values for eye lens, kidney, and lung. BED: biologically effective dose; NSh: no shielding of organ required; Sh: shielding of organ required; TBI: total-body irradiation; Y: BED value > 15 Gy.

Tabelle 3. Zusammenstellung von Ganzkörperbestrahlungs-Regimen mit den Bedingungen minimaler BED-Werte für Leukämiezellen und maximaler BED-Werte für Linse, Niere und Lunge. BED: biologisch effektive Dosis; NSh: keine Organabschirmung erforderlich; Sh: Organabschirmung erforderlich; TBI (total-body irradiation): Ganzkörperbestrahlung; Y: BED > 15 Gy.

	1 × 5 Gy	1 × 7.5 Gy	1 × 9/9.2 Gy	1 × 10 Gy	3 × 3.3 Gy	5 × 2.2 Gy	6 × 1.67 Gy	6 × 2 Gy	6 × 2.25 Gy	7 × 2.25 Gy	8 × 1.65 Gy	11 × 1.2 Gy	11 × 1.35 Gy
BED leukemia > 15 Gy								Y	Y	Y		Y	
BED eye lens < 45 Gy	NSh	Sh	Sh	Sh	NSh	NSh	NSh	NSh	Sh	Sh	NSh	NSh	NSh
BED kidney < 17 Gy	NSh	Sh	Sh	Sh	Sh	Sh	NSh	Sh	Sh	Sh	Sh	Sh	Sh
BED lung < 15 Gy	NSh	Sh	Sh	Sh	Sh	Sh	NSh	Sh	Sh	Sh	Sh	Sh	Sh

We restricted ourselves to the results of patients who suffered from AL, underwent high-dose TBI, and received allogeneic HSCT. AL is known to relapse predominantly within the first 2 years after HSCT [7, 8]. Studies were included, if the follow-up time was at least 3 years.

From the three randomized studies found in the literature no meaningful conclusions could be drawn, probably due to the relatively low number of patients per treatment arm. For the RR analysis we therefore decided to pool all available data. We observed a significantly lower relapse incidence, a higher disease-free survival, less treatment-related mortality, and a significantly higher overall survival for the high-BED treatments. The results were as expected, based on the assumption that at higher BEDs the leukemic cell kill is increased.

The dose-effect relationships for the four endpoints show the tendencies as mentioned before. Our analysis of the pooled data therefore indicates a benefit for higher BED values.

A relatively high BED for leukemic cells can only be applied taking the tolerance BED of normal tissues into account [25, 27]. In most of the studies, the lung dose was restricted to a total dose of 8–9 Gy corresponding to a BED value for lung tissue of 12–14 Gy. In a number of publications it was recommended to limit the dose to the kidneys to 10–12 Gy in a fractionated regimen [5, 23, 24, 29, 31]. This corresponds to a BED value of about 17 Gy [26]. In Figure 3, the BED values for leukemia, lungs, kidneys, and eye lenses for the various TBI schemes, assuming no shielding of the organs (Table 1), are shown. It indicates that in the majority of the TBI treatments the kidney dose applied might have been too high in view of the recommended kidney dose limit. The TBI schemes with the highest kidney BED values are those using single doses (e.g., [3, 14, 20]). The incidence of severe cataracts for BED values of the lens tissue of less than about 40–45 Gy is negligible [44]. In about half of the TBI treatments the "safe" lens dose is exceeded. The highest BED values for eye lens were found for single-dose regimens.

The requirements for an optimal TBI scheme therefore are: BED for leukemic cells as large as possible, i.e., BEDs of 15 Gy and larger, and BED for lungs, kidneys and eye lenses not exceeding 15 Gy, 17 Gy, and 45 Gy, respectively.

In Table 3, the TBI schemes of Table 1 are summarized. The TBI schemes with single doses (> 5 Gy) and almost all of the fractionated dose schedules should all be applied with shielding of the lungs, kidneys, and eyes. Only the scheme with 6 × 1.67 Gy can be applied without shielding. However, the $BED_{leukemia}$ is low (BED = 11.6 Gy). The schemes with high $BED_{leukemia}$ values can only be applied with adequate shielding. The most widely used scheme in this survey is 6 × 2 Gy. Lung and kidney shielding (no eye shielding) has to be applied, the leukemic cell kill, however, is considered suboptimal (< 15 Gy). Shielding will not only result in a lower BED for the shielded organ, it also causes a lower BED for the leukemic cells and the bone marrow present in the tissues (e.g., ribs) in the shadow of the shielding blocks. The highly fractionated schemes must be considered to be the most effective. For example, with the scheme of 11 × 1.35 Gy, the $BED_{leukemia}$ is 16.8 Gy, and the BED_{kidney} is 22.8 Gy (Table 1). With shielding of the kidneys to 11 × 1.1 Gy, resulting in a BED_{kidney} of 17.4 Gy, the dose reduction is only 20% and the $BED_{leukemia}$ behind the shielding is still 13.3 Gy. For a single-dose treatment, e.g., 1 × 10 Gy (Table 1), the $BED_{leukemia}$ is 13.1 Gy, and the BED_{kidney} is 34.4 Gy. The dose reduction must be 34% to 1 × 6.6 Gy resulting in a BED_{kidney} behind the shielding of 17.2 Gy; however, the $BED_{leukemia}$ behind the shielding is only 8 Gy.

Conclusion

High BED values appear to cause less leukemia relapses and a higher disease-free and overall survival. With highly fractionated schemes a high $BED_{leukemia}$ can be obtained. Shielding of lungs and kidneys during TBI seems to be unavoidable. However, the measure of shielding in highly fractionated schemes is relatively limited as compared to hypofractionated or single-dose TBI schemes. The question posed by Bieri et al. [4] whether more dose is better in TBI, can be answered positively. Prospective trials, in which TBI schemes with multiple fractions are compared with a low number of fractions schemes, are warranted using the BED concept. Purpose should be to elucidate whether highly fractionated schemes with a high total dose indeed yield better treatment results than single-dose regimens or regimens with a low number of fractions.

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