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Splenic irradiation before hematopoietic stem cell transplantation for chronic myeloid leukemia: long-term follow-up of a prospective randomized study

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Abstract In the context of discussions on the reproducibility of clinical studies, we reanalyzed a prospective randomized study on the role of splenic irradiation as adjunct to the conditioning for hematopoietic stem cell transplantation (HSCT) for chronic myeloid leukemia (CML). Between 1986 and 1989, a total of 229 patients with CML were randomized; of these, 225 (98 %; 112 with, 113 without splenic irradiation) could be identified in the database and their survival updated.

Results confirmed the early findings with no significant differences in all measured endpoints (overall survival at 25 years: 42.7 %, 32.0–52.4 % vs 52.9 %, 43.2–62.6 %; $p=0.355$, log rank test). Additional splenic irradiation failed to reduce relapse incidence. It did not increase non-relapse mortality nor the risk of late secondary malignancies. Comforting are the long-term results from this predefined consecutive cohort of patients: more than 60 % were alive at plus 25 years when they

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were transplanted with a low European Society for Blood and Marrow Transplantation (EBMT) risk score. This needs to be considered today when treatment options are discussed for patients who failed initial tyrosine kinase inhibitor therapy and have an available low risk HLA-identical donor.

Keywords HSCT · CML · Splenic irradiation · Randomized trial · Long-term follow-up

Introduction

When hematopoietic stem cell transplantation (HSCT) was introduced as a novel approach for patients with chronic myeloid leukemia (CML) half a decade ago, the transplant was primarily performed in advanced disease stage. Debulking of the tumor load by removing the big spleen, a then hallmark of disease progression, was considered essential. Splenectomy or splenic irradiation was performed routinely prior to the transplant [1, 2]. Retrospective observational cohort studies failed to confirm a benefit of splenectomy [3]. Consequently, a prospective randomized study was initiated by the European Society for Blood and Marrow Transplantation (EBMT) to investigate the potential role of splenic irradiation. Early results and an update with a 3-year follow-up showed no significant differences between the groups [4, 5]. Splenectomy and splenic irradiation were abandoned. Interest into this question further diminished with the advent of targeted therapy for CML by tyrosine kinase inhibitors (TKI) [6]. Numbers of HSCT for CML rapidly declined; HSCT became considered as salvage therapy for patients refractory to lines of TKIs or for those in advanced phase of the disease or in blast crisis [7].

The topic of both questions, the place of HSCT in the treatment algorithm for CML and the role of splenic pre-treatment has regained interest in recent years, for several reasons. Myeloproliferative neoplasias other than CML have become a target for HSCT; optimal management of patients with

splenomegaly before HSCT has become a matter of debate [8]. Recently reported excellent results with early transplants for selected patients with a low risk transplant donor have renewed interest in HSCT [9, 10]. Increasing awareness of cost effectiveness considerations might favor earlier HSCT in patients non-responding to first-line TKI but with low transplant risks rather than long-term TKI treatment [11, 12]. And, recent discussions about reproducibility of clinical study results mandate a second look beyond short-term outcome [13]. In this context, long-term outcome of a predefined group becomes of interest. The Chronic Malignancies Working Party of the EBMT has therefore undertaken the efforts to have a second look at this defined study cohort and to update the results.

Patients and methods

This analysis was based on the prospective randomized study conducted between 1986 and 1989 [4, 5]. A total of 229 patients with CML in first chronic phase and planned to undergo HSCT from an HLA-identical donor were randomized not to receive ($N=115$) or to receive ($N=114$) splenic irradiation in one of three options, 10 Gy single dose, 5 Gy in two doses, or 3.3 Gy in three doses. Randomization was performed centrally in blocks of six patients, stratified by age (≤ 25 years, >25 years) and whether or not T cell depletion (TCD) was used. The Ethics Committee of the then Kantonsspital Basel, now University Hospital Basel, approved the protocol; all patients gave informed consent.

Of these 229 patients, 225 (98 %; 112 with, 113 without splenic irradiation) could be identified in the current CMWP data file. Their characteristics are listed in Table 1. Not all remained in chronic phase until the time of transplant; in some, the diagnosis of CML was modified to MDS or MPN over time, according to the then available diagnostic tools. The analysis followed the intention to treat principle. All patients randomized to splenic irradiation indeed were treated accordingly and received splenic irradiation; none of the patients randomized to no splenic irradiation did receive splenic irradiation. Their survival status was updated as of January 1, 2015, with a median follow-up time of the living patients of 239 months (7–335 months, range). Main endpoint of the analysis was overall survival by randomization group using Cox regression as model. Comparisons were adjusted for the stratification (T cell depletion; TCD+ and TCD–), the EBMT risk score [14], and the number of basophils in the circulating blood prior to HSCT (baso <3 vs ≥ 3 %). Secondary endpoints were relapse incidence, non-relapse mortality, which includes any death without relapse and relapse free survival. An additional secondary endpoint was the probability of developing a secondary malignancy.

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Table 1 Patients' characteristics by randomization group

	No splenic irradiation (<i>N</i> (%))	Splenic irradiation (<i>N</i> (%))	Total (<i>N</i> (%))	<i>P</i> value
<i>N</i> , initial cohort	115 (50 %)	114 (50 %)	229 (100 %)	
<i>N</i> , cohort 2015	113 (50 %)	112 (50 %)	225 (100 %)	
Diagnosis				0.401
CML	105 (93 %)	107 (96 %)	212 (94 %)	
MDS/MPN	8 (7 %)	5 (4 %)	13 (6 %)	
^a Stage of disease at transplant (<i>N</i> =222)				0.262
First Chronic phase	102 (93 %)	98 (87 %)	200 (90 %)	
Not first chronic phase (CP2/AP/BC, <i>N</i> =1/20/1)	8 (7 %)	14 (13 %)	22 (10 %)	
Sex				0.376
Males	76 (67 %)	69 (62 %)	145 (64 %)	
Females	37 (33 %)	43 (38 %)	80 (36 %)	
Age				0.576
≤25 years	18 (16 %)	21 (19 %)	39 (17 %)	
≥25 years	95 (84 %)	91 (81 %)	186 (83 %)	
Years; median (range)	33 (9–50)	34 (8–52)	34 (8–52)	0.547
Age donor years; median (range) (<i>N</i> =207)	33 (7–62)	35 (8–71)	34 (7–71)	0.602
T cell depletion				0.062 ^b
Yes	23 (20 %)	35 (31 %)	58 (26 %)	
No	90 (80 %)	77 (69 %)	167 (74 %)	
Conditioning (<i>N</i> =222)				0.345
with TBI	95 (85 %)	98 (89 %)	193 (87 %)	
without TBI	17 (15 %)	12 (11 %)	29 (13 %)	
<i>N</i> basophils (<i>N</i> =215)				0.840
<3 %	57 (53 %)	55 (51 %)	112 (52 %)	
≥3 %	51 (47 %)	52 (49 %)	103 (48 %)	
Combination TCD/basophils ^c (<i>N</i> =215)				0.184
TCD-/baso <3 %	46 (43 %)	35 (33 %)	81 (38 %)	
TCD+/baso <3 %	11 (10 %)	20 (19 %)	31 (14 %)	
TCD-/baso ≥3 %	40 (37 %)	37 (34 %)	77 (36 %)	
TCD+/baso ≥3 %	11 (10 %)	15 (14 %)	26 (12 %)	
EBMT risk score (<i>N</i> =213)				0.829
0	4 (4 %)	5 (5 %)	9 (4 %)	
I	30 (29 %)	25 (23 %)	55 (26 %)	
II	39 (37 %)	48 (44 %)	87 (41 %)	
III	23 (22 %)	24 (22 %)	47 (22 %)	
IV	7 (6 %)	5 (5 %)	12 (6 %)	
V	2 (2 %)	1 (1 %)	3 (1 %)	
Follow-up time months; median (range)	246; 62–334	211; 7–335	239; 7–335	0.706
<i>N</i> alive	52 (46 %)	61 (54 %)	113 (50.2 %)	
<i>N</i> alive without relapse	39 (75 %)	42 (69 %)	81 (72 %)	
<i>N</i> alive after relapse	13 (25 %)	19 (31 %)	32 (28 %)	
<i>N</i> died	61 (54 %)	51 (46 %)	112 (49.8 %)	
<i>N</i> died NRM	44 (72 %)	40 (78 %)	84 (75 %)	0.573
GvHD	12 (27 %)	16 (40 %)	28 (33 %)	
Infection	16 (36 %)	14 (35 %)	30 (36 %)	
Organ failure	5 (11 %)	4 (10 %)	9 (11 %)	
Secondary malign.	2 (5 %)	0 (0 %)	2 (2 %)	
Other	9 (21 %)	6 (15 %)	15 (18 %)	
<i>N</i> died REL	17 (28 %)	11 (22 %)	28 (25 %)	

Note that all patients were diagnosed as CML and classified as CML at time of randomization. Some of them were diagnosed as Ph-negative CML, according to the state of the art at that time; some of them were re-labeled as myeloproliferative neoplasia or myelodysplastic syndrome later in the course. All were kept in the analysis in order to follow the intention to treat principle. EBMT risk score: for definitions, see (Gratwohl 2012)

CML chronic myeloid leukemia, MDS/MPN myelodysplastic syndrome/myeloproliferative neoplasia, TCD T cell depletion, baso = basophil count < or ≥3 % at time of randomization, TBI total body irradiation, NRM Non-relapse mortality, REL relapse incidence, Note that some numbers do not add up due to missing values

^a Stage of disease at time of transplant: note that all patients were in first chronic phase at time of randomization; some progressed during waiting. They were included in the analysis according to the intention to treat principle

^b There were no significant differences between the groups, but note the imbalance for TCD despite TCD being a stratification factor

^c The four strata did present different characteristics for calendar year ($p=0.007$, but with no monotonic trend; $p=0.955$), diagnosis ($p=0.003$), patient gender ($p=0.020$), donor age ($p=0.086$), and donor age ($p=0.039$). The analyses, taking into account the strata, were carried out by multivariable models adjusted for these factors

Results

Both groups were well balanced concerning their main key pre-transplant risk factors and transplant techniques, with one minor exception (Table 1). Despite stratification, we observed a trend towards more patients with TCD+ in the splenic irradiation group (31 vs 20 %; $p=0.062$).

At the time of the analysis, 113 patients were alive (50.2 %), 112 (49.8 %) had died, 84 (75 %) of them from non-relapse mortality, and 28 (25 %) from relapse.

Probabilities of overall survival at 15 and 25 years for the whole group were 49.6 and 47.5 %, respectively. Of note, seven of nine patients with EBMT risk score 0 (77 %) and 36 of 63 patients with EBMT risk scores 0 and I were still alive (57 %) in contrast to 6 of 15 (40 %) with risk scores IV and V and 1 of 3 (33 %) with risk score V.

The comparison of patients without or with splenic irradiation confirmed the early findings, presented 20 years ago, with no significant differences between groups in overall survival (at 15 years: 45.3 %, 35.7–54.9 % vs 54.2 %, 35.7–54.9 % vs 54.2 %, respectively).

Fig. 1 Outcome of 225 patients with HLA-identical sibling donor HSCT for CML and randomized to splenic irradiation or not. The graph depicts probabilities according the intention to treat analysis by months post HSCT and the numbers of patients at risk at the given time points in the

two arms. *Black curves* indicate no splenic irradiation; *gray curves* indicate splenic irradiation. **a** Overall survival. **b** Non-relapse mortality. **c** Relapse incidence. **d** Secondary malignancies

44.6–63.8 %; at 25 years: 42.7 %, 32.0–52.4 % vs 52.9 %, 43.2–62.6 %; $p=0.355$, log rank test), non-relapse mortality (at 15 years: 38.3 %, 29.1–47.5 % vs 35.8 %, 26.7–44.8 %; at 25 years: 41.0 %, 31.5–50.5 % vs 37.1 %, 27.9–46.4 %; $p=0.803$, Gray test), relapse incidence (at 15 years: 27.5 %, 19.0–35.9 % vs 27.5 %, 18.9–36.0 %; at 25 years: 27.5 %, 19.0–35.9 % vs 30.0 %, 20.4–39.5 %; $p=0.977$, Gray test), and relapse-free survival (at 15 years: 34.2 %, 25.1–43.4 % vs 36.8 %, 27.5–46.1 %; at 25 years: 31.5 %, 22.3–40.7 % vs 32.9 %, 23.0–42.8 %, $p=0.745$, logrank test) (Fig. 1).

Both treatment arms were compared for the stratification factor (TCD+/-) and the basophil count ($<3\%$ / $\geq 3\%$) in the four TCD/basophil count groups. There were no significant differences in any of the four endpoints in any of the four groups in univariate as well as multivariate analysis. A suggested trend from the last analysis [5] for better survival with splenic irradiation in the TCD+/ $\geq 3\%$ basophils could not be substantiated at long-term follow-up. There were no significant differences in the causes of death (Table 1; $p=0.573$), and there was no difference in the probability of developing a secondary malignancy at 25 years (8.7 %, 2.5–14.9 % vs 10.7 %, 2.3–19.0 %; $p=0.993$, Gray test) (Fig. 1d).

Discussion

The results confirm the previously published early findings after a follow-up time of now plus 25 years: splenic irradiation did not confer an advantage for patients transplanted with CML nor cause harm. These results are comforting, despite the absence of a benefit. The early results could be substantiated; a suggested trend in one of the subgroups of TCD+ patients was not verified. Additional splenic irradiation prior to the transplant failed to reduce relapse incidence. It did as well not increase the risk of non-relapse mortality nor the risk of late secondary malignancies.

There is no need to reconsider the initial question. Splenic irradiation is no longer of interest for patients with CML. The results of this long-term follow-up study might, in contrast, be of relevance in today's discussion concerning the role of splenectomy or splenic irradiation for patients with other myeloproliferative disorders [8]. It is likely that the observations from patients with CML hold true as well for patients with splenomegaly but other myeloproliferative disorders.

The study adds to and supports the ongoing discussion on reproducibility of clinical studies. It documents the potential of investigator initiated studies in follow-up continuation [13, 15]. Ninety-eight percent of the initial patient cohort could be identified and update be obtained, this with very limited resources and no direct industrial support. The results add as well to the discussion on the role and

potential of outcome registries. They can indeed contribute most valuable information [16].

Most satisfying are the long-term results from this predefined consecutive cohort of patients. Half of them were alive, more than 25 years after HSCT for CML, more than 60 % when transplanted with a low EBMT risk score. This needs to be considered when treatment options are discussed for patients who failed initial TKI therapy in still early disease but have an available low risk HLA-identical donor [7, 10].

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Compliance with ethical standards

Conflicts of interest There are no conflicts of interest to declare.

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Appendix

List of participating centers with *past* (ref Gratwohl et al. 1996) and current principal investigators.

Basel: Kantonsspital (today University Hospital; B. Speck, A. Gratwohl, J. Passweg); Berlin: University Hospital Rudolf Virchow (W. Siebert, R. Arnold); Birmingham: Queen Elizabeth Hospital (I.M. Franklin, C. Craddock); Brussels: Insitut J. Bordet (L. Debusscher, D. Bron), Hôpital Universitaire St. Luc (A. Ferrant, X. Poiré); Caen: Centre Hospitalier (X. Troussard, O. Reman); Copenhagen: University Hospital (N. Jacobsen, H. Sengeloev); Córdoba: Hospital Reina Sofia (A. Torrez-Gomez, P. Gomez Garcia); Créteil: Hôpital Mondor (J.-P. Vernant, C. Cordonnier); Dublin: St. James' Hospital (S.R. McCann, P. Browne); Edinburgh: Royal Infirmary (A.C. Parker, A.J.M. Broom); Genova: Ospedale San Martino (A. Bacigalupo, F. Frassoni, A. Bacigalupo); Hannover: Medizinische Hochschule (H. Link, A. Ganser); Helsinki: University of Helsinki Hospital (T. Ruutu, L. Volin); Huddinge: Karolinska Institute (B. Lönnqvist, G. Gahrton, O. Ringden, P. Ljungman); Innsbruck: University Hospital (D. Niederwieser, G. Gastl); Kiel: Christian Albrechts University Hospital (N. Schmitz, M. Gramatzki); Leiden: University Hospital (F. Zwaan, W. Fibbe, J.H. Veelken); Lisbon: Ins. Portuges Oncologia (M. Abecasis, M. Abecasis); London: Harley Street clinic (P.J. Gravett), Royal Marsden Hospital (R. Powles, G. Helenglass, M. Potter), Royal Free Hospital (H.G. Prentice, S.

McKinnon); Munich: Ludwig Maximilian University Hospital (*H.J. Kolb, W.Hiddemann, J. Tischer*); Nijmegen: Sint Radboud Ziekenhuis (*T. de Witte, T. Schattenberg, N. Schaap*); Paris: Centre Hospitalier St. Antoine (*N.C. Gorin, L.Fouillard, M. Mohty*); Pessac: Centre Hospitalier (*J. Reiffers, N. Millpied*); Riyadh: King Faisal Hospital (*P. Ernst, M. Aljurf*); Rome: UniversitadegliStudi di Roma La Sapienza (*W. Arcese, P. de Fabritiis, R. Foa*); Santander: Hospital Nacional “Marques de Valdecilla” (*A. Iriando, C. Richard Espiga*); Vienna: Allgemeines Krankenhaus der Stadt Wien (*W. Hinterberger, P. Kahls*)

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