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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Clinical course and end-of-life care in patients who have died after allogeneic stem cell transplantation

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Abstract
Purpose Allogeneic stem cell transplantation may cure approximately 50% of patients, however, a significant part of the other half might benefit from a high-quality palliative care medicine at the end of life. Somatic, psychic and spiritual needs of these patients may differ from those of patients suffering from incurable solid tumours and are not comprehensively evaluated so far.
Methods To address this question, data from charts of 123 patients who have died after allogeneic stem cell transplantation were extracted. In detail, the time line of the clinical course, the symptoms, the administered drugs and other applied procedures were analysed.
Results Approximately one half of the patients, who have died after stem cell transplantation, did not live more than 5 months. Two-thirds of patients died within 14 months after SCT. 28.5% of the patients could not be discharged after transplantation. However, a significant proportion had a low ECOG-score (0–1) prior to death, indicating a high degree of mobility. Major symptoms were weakness, fatigue and need for aid at daily activities. Severe pain, dyspnoea and obstipation, as known from patients suffering from advanced solid tumours, were rare. In consequence, use of opioids seemed to be less frequent than in patients with solid tumours. Measures of intensive care and i.v.-drug administration were applied to a significant proportion of patients.
Conclusion The present investigation indicates that the somatic, psychic and spiritual end-of-life-care after allogeneic stem cell transplantation could be optimised. A significant problem for the transplantation team seems to be the realisation of necessity to switch the curative concept into a palliative ambition. Requirements are a subsequent prospectively conducted investigation and an intensification of cooperation between transplant and palliative care teams.

Keywords Allogeneic stem cell transplantation · Complications · End of life care · Palliative care

Introduction

Allogeneic stem cell transplantation (alloSCT) has made a variety of otherwise infaust diseases curable (Forman et al. 1999). The prognosis after alloSCT has improved substantially over the last decades and the development of the 'reduced-intense-conditioning' (RIC) or 'non-myeloablative conditioning' therapy protocols allows successful transplantation of elderly or heavily pre-treated patients (Niederwieser et al. 2003). In addition, introduction of a variety of drugs into supportive therapy led to a further improvement of prognosis. This includes antimycotic and antiviral therapy (Marr et al. 2002; Mora-Duarte et al. 2002; Yahav et al. 2009). In addition, improvement of molecular diagnostic facilitates early detection of rare or otherwise difficult to diagnose infections (Busemann et al. 2012). The identification of an

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appropriate stem cell donor is no problem in Europe since large registries have been established. The long-term outcome after alloSCT depends on a variety of factors such as underlying disease, donor's HLA-match, patient's age and performance and complications, e.g. manifestation of acute or chronic Graft-versus-Host disease (GvHD). Generally, there is a broad range of overall survival from >80% down to <10%. In general, for all patients, long-term survival after alloSCT has been reported for less than 50% (Gooley et al. 2010). Vice versa, from this fact, it can be clearly deduced that a significant proportion of the other half of all alloSCT patients might benefit from appropriate palliative care measures during their end of life period.

The most important element in the concept of alloSCT is a curative treatment approach under acceptance of considerable to life-threatening side effects and a substantially lowered quality of life for a limited period. In contrast to the common patients of standard intensive care units, patients undergoing an allogeneic transplantation start usually in a relative good healthy condition. The following treatment, however, is extremely physical and mental demanding, and associated with a considerable therapy related morbidity and mortality. In contrast, palliative care wants to control the symptoms of the illness and to preserve the best quality of life for the remaining lifetime of the patient (Joske and McGrath 2007). Both approaches seem to be very controversial. The staff of each discipline, SCT and palliative care, may not have the best opinion about the other group (Chung et al. 2009). However, even in the field of alloSCT, the symptom control has an irreplaceable role. Myeloablative conditioning may lead to a mucositis requiring a substantial analgesic therapy, graft-versus host disease can induce severe diarrhoea and damages of the integument (Deeg 2007). Nausea and vomiting under conditioning may be very intensive and need special prophylactic measures and a management by a dedicated team of experts (Bearman et al. 1989). In conclusion, the concepts of alloSCT and palliative care are not as controversial as it may seem at a first and unreflected view.

The most awesome situation for the patient after alloSCT is the break when it becomes evident that the clearly curative concept of transplantation needs to be abandoned and a palliative concept is necessary for further optimal management his disease. Even for the staff of the transplant program, it might be difficult to recognise this point of no return. Physicians, nurses and other professionals even have to abandon the curative concept and to accept that the patient will die from his disease or from related complications. In contrast to oncologists, taking care of patients suffering from solid tumours, there are publications suggesting that haematologists hesitate to switch the therapy goal to symptom control and to consult the palliative care team (Lafond et al. 2015; LeBlanc et al. 2015). To address the important question what means end of life care in alloSCT patients, we have retrospectively analysed the charts of 123 patients who have died after alloSCT in our unit.

Patients and methods

Demography, diagnoses and transplant procedure

A total of 239 patients underwent allogeneic stem cell transplantation (alloSCT) at Greifswald University Hospital from March 1999 until November 2013. The charts from 123 patients, who have died after alloSCT, were available for this investigation. Their median age at the time of transplantation was 53 (range 18–72) years. Major indications for alloSCT were acute leukaemias ($n = 49$, 39.8%), followed by aggressive non-Hodgkin's lymphomas ($n = 24$, 19.5%), myelodysplastic syndrome ($n = 12$, 9.8%), and chronic lymphocytic leukaemia ($n = 10$, 8.1%). Less than ten patients each suffered from multiple myeloma ($n = 9$, 7.3%), chronic myeloid leukaemia ($n = 8$, 6.5%), indolent non-Hodgkin's lymphomas ($n = 3$, 2.4%), Hodgkin's lymphoma, and myeloproliferative syndromes ($n = 2$, 1.6%, each). Two patients were allografted for solid tumours or other diagnoses, respectively. The median pre-treatment consisted of 5 (range 0–27) cycles of chemotherapy and the median Sorror-score was 3 (range 0–9), indicating a high-risk situation for at least 50% of patients (Table 1) (Sorror 2009; Späth et al. 2014).

41 patients (33.3%) were grafted in complete remission of the underlying disease. The other patients had a partial remission ($n = 30$, 24.4%), progress/relapse ($n = 46$, 37.4%), a chronic phase ($n = 5$, 4.1%) or refractory disease ($n = 1$, 0.8%) at time of transplantation.

Thirty-three patients (26.8%) were conditioned with a myeloablative protocol, 51 patients (41.5%) received a reduced-intense conditioning and 39 patients (31.7%) were prepared with a non-myeloablative protocol, according the classification by Bacigalupo et al. (2009). The reasons for choosing a reduced-intense or a non-myeloablative conditioning were mainly co-morbidities, an intensive pre-treatment or the patient's age. Additionally, in 69 cases (56.1%), antibody-mediated in vivo-T cell-depletion was compound of conditioning regimen (Finke et al. 2009). 32 patients (26%) were grafted from a matched related donor and 91 (74.0%) from an unrelated donor with at least a 7/8 or 9/10 match. A median of 5.7 (range 0.5–19.1) $\times$ 10^6 $CD34^+$ cells per kg were transplanted. GvHD-prophylaxis was cyclosporine-A, either in combination with short-course methotrexate or mycophenolate. Supportive therapy followed published standards. Regimen-related toxicity was low, and lethal toxicity did not occur (Tables 1, 2). Leukocytes engrafted with 1 cell/nl in 111 patients (90.2%). Thrombocyte engraftment occurred in 85 patients (69.1%)

Table 1 Patients characteristics

	N	%	Parameter	Median	Range
Demographics					
Gender					
Male	82	66.7	Age at SCT (years)	53	18–72
Female	41	33.3			

Diagnoses	*N*	%	Parameter	Median	Range
Diagnoses and pre-treatment					
AL	49	39.8	Preceding CTX regimen	3	0–11
Aggressive NHL	24	19.5	Preceding CTX cycles	5	0–27
MDS	12	9.8			
CLL	10	8.1	Preceding radiatio	*N* = 27	22%
MM	9	7.3	Preceding alloSCT[a]	*N* = 8	6.5%
CML	8	6.5			
Indolent NHL	3	2.4	Conditioning intensity	*N*	%
HL	2	1.6	MAC	33	26.8
MPS	2	1.6	RIC	51	41.5
Other	2	1.6	NMA	39	31.7
Solid tumours	2	1.6			

Sorror-score			
Median	3	≤2	61 (49.6%)
Range	0–9	>2	62 (50.5%)

Conditioning regimens are explained in the text

AL acute leukaemia, *NHL* non-Hodgkin's lymphoma, *MDS* myelodysplastic syndrome, *CLL* chronic lymphocytic leukaemia, *MM* multiple myeloma, *CML* chronic myeloid leukaemia, *HL* Hodgkin's lymphoma, *MPS* myeloproliferative syndrome (non-CML), *CTX* chemotherapy

[a] Only the last transplantation was considered in this analysis

with 20 platelets/nl and in 66 patients (53.7%) with 50 platelets/nl.

Complications, end of life care and palliative care

In case of complications, relapse or other clinical problems, the patients were re-assigned to our hospital, either as outpatients or inpatients, upon their medical needs. A dedicated palliative care unit was instituted in February 2011.

Palliative care assessment

Assessments during the end-of-life period, related problems and palliative care measures were done retrospectively by revision of the patient's charts using a HOPE-questionnaire (HOPE: hospice and palliative recording) to capture clinical problems and the MIDOS-questionnaire to capture the symptoms and their intensity (Schmidt-Wolf et al. 2013; Radbruch et al. 2000; Stiel et al. 2011). The symptoms were transferred into a semi-quantitative scale to facilitate analysis and to define a cumulative symptom index: No symptoms = 0, light = 1, moderate = 2 and severe = 3. Pancytopenia is rather a laboratory finding than a symptom; however, it was added because it is frequent in these patients and may lead to considerable problems. The authors are aware that HOPE-questionnaire has not been validated for a retrospective chart analysis. However, to ensure comparability with published investigations based on the HOPE-questionnaire, the authors decided to accept this limitation.

Additionally, the medication and measures were documented. Assessment points were the time of last stationary admission and one week prior to death or last discharge for final care.

Measuring points

Four measuring points were defined for palliative care assessment, performance state and for documentation of administered drugs: At discharge from the transplant ward,

Table 2 Toxicity, acute and chronic GvHD

Organ	Toxicity				
	0°	1°	2°	3°	4°
GI-tract	111 (90.2%)	9 (7.3%)	1 (0.8%)	2 (1.6%)	0
Bladder	120 (97.6%)	0	2 (1.6%)	1 (0.8%)	0
Skin	0	0	0	0	0
Cardiac	111 (90.2%)	3 (2.4%)	5 (4.1%)	4 (3.3%)	0
Liver	78 (63.4%)	30 (24.4%)	14 (11.4%)	1 (0.8%)	0
Lung	111 (9.2%)	3 (2.4%)	6 (4.9%)	3 (2.4%)	0
Mucosal	78 (63.4%)	16 (13.0%)	26 (21.1%)	3 (2.4%)	0
Renal	92 (74.8%)	19 (15.4%)	11 (8.9%)	1 (0.8%)	0
CNS	119 (96.7%)	2 (1.6%)	2 (1.6%)	0	0
Stage/grade	Acute graft-versus-host disease				
	0	1	2	3	4
Skin	86 (69.9%)	13 (10.6%)	11 (8.9%)	12 (9.8%)	1 (0.8%)
Liver	110 (89.4%)	4 (3.3%)	0	7 (5.7%)	2 (1.6%)
Gut	93 (75.6%)	9 (7.3%)	8 (6.5%)	8 (6.5%)	5 (4.1%)
Overall	86 (69.9%)	1 (0.8%)	13 (10.6%)	19 (15.4%)	4 (3.3%)

at last stationary admission, 7 days prior to death or discharge and at the time of death. When the patients were not discharged, the measure points were day +30 and half of time to the third point of assessment.

Data collection and Statistics

Special data sheets were used for extraction from charts. Data were transferred for electronical processing into MS-Excel (Microsoft, Munich, Germany) and analysed with WinStat for Excel (http://www.winstat.de). Statistical tests are mentioned within the results section where appropriate.

Results

Discharge and outpatient management

The last stationary admission of the patients was at median 3.9 months after allogeneic stem cell transplantation with a range from 3.4 months prior to 105.0 months after alloSCT. This wide span is related to the fact that 35 patients (28.5%) could not be discharged from hospital after alloSCT due to complications and that a part of patients proceeded directly from preceding conventional chemotherapy to transplantation. 88 patients were re-admitted, since they had been discharged to their home ($n = 83$, 67.5%), transferred to another hospital ($n = 3$, 2.4%) or to a medical stationary rehabilitation after in-patient stay for allogeneic transplantation (Table 3).

Table 3 Discharge and problems after discharge

Discharge from the SCT-unit			Chronic GvHD and affected organs		
	N	%		*N*	%
Discharge after alloSCT			cGvHD		
Secondary hospital	3	2.4	Overall	19	15.6
No discharge	35	28.5	Ltd./ext. disease	7/12	5.7/9.8
Home	83	67.5	Sicca syndrome	7	5.7
Stationary rehabilitation	2	1.6	Lung	1	0.8
			Skin	15	12.2
Other complications			Liver	3	2.4
Primary GF	14	11.4	Joints	0	0
Secondary GF	5	4.1	Mucosa	3	2.4
Relapse/progess	48	39.0	Wasting	6	4.9
Secondary malignancy	7	5.7			

GF graft failure

Palliative care concept vs. no palliative care concept

The analysis of the charts revealed a switch to a palliative care concept in 75/123 (61%) cases. The change to a palliative care concept was identified either by entries in the charts or when therapies with a curative approach were terminated. Neither the Sorror score nor the patient's age pre-SCT correlated this change.

Clinical performance score

Measuring points for the clinical performance according the ECOG-score were 'last admission' and '7 days prior to death or last discharge'. The median ECOG score increased from 1st to 2nd assessment from 2 (range 0–4) to 4 (same range). Fifty-one patients (64.9%) had an ECOG-score of 0 or 1 at first and 33 (26.8%) at the second assessment (Table 4). At first assessment, patients with a palliative care concept had a significantly higher ECOG-score compared to patients without [mean (CI) 2.1 (±0.2) vs. 1.5 (±0.2), $p < 0.001$; independent t test]. This was not valid for the second assessment [mean (CI) 2.5 (±0.4) vs. 2.7 (±0.5), n. s.; independent t test].

Symptoms

The leading symptom at the measuring point 'last admission' was weakness with an incidence of 48%, followed by 'need for aid' (53.9%) and pancytopenia (36.6%). 34.1% of the patients suffered from pain, in 16 cases (13%) each moderately and severely. Fatigue was seen in 38 cases (70.9%). Common symptoms in patients suffering from disseminated solid tumours, such as nausea, emesis dyspnoea and obstipation, were less frequent to nearly absent in the study group at the measure point 'last admission' (Table 4).

At the second measuring point, the symptom panel showed some differences compared to the first measuring. The incidence of moderate-to-severe pain decreased to 16.3% ($n = 20$). Free of weakness were 74 patients (60.2%) compared to 64 (52%) at the first assessment. Fatigue remained constant with presence in app. 30% of patients. The incidence of pancytopenia increased from 30.9 to 54.4%, and the need for aid at daily activities showed the strongest increase from 43.9 to 67.5%. Surprisingly, infections showed only an increase from 13.8 to 17.9%. The incidence of graft-versus-host disease problems remained constant with 11.4%. Emesis and obstipation at the end of life were only a problem in less of 10 patients, respectively (Table 4).

The cumulative symptom index was 6 (median, range 0–37) at the first and 8 (median, range 0–39 at the second assessment point. At first assessment, patients with a palliative care concept had a significantly higher symptom index compared to patients without [mean (CI) 9.1

Table 4 Symptoms at last inpatient admission and 7 days prior to last discharge or death

Time	Last admission				7 days before death or last discharge			
ECOG mean, (median/range)	1.8 (2, 0–4)				2.6 (3, 0–4)			
Symptom/intensity, *n* (%)	Absent	Mild	Moderate	Severe	Absent	Mild	Moderate	Severe
Pain	*81 (65.9)*	10 (8.1)	*16 (13.0)*	*16 (13.0)*	94 (76.4)	9 (7.3)	12 (9.8)	8 (6.5)
Nausea	105 (85.4)	4 (3.3)	14 (11.4)	0 (0)	107 (87.0)	4 (3.3)	9 (7.3)	3 (2.4)
Emesis	110 (89.4)	2 (1.6)	11 (8.9)	0 (0)	114 (92.7)	1 (0.8)	7 (5.7)	1 (0.8)
Dyspnea	99 (80.5)	4 (3.3)	12 (9.8)	8 (6.5)	95 (77.2)	9 (7.3)	10 (8.1)	9 (7.3)
Obstipation	121 (98.4)	1 (0.8)	1 (0.8)	0 (0)	118 (95.9)	3 (2.4)	2 (1.6)	0 (0)
Weakness	*64 (52.0)*	6 (4.9)	*36 (29.3)*	*17 (13.8)*	*74 (60.2)*	4 (3.3)	*24 (19.5)*	*21 (17.1)*
Poor appetite	*82 (66.7)*	6 (4.9)	*22 (17.9)*	8 (6.5)	100 (81.3)	1 (0.8)	*17 (13.8)*	5 (4.1)
Fatigue	*85 (69.1)*	9 (7.3)	*21 (17.1)*	8 (6.5)	*86 (69.9)*	8 (6.5)	10 (8.1)	19 (15.4)
Care problems (wounds, decubitus)	121 (98.4)	1 (0.8)	1 (0.8)	0 (0)	102 (82.9)	3 (2.4)	11 (8.9)	7 (5.7)
Need for aid (daily activities)	*69 (56.1)*	*28 (22.8)*	*17 (13.8)*	9 (7.3)	*40 (32.5)*	*17 (13.8)*	*23 (18.7)*	*43 (35.0)*
Depression	114 (92.7)	4 (3.3)	4 (3.3)	1 (0.8)	105 (85.4)	8 (6.5)	8 (6.5)	2 (1.6)
Anxiety	113 (91.9)	2 (1.6)	6 (4.9)	2 (1.6)	106 (86.2)	3 (2.4)	7 (5.7)	7 (5.7)
Strain	110 (89.4)	2 (1.6)	8 (6.5)	3 (2.4)	102 (82.9)	3 (2.4)	11 (8.9)	7 (5.7)
Disorientation/confusion	120 (97.6)	2 (1.6)	0 (0)	1 (0.8)	104 (84.6)	7 (5.7)	10 (8.1)	2 (1.6)
Patients care not ensured	122 (99.2)	1 (0.8)	0 (0)	0 (0)	117 (95.1)	5 (4.1)	1 (0.8)	0 (0)
Excessive demands of caregiver	119 (96.7)	2 (1.6)	2 (1.6)	0 (0)	112 (91.1)	4 (3.3)	5 (4.1)	2 (1.6)
Fever	93 (75.6)	7 (5.7)	12 (9.8)	11 (8.9)	94 (76.4)	6 (4.9)	9 (7.3)	*14 (11.4)*
Bleeding	119 (96.7)	4 (3.3)	0 (0)	0 (0)	107 (87.0)	7 (5.7)	3 (2.4)	6 (4.9)
Infection	106 (86.2)	3 (2.4)	11 (8.9)	3 (2.4)	101 (82.1)	2 (1.6)	8 (6.5)	12 (9.8)
GvHD	109 (88.6)	4 (3.3)	7 (5.7)	3 (2.4)	109 (88.6)	4 (3.3)	5 (4.1)	5 (4.1)
Pancytopenia	*78 (63.4)*	3 (2.4)	*29 (23.6)*	*13 (10.6)*	*67 (54.5)*	2 (1.6)	*26 (21.1)*	*28 (22.8)*

Fields are italicised, when symptoms were absent in less than 75% or were present in at least 10% of patients

(±1.5) vs. 4.4 (±1.3), $p < 0.01$; independent t test]. This was not valid for the second assessment [mean (CI) 9.8 (±2.0) vs. 8.6 (±2.6), n. s.; independent t test].

Drugs

At the measuring point 'discharge', more than 10% of patients, each, were treated with drugs from seven classes, as shown in Table 5. Medication consisted mainly of immunosuppressive agents, antimicrobial and antiviral prophylaxis. However, nearly ¾ of patients received proton pump inhibitors and more than 2/3 a cardiologic co-medication. The use of these drug classes was rather constant during the further course. The administration of strong opioids increased from 0.8 to 71.8% and the use of sedatives/anxiolytics from 8.9 to 37.4% at the time of death. The increases for some other drugs were even considerable but less impressive: steroids: 9.8% to maximal 36.6%, antiemetic drugs: 1.6–23.6%, laxatives: 3.3% to maximal 15.4%. The use of anti-infective drugs showed a slight decrease and immunosuppressive agents were given to only 20.3% of patients at the end of life. In general, more than 10% of patients each received drugs from 13 of 17 documented classes at the end of life (Table 5).

Measures at the end of life

A variety of measures were applied to the patients at their end of life as shown in Table 6. The performed measures at the end of life can be divided into common procedures within a palliative care concept, in uncommon measures and in measures which do not fit into a palliative care concept (intensive care procedures) (Table 6).

Common Common palliative care procedures are listed in Table 6. The majority of patients experienced companionship of their relatives.

Uncommon A considerable group ($n = 83$, 67.5%) received parenteral nutrition. In addition, in nine cases (7.3%) a new central venous line was inserted and in more than the half of patients an existing central venous line was cared by the staff. In consequence, the majority of patients ($n = 87$, 70.7%) received at least one drug intravenously. Ten patients (8.1%) experienced a bone marrow puncture as an invasive diagnostic measure at their end of life.

Intensive care More than 1/3 of patients were treated with artificial respiration in their final phase, either invasive or non-invasive. One patient was subjected to extracorporeal membrane oxygenation (ECMO). Circulatory support with catecholamine infusions was performed in 18 cases (14.6%).

Route of drug administration Opioids were chosen as the indicator drug for analysis of the route of

Table 5 Drugs at discharge after alloSCT, at last inpatient admission and 7 days prior to last discharge or death

Drug class	Discharge after alloSCT		Last admission		7 days prior to death/discharge		At time of death	
	N	%	*N*	%	*n*	%	*N*	%
Non-opioid analgesics	1	0.8	8	6.5	16	*13.0*	21	*17.1*
Opioids I	7	5.7	7	5.7	6	4.9	3	2.4
Opioids II	1	0.8	15	*12.2*	37	*30.1*	76	*71.8*
Co-analgesics	1	0.8	2	1.6	1	0.8	5	4.1
Steroids	12	9.8	25	*20.3*	45	*36.6*	38	*30.9*
Anti-depressive	7	5.7	13	*10.6*	9	7.3	8	6.5
Antiemetic	2	1.6	18	*14.6*	29	*23.6*	29	*23.6*
Neuroleptics	3	2.4	10	8.1	10	8.1	6	4.9
Sedatives/anxiolytics	11	8.9	17	*13.8*	30	*24.4*	46	*37.4*
Proton pump inhibitors	78	*73.4*	94	*76.4*	85	*69.1*	66	*53.7*
Laxatives	4	3.3	9	7.3	19	*15.4*	13	*10.6*
Antibiotics	79	*64.2*	70	*56.9*	68	*69.9*	68	*55.3*
Antifungals	84	*68.3*	74	*60.2*	75	*61.0*	53	*43.1*
Antivirals	56	*45.5*	45	*36.6*	59	*48.0*	33	*26.8*
Diuretics	17	*13.8*	18	*14.6*	54	*43.9*	32	*26.0*
Cardiologic	52	*42.3*	49	*39.8*	52	*42.3*	32	*26.0*
Immunosuppressive agents	84	*68.3*	32	*26.0*	51	*41.5*	25	*20.3*
Other (median, range)	2 (0–7)		2 (0–10)		4 (0–22)		2 (0–19)	

Percentages of ≥10 are italicised

Table 6 Measures at the end of life

Measure	*N* (%)	Measure	*N* (%)
Palliative care			
Enteral nutrition	83 (67.5)	Care of stoma/PEG	8 (6.5)
Parenteral nutrition	63 (51.2)	Enema	4 (3.3)
Chemotherapy	14 (11.4)	Multimodal analgesia	3 (2.4)
Radiotherapy	2 (1.6)	Terminal sedation	7 (5.7)
Surgery/endoscopy	20 (16.3)		
Red cell transfusion	76 (61.8)	Placing therapy	43 (35.0)
Platelet transfusion	67 (54.5)	Physiotherapy	69 (56.1)
Clotting factor substitution	18 (14.6)	Drugs i. v.	87 (70.7)
G-CSF	39 (31.7)	Drugs s. c.	21 (17.1)
Pleural puncture	6 (4.9)	Psychological care	20 (16.3)
Ascites puncture	3 (2.4)	Spiritual care	3 (2.4)
CSF puncture	6 (4.9)	Social work	12 (9.8)
BM aspiration	10 (8.1)	Companionship of family	85 (69.1)
CVL change/insertion	9 (7.3)	Caregiver instruction	5 (4.1)
Care of CVL	64 (52.0)	Outpatient hospice care	1 (0.8)
Urine catheter insertion	30 (24.4)		
Intensive care			
Non-invasive ventilation	19 (15.4)	Invasive ventilation	24 (19.5)
ECMO	1 (0.8)	Haemodialysis	21 (17.1)
Analgo-sedation	7 (5.7)	Catecholamine	18 (14.6)
Route of opioid application			
Orally/PEG	11 (8.9)	Intravenously	64 (52.0)
Subcutaneously	6 (4.9)	CADD	1 (0.8)
Transnasal/buccal	0 (0)	Transdermal	8 (6.5)

G-CSF granulocyte-colony stimulating factor, *CSF* cerebrospinal fluid, *BM* bone marrow, *CVL* central venous line, *ECMO* extracorporal membrane oxygenation

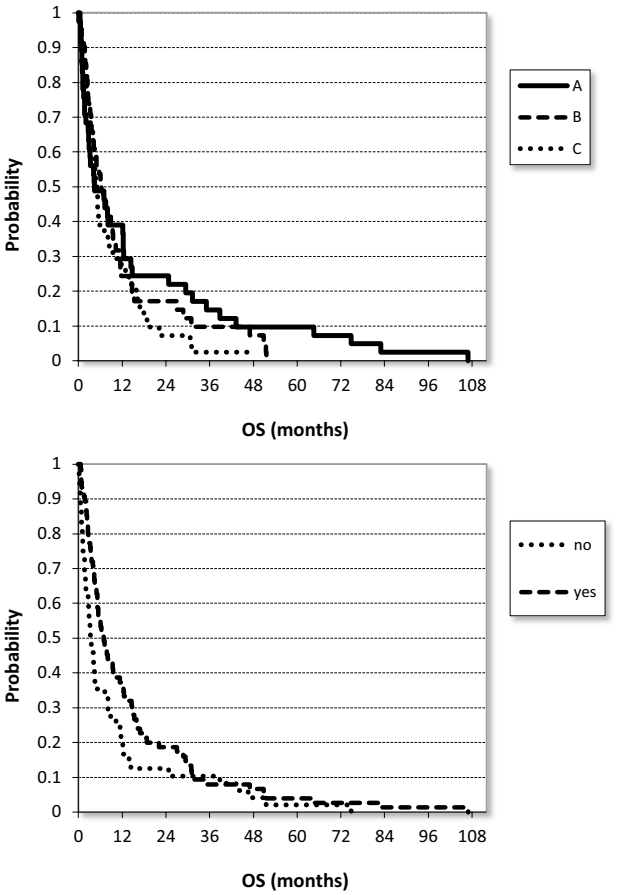

Fig. 1 Survival curves of 123 patients, who have died after allogeneic stem cell transplantation. *Top* survival of patients depending from the period of transplantation. *A* 1999–2004, *B* 2004–2008, *C* 2008–2012, ($n = 41$, each, n. s.). *Bottom* survival of patients with (yes, $n = 75$) and without (no, $n = 48$) a palliative care concept, $p = 0.049$ (log-rank test)

administration. Only 59 patients (48.0%) received the analgesics non-intravenously.

Time intervals and survival time

The patients were allografted 8.6 months (median, range 1.3–207.2) after primary diagnosis. Time between diagnosis and death was 19.1 (4.5–208.3) months. The median survival time of all patients, who have died after allogeneic transplantation, was 5.2 months (range 0.1–106.9) after alloSCT. 75% of the patients have died within 15 months after transplantation. To analyse, if the epoch influenced survival, the entire collective was divided into three parts of 41 patients, each. Differences in survival were not seen (Fig. 1). To discover possible differences between patients treated within an expressed palliative care concept compared to patients without, the survival of both groups were compared. The median overall survival of patients with a palliative care concept with 7.0 months (range 0.6–106.9), was significantly longer compared to patients without such a concept (median 3.6 months, range 0.1–74.8), $p < 0.05$, log-rank test (Fig. 1).

Death

Patients grafted in complete remission had a significantly lower risk for an early death after SCT within the first hundred days compared to those in non-CR [8/41 (19.5%) vs. 33/82 (40.2%); $p = 0.02$, Fisher's exact test]. Thirty-seven patients (30.1%) have died at the intensive care unit, followed by 29 patients (23.6%) at the transplant unit. Only 31 (25.2%) patients have died either at home, at the palliative care unit or at the hospice. Details are shown in Table 7.

Table 7 Final care and death

Diagnosis	*N*	%	Location	*N*	%
Cause of death			Place of death		
Relapse/progress	42	34.1	Intensive care unit	37	30.1
Septicaemia/multi-organ failure	31	25.2	Transplant ward	29	23.6
Pneumonitis	11	8.9	At home	23	18.7
Bleeding	7	5.7	Haematological ward	17	13.8
GvHD	5	4.1	Unknown	9	7.3
ARDS	4	3.3	Palliative care ward	5	4.1
Cardiac	4	3.3	Hospice	3	2.4
Toxoplasmosis	4	3.3			
Secondary malignancy	3	2.4			
Unknown	3	2.4			
EBV-LPD	2	1.6			
GF/MOF	2	1.6			
CMV-disease	1	0.8			
COPD	1	0.8			
Infection (other)	1	0.8			
Suicide	1	0.8			
TTP-HUS	1	0.8			

GvHD graft-versus-host disease, *GF* graft failure, *ARDS* acute respiratory distress syndrome, *MOF* multi-organ failure, *EBV-LPD* Epstein-Barr-virus associated lymphoproliferative disease

The reason for dying were infections in 50 patients (40.7%), followed by the relapse or progress of the underlying malignancy ($n = 42$, 34.1%). Seven patients (5.7%) have died from bleeding complications. Other reasons for death were seen in maximal 5% of patients, each. Three patients (2.4%) died from secondary malignancy and one patient committed suicide because of suspected secondary cancer (Table 7).

Discussion

This retrospective analysis was based on the revision of the charts of 123 patients who have died after allogeneic haemopoietic stem cell transplantation. Major goal of this investigation was the identification and description of specific problems and particular needs of the patient collective in the end-of-life phase. Finally, approaches to optimise the abrupt shift of the therapy objective and the patient care in their final phase will be discussed.

If a patient suffering from a solid tumour cannot be cured by surgery with or without subsequent adjuvant chemo- or radiotherapy, the therapy objective is, with some exceptions, primarily palliative (Van et al. 2016). However, antineoplastic therapies can lead to substantial prolongation of life in a considerable percentage of patients (Sievers et al. 2016). Patients with disseminated breast cancer or colorectal cancer, for instance, have a life expectancy of years under modern systemic therapy of their disease (Sievers et al. 2016; Zeichner et al. 2016). Thus, the time interval from the diagnosis to the end phase of an incurable malignancy is long enough to allow a psychical and mental processing parallel to the gradual somatic deterioration caused by the underlying disease in many cases. Patients are mainly at home. Despite the time interval from diagnosis to death in our investigation with a median 19.1 (4.5–208.3) months differs not necessarily from that of patients suffering from metastatic carcinomas, the therapy objective remains clearly curative until the failure of allogeneic transplantation becomes evident.

Our data show that 50% of patients dying after allogeneic stem cell transplantation will die within the first 6 months after transplantation and the vast majority dies within the first year. In this context, it should be mentioned that the time to process this dramatic shift is further shortened by the fact that the event that determines the palliative situation, the relapse of the underlying disease or another non-acute infaust complication, commonly does not occur within the first month after stem cell transplantation. Death by acute complications is excepted here. Patients grafted in non-CR were at higher risk for an early death within the first hundred days after SCT compared to those in CR. These high-risk patients could be having benefit from an early inclusion of a palliative care team into process of SCT.

In contrast to solid tumours, treatment and allogeneic stem cell transplantation of haematological cancer is mostly a long-term inpatient therapy, hospitalising the patients for several weeks to months. This is reflected by the observations that the last stationary admission was at the earliest 3.4 months before transplantation and that 28.5% of the patients could not be discharged after transplantation. Thus, mental and psychical processing is further aggravated, particularly, since a considerable proportion of patients cannot be visited by their relatives or caregivers each day.

From last admission to the last evaluation, the median ECOG-score increased from 2 to 3, however, both times with the same range from 0 to 3. The wide range of the ECOG score and the fact that more than one-fourth of patients had an ECOG-score of 1 and less at last assessment which shows 1st a broad variety in clinical performance and 2nd that a considerable part of alloSCT-patients is very active, even in the final phase of life.

Continuous clinical problems over the entire course patients were weakness, poor appetite, fatigue and need for aid at daily activities. Pain is a major problem in patients with disseminated solid cancers with an occurrence from ca. 70% in gastrointestinal and breast cancer up to 90% in lung cancer (Gencer et al. 2009; Irvin et al. 2011; Polanski

et al. 2016). It was a minor problem after allogeneic stem cell transplantation. Pain was absent in 2/3 of patients at last admission and in 23.6% at last assessment. Even nausea, emesis, dyspnoea and obstipation were infrequent.

Pancytopenia was more frequent. The incidence increased from 36.6% (1st assessment) to 45.5% (2nd assessment). However, moderate and severe bleedings occurred in only 9 patients (7.3%) at final assessment. Infections, another typical cytopenia-related problem, were evident in 17.9% of patients in the final phase. Furthermore, infections may have other reasons, such as GvHD. The clinical consequences of anaemia, such as weakness and fatigue, were frequent as discussed above; however, a clear relation to anaemia could not be identified due to the retrospective base of this investigation.

Moderate and severe Graft-versus-Host disease were a problem in 10 patients (8.1%) in the final phase. This is remarkable, since chronic GvHD is discussed as a major reason for non-relapse mortality in the literature (Horwitz and Sullivan 2006).

The use of drugs was evaluated at four measuring points, and showed an increase during the course. Drugs classes with a continuous use were antimicrobials, immunosuppressive agents and cardiologicals. Classes with an increase of use from the first to the last assessment point were analgesics, opioids and non-opioids, anti-depressive agents and anxiolytics. The use of laxatives increased only slightly to 10.6% at the last assessment. This is in accordance with the observation that obstipation is no major problem after SCT. In addition, the consumption of opioids seems to be generally lower after SCT than in advanced solid tumours, despite even after alloSCT an increase of use during clinical course was recognised as described for patients with solid tumours (Gagnon et al. 2015).

The application of measures of intensive care and the frequent intravenously application of drugs might be a hint that the shift from a curative to a palliative concept could be delayed in some patients, or in other words that the transplant physicians and the patients cannot react in a timely manner to the abrupt occurrence of an incurable situation. This might be improved by a closer cooperation of transplant and palliative care teams.

The survival of patients with a palliative care concept was longer, compared to patients without. This should not be interpreted as an effect of palliative care, rather in patients with a longer survival there could have been time enough to reflect the situation and to abandon the curative path in favour of palliative care.

Effects of the opening of the palliative care unit and the availability of a palliative care team from this time could not be extracted from the charts with this retrospective investigation.

In conclusion, this retrospective analysis shows that the time course from a curative to a palliative concept in patients after allogeneic stem cell transplantation differs considerably from that of patients with solid tumours. The shift is very abrupt and the course is remarkably shorter than in patients with solid tumours. A proportion of SCT-patients has no opportunity to be discharged from hospital and to spend time in their familiar surrounding at home before death. In consequence, the psychosocial and spiritual needs of SCT-patients may be different from those of classical palliative care patients (Roeland et al. 2010). The authors suggest the intensification of cooperation between transplant and palliative care team and related professional groups to allow a timely interdisciplinary reaction, if a patient cannot be cured anymore.

The present investigation furthermore revealed that somatic problems and the drug panel necessary for a sufficient symptom control shows differences to those of palliative care patients with solid tumours. The authors are aware that the presented results were extracted retrospectively from the charts and have in consequence limitations. A subsequent prospectively accompanying investigation of the end-of-life care after allogeneic stem cell transplantation is planned.

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Compliance with ethical standards

Conflict of interest No author has to declare any conflict of interest. The presented results were deduced from a non-interventional retrospective investigation.

Informed consent All patients gave their informed consent to allogeneic stem cell transplantation and to the evaluation of their anonymised treatment data.

Ethical consideration All clinical procedures were in accordance with the declaration from Helsinki.

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