Induction of Severe Cataract and Late Renal Dysfunction Following Total Body Irradiation: Dose–Effect Relationships

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Abstract. *Background: Severe cataract and renal dysfunction are late effects following myeloablative total body irradiation (TBI) and hematopoietic stem cell transplantation in patients with hematological malignancies. The aim of the study was to determine radiation dose-response relationships for these late effects. Materials and Methods: A retrospective review of articles reporting incidences for cataract induction and late renal dysfunction was performed, using PubMed. The radiation regimens identified were normalized using the linear-quadratic model; biologically effective doses (BEDs) were calculated. Results: For cataract induction, 17 articles were identified allowing a dose–effect relationship to be derived. A threshold BED of ~40 Gy was indicated below which severe cataract seldom occurs. For late renal toxicity, 14 articles were found. The resulting dose–effect relationship indicates a threshold BED of ~16 Gy. Conclusion: To prevent severe cataract, fractionated TBI should be applied to keep the BED <40 Gy. Only when single-dose TBI cannot be avoided should eye shielding be applied. To prevent late renal toxicity, fractionated TBI is recommended, but kidney shielding remains necessary for almost all myeloablative TBI regimens.*

Cataract formation is one of the widely reported late effects following total body irradiation (TBI) and hematopoietic stem cell transplantation (HSCT). Several factors are known to influence cataractogenesis after HSCT such as TBI dose, fractionation scheme, dose rate, steroid treatment and administration of heparin (1, 2). Cataract induction can hardly be prevented; it is, however, the degree of the cataract determining the complaints of the patient that counts (3). It is possible to prevent severe cataract, *i.e.* cataract causing complaints requiring surgery, by applying a TBI regimen with a biologically effective dose (BED) below the threshold dose for severe cataract induction. Hence, a prerequisite for preventing severe cataract induction is a BED for the eye lens not exceeding the tolerance dose and a BED as high as possible for leukemic cells (4). Depending on the fractionation and or dose rate of the TBI, some centers apply eye shielding although the use of eye shielding is controversial, as the eyes are regarded as sanctuary sites.

Chronic renal dysfunction affects the health, well-being and life expectancy of people otherwise cured of the cancer for which TBI and HSCT were performed. Renal dysfunction is largely ascribed to radiation nephropathy, usually characterized by an increase in serum creatinine, proteinuria, anemia and/or hypertension. The clinical manifestations generally occur 1-1.5 years after TBI. Partial kidney shielding at the time of TBI has reduced the occurrence rates of renal dysfunction (5, 6). Kal and van Kempen-Harteveld reported the incidence of late renal dysfunction secondary to TBI as a function of the BED (7). Cheng *et al.* confirmed the hypothesis that a quantitative relationship exists among renal dose, fractionation, dose rate and the incidence of late renal complications (8).

Severe cataract and chronic renal dysfunction can be prevented: the BED of the TBI should be kept below a threshold dose. Dose–effect relationships give insight into the magnitude of the threshold BED values. However, to eradicate remaining leukemic cells, the BED for leukemic cells should be as high as possible and this can be obtained with proper fractionation of the TBI.

In the present study, we reviewed the literature and updated the dose-response relationships as described by van Kempen-Harteveld *et al.* (9) for cataract induction and Kal *et al.* (7) for renal dysfunction.

Materials and Methods

A retrospective review of articles reporting incidences or dose-response relationships of cataract induction and late renal dysfunction following TBI and HSCT was performed using Pubmed.

To compare the different TBI schedules that have been described in the articles, BEDs were calculated using the linear-quadratic and BED (LQ-BED) concept. The occurrence of a biological effect E depends

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Key Words: Cataract induction, late renal dysfunction, dose-effect relationship, biologically effective dose.

Table I. *Cataract incidence after TBI .*

Authors	N. Pts	N. fract.	Fraction dose (Gy)	Dose rate (cGy/min)	Inc. (%)	BED (Gy)
Belkacémi *et al*. (2)	36	1	10	<4.8	0	81.3
	221	1	10	7	32	97
	34	1	10	>9	59	102.7
	121	6	2	<4.8	4	39.6
	80	6	2	7	23	41.1
van Kempen *et al*. (9)					100	115
					78*	107.5
					56*	92.5
					64*	77.5
					56*	62.5
					10	45
					0	35
Fyles *et al*. (12)	166	1	5	42-91	0	37.4
Bray *et al*. (13)	13	3	3.5	25	15.4	57.1
	17	6	2	25	6.8	43.1
Calissendorff *et al*. (14)	43	1	10	4	44.7	74.5
Ozsahin *et al*. (15)	49	6	2	3	4	37.5
Benyunes *et al*. (16)	74	1	10	6	59	89.3
	333	6	2	6	22	40.5
	117	7	2.25	6	33	57.2
	51	6	2	6	22	40.5
Chou *et al*. (17)	17	6	2	15	11.8	42.5
Zierhut *et al*. (18)	85	12	1.2	7-18	7.1	36.7
Frisk *et al*. (19)	20	1	7.5	15	30	70.6
Thomas *et al*. (20)	150	6	2	14	8.6	42.4
Beyzadeoglu *et al*. (21)	37	6	2	2.2	0	35.6
Aristei *et al*. (22)	86	1	8	16	12.8	79.8
	107	12	1.2	9.5	1.9	36.4
Oysul *et al*. (23)	105	6	2	10*	5	41.8
Lähteenmäki *et al*. (24)	14	1	10	5-8	50	92.1
Flandin *et al*. (25)	32	6	2	10*	19	41.8
Schneider *et al*. (26)	257	6	2	10*	6.6	41.8

*Estimated by the authors; Inc.: incidence; BED: biologically effective dose.

Table II. *Renal dysfunction after TBI.*

Authors	N. pts	N. fract.	Fraction $dose_{kidney}$ (Gy)	Dose rate (cGy/min)	Dysf (%)	BED_{kidney} (Gy)
Igaki *et al*. (5)	70	6	2	10**	21.5	21.2
	39	6	1.7	8.5	0	16.5
Lawton *et al*. (6)	72	9	1.55	14	29	22.4
	68	9	1.32	11.9	14	18.0
	17	9	1.09	9.8	0	14.0
Chou *et al*. (17)	58	6	2	15	10	21.4
	15	1	7	15	25	24.9
Schneider *et al*. (26)	257	6	2	10*	3.5	21.2
Tarbell *et al*. (27)	12	8	1.75	10	33.3	23.5
	15	6	2	10	46.7	21.2
Lönnerholm *et al*. (28)	41	1	7.5	15	24.4	27.9
VanWhy *et al*. (29)	39	8	1.65	14*	43	21.7
Rabinowe *et al*. (30)	112	6	2	7.5	9.8	21.1
Miralbell *et al*. (31)	24	6	1.67	16	5	16.6
	32	6	2	16	26	21.4
	23	6	2.25	16	45	25.3
Bradley *et al*. (32)	77	9	1.5	12	9	21.4
Borg *et al*. (33)	59	6	2	7.5	15	21.1
Frisk *et al*. (34)	26	1	7.5	15	26.9	28.0
Cohen *et al*. (35)	88	9	1.55	8-20	10.2	22.5
Kersting *et al*. (36)	266	2	5	15	23	28.8

Dysf: dysfunction; BED: biologically effective dose. *Dose rate estimated by present authors,**personal communication (Dr Igaki, December 2005).

on the dose in a linear and quadratic fashion: $E=n(\alpha d+\beta d^2)$ with n being the number of fractions, d being the dose per fraction, and α and β being parameters that determine the initial slope and curvature of the underlying cell-survival curve. From this equation, the BED can be calculated as: $BED=nd\,[1+d/(\alpha/\beta)]$ (10, 11). For low dose rate irradiation, $BED=nRT\,[1+kR/(\alpha/\beta)]$, where R is the dose rate, T is the treatment time per fraction, and $k=2[1-\{1-\exp(-\mu T)\}/(\mu T)]/\mu$. The factor k depends on the sublethal damage repair rate μ during the low dose rate irradiation, and treatment time T. The parameter μ is related to the half-time for mono-exponential repair of sublethal damage, T½, where $T½=\ln 2/\mu$. We applied μ-values for cataract induction and renal dysfunction of 0.65 and 0.35 h^{-1}, respectively (7, 9).

It is widely accepted that α/β is ~10 Gy for acute-reacting tissues; it is in the range of 1-3 Gy for late-reacting ones. For cataract and kidney as late-reacting tissues, we applied $\alpha/\beta=0.65$ Gy and $\alpha/\beta=2.5$ Gy, respectively (7, 9).

It is the strength of the LQ-BED concept that for a specific isoeffect the BED values are equal for treatments with different fractionation regimens.

After myeloablative TBI, cataract induction with varying grades of severity occurs in a large proportion of patients. The endpoint we used here was severe cataract, *i.e.* cataract causing complaints about visual impairment interfering with normal daily functioning and needing surgery. Late renal dysfunction was the other analyzed treatment endpoint. Late renal dysfunction is assumed to be mainly attributable to radiation nephropathy, which is characterized by an increase of serum creatinine, proteinuria, anaemia, and hypertension. Curve fitting was applied using Microsoft Excel for linear fitting.

Results

Seventeen articles on cataract induction were identified (2, 9, 12-26), of which one reported a dose–effect relationship (9). This dose–effect relationship was based on the data of 302 patients collected by the European Group for Blood and Marrow Transplantation who underwent HSCT for acute leukemia and received single-dose TBI without steroid treatment and heparin administration. In Table I, the incidence of severe cataracts after TBI and HSCT as found in the literature and the calculated BED values are shown.

In Figure 1, the data points of the incidence rates as function of the BED as depicted in Table I are shown. The data points were fitted by a linear function. The resulting

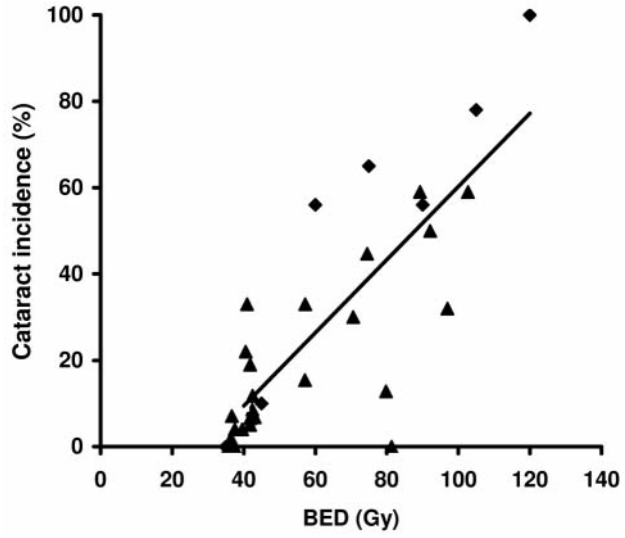

Figure 1. *Cataract incidence after total body irradiation and hematopoietic stem cell transplantation as a function of the biologically effective dose (BED). Diamonds, data points published earlier by van Kempen-Harteveld et al. (9). Triangles are data points derived from recent publications. The curve was fitted to the data points.*

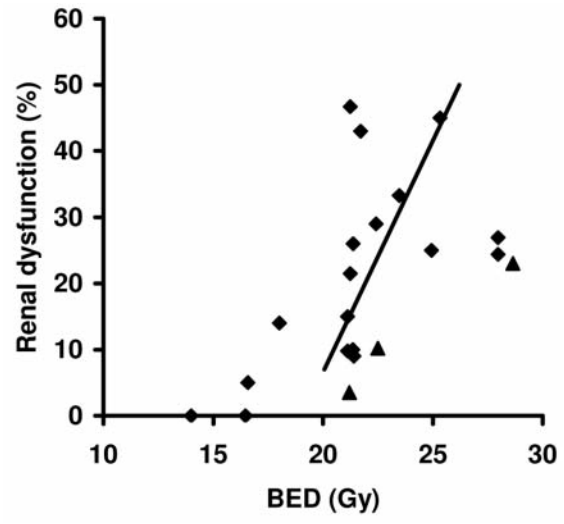

Figure 2. *Renal dysfunction after total body irradiation and hematopoietic stem cell transplantation as a function of the biologically effective dose (BED). Diamonds are data points published earlier by Kal et al. (7). Triangles are data points derived from recent publications. The curve was fitted to the data points.*

dose–effect relationship suggests that for BED <40 Gy, severe cataract incidence will be rare.

Fourteen studies on late renal dysfunction were identified (5, 6, 17, 26-36). In Table II, the frequency of late renal dysfunction and the calculated BED values are shown. A linear dose–effect relationship was constructed and is shown in Figure 2. From this figure it can be derived that BED values <16 Gy result in a low risk of late renal damage.

Several studies could not be included because of the obscurity of the dose rate, too few patients were included, or because the relationship between the dose and frequency of the occurrence of severe cataract or late renal dysfunction was not indicated.

Discussion

Myeloablative TBI is an important component of many preparative regimens used in HSCT for the treatment of hematological malignancies. As the long-term survival improves with advances in HSCT, late complications affecting the quality of life following HSCT and TBI, such as cataractogenesis and chronic renal dysfunction, become important. TBI, and particularly single-dose TBI, was found to be the most important risk factor for cataract induction (2, 22, 26, 37-39). High-dose-rate TBI was more effective in cataract induction than low-dose-rate TBI (2, 21, 37). Igaki *et al.* and others showed that TBI dose was significantly associated with renal dysfunction (5, 6, 8, 40). Hingorani *et al.*, however, reported that TBI was not associated with an increased risk of chronic kidney disease (41). This is probably due to the fractionation regimens they used which resulted in BED values below the kidney tolerance dose. The characteristics, single-dose and high-dose-rate TBI, are descriptive. The need to convert the radiotherapy parameters into a single value and to relate this value to the incidence of cataract induction or induction of chronic renal dysfunction is obvious. In the present study we applied the LQ-BED concept and also updated the dose–effect relationships for cataract and renal dysfunction induction that were published earlier (7, 9).

For cataract induction, we added 25 data points (references 2, 12-26, Table I) to the data points published earlier (9), shown in Figure 1. The curve was fitted to all data points. The curve indicates that for BED values below 40 Gy the frequency of cataract induction is less than 10%. van Kempen-Harteveld *et al.* concluded that the assumption that the eye as a sanctuary site is more vulnerable for relapse might not be valid (42). Therefore, one could consider shielding the eyes during TBI in such a way that the BED<40 Gy. For multifractionated TBI shielding probably is not necessary, however, for single-dose and hypofractionated myeloablative TBI, shielding of the eye lens should be considered (4).

Kidney function, in general, declines with age and, as better survival of HSTC patients over the years is reported, progressive loss of kidney function may lead to kidney failure or decreased life expectancy caused by problems related to the

results of renal dysfunction such as hypertension. Therefore, knowledge of the dose–effect relationship and threshold dose for chronic kidney dysfunction might lead to appropriate TBI schemes and/or degree of renal shielding during TBI.

Dose–effect relationships were reported by Moulder and Cohen (43) and Kal and van Kempen-Harteveld (7), largely based on the same dataset, but on different assumptions about dose rate effects (44, 45). However, Moulder and Cohen (43) reported renal dysfunction incidence as a function of single doses. For renal dysfunction, we added 3 data points (26, 35, 36) to the data points published earlier (Figure 2). The curve was fitted to all data points. It still indicates that the threshold dose of about 16 Gy reported earlier may still be true. Only few authors reported the influence of shielding kidneys during TBI on relapse incidence and/or overall survival. No influence of kidney shielding on overall survival was found (5, 6), although duration of the follow-up was limited. In addition, in the study of van Kempen-Harteveld *et al*., it was not possible to correlate the dose on shielded kidneys to overall survival or relapse incidence (42). From this, we recommend that during TBI the kidney should be shielded to a BED<16 Gy. From a literature study by Kal *et al*. it was concluded that for almost every myeloablative TBI scheme found in the literature the kidneys should be shielded (7). For example, for a frequently used TBI scheme of 6 fractions of 2 Gy, the kidneys should be shielded to 6×1.7 Gy to prevent chronic renal failure.

In conclusion, to prevent induction of severe cataract, the BED must be below the threshold dose, which can be reached with fractionation of the TBI. Only when single-dose TBI cannot be avoided, one could consider shielding the eyes. To prevent late renal damage, fractionated TBI should be applied. Although kidney shielding is still necessary, the required dose reduction is limited.

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