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Initially fewer bloodstream infections for allogeneic *vs.* autologous stem-cell transplants in neutropenic patients

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SUMMARY

Chemotherapy and/or radiotherapy used as conditioning regimens before autologous or allogeneic haematopoietic cell transplantations (HCTs) cause neutropenia, which is the main reason for bloodstream infections. Autologous HCTs are considered to be superior to allogeneic HCTs in terms of infection outcome. A previous analysis suggested that patients with allogeneic HCTs are exposed to a reduced infection hazard and that an unfavourable infection outcome of allogeneic HCTs may be mediated through prolonged neutropenia. Therefore, we investigated whether allogeneic HCTs initially lead to fewer infections. We evaluated data from a prospective non-randomized multi-centre cohort study, with a total of 1616 patients. Of these, 703 patients received autologous and 913 patients received allogeneic HCTs from January 2000 to June 2004. The retrospective analysis used simultaneous confidence bands for the cumulative infection probability in the presence of competing risks. Patients with allogeneic HCTs experienced fewer infections during the early phase of neutropenia. As patients with autologous HCTs are not necessarily subject to antibiotic prophylaxis, a future study should investigate this policy. A limitation of the analysis is that it did not find the effect of crossing cumulative infection probabilities to be significant.

Key words: Competing risks, confidence bands, cumulative incidence function, hospital infection, neutropenia, peripheral blood stem-cell transplantation.

INTRODUCTION

Autologous and allogeneic haematopoietic cell transplantations (auto-HCTs, allo-HCTs) have become a successful therapy to cure patients with haematological malignancies [1]. However, due to conditioning regimens before HCTs, patients become neutropenic [2]. Neutropenia is a condition characterized by a low count of neutrophils, a type of white blood cells. White blood cells are the cells that primarily avert infections. The occurrence of bloodstream infection (BSI) during neutropenia constitutes a severe

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complication [3]. Allo-HCTs are considered to lead to more infections [4].

Analysing the impact of a potential risk factor such as the transplant type on subsequent BSI outcome must account for so-called competing risks [5, 6]. Competing risks describe a situation where the time until some first event and the type of that first event are investigated [7]. That is, patients may either acquire BSI during neutropenia or neutropenia ends without prior BSI or patients may die during neutropenia without prior BSI. This implies that the effects of the transplant type on BSI, on the end of neutropenia without prior BSI, and on death during neutropenia without prior BSI need to be analysed. It is worthwhile to point out the relevance of this approach: ignoring competing risks may produce misleading results [6, 8], but studies do not always account for the presence of different event types [9].

We used data from the surveillance system ONKO-KISS [KISS – Hospital Infection Surveillance System (www.nrz-hygiene.de)], a prospective non-randomized, multi-centre cohort study, which provides reference data and assesses risk factors for the occurrence of BSIs and pneumonia during neutropenia in patients with hematological malignancies [10]. ONKO-KISS is part of the surveillance programme of the German National Reference Centre for Surveillance of Nosocomial Infections.

Our study does not aim to investigate mortality during neutropenia. This is justified by both the overall low mortality during neutropenia *without prior BSI* and the fact that the occurrence of BSI is a well known risk factor for subsequent death [11–13].

The original data analysis [14] was performed using the Fine–Gray regression model which directly models the cumulative infection probability [15]. The analysis found a non-significant higher probability of BSI with allo-HCTs. A statistical paper [16] suggested that patients with allo-HCTs were, in fact, exposed to a reduced BSI hazard but also to an even more dominantly reduced end-of-neutropenia (without prior BSI) hazard. An increase in the number of infected patients could therefore only be the result of a considerably prolonged phase of neutropenia during which patients were exposed to an only slightly reduced BSI hazard. However, such an increased number of infections would not occur initially but only eventually.

The aim of this paper is to investigate in a retrospective analysis whether there is significant evidence in the ONKO-KISS data that allo-HCTs initially lead to fewer infections. In order to study this question, we analyse simultaneous confidence bands for the cumulative infection probability [5, 17, 18]. For illustrative purposes only, we supplement this with a standard Cox analysis of the cause-specific hazards (see part II of Klein *et al*. [19]). We note that if allo-HCTs initially lead to fewer BSIs, this would motivate future investigations of preventive measures such as antibiotic prophylaxis.

MATERIAL AND METHODS

Settings and study population

At the time of the original analysis [14], the ONKO-KISS database comprised 1616 patients with haematological malignancies who had undergone auto-HCT or allo-HCT from January 2000 to June 2004 and who were eligible for our analysis.

The stem cell source of the transplant graft for all patients was peripheral blood. Of the 1616 patients, 319 (19·7%) acquired BSI during neutropenia. Neutropenia was defined as an absolute white blood cell count $<1\times10^9/1$ and ended with a blood cell count $>1\times10^9/1$ for $\geqslant2$ consecutive days. For 1280 (79·2%) patients, neutropenia ended without prior BSI. Observation ceased during neutropenia without preceding BSI for 17 (1·1%) patients who were administratively censored. End of neutropenia without prior BSI was typically reached alive; only 20 (1·2%) patients died during neutropenia without prior BSI.

Allo-HCTs were performed on 913 (56·5%) patients. There were 703 (43·5%) patients that received an auto-HCT. BSI was acquired by 193 (21·1%) allo-HCT patients and 126 (17·9%) auto-HCT patients.

This ONKO-KISS Surveillance Project was approved by the Institutional Review Board of the University Medical Centre Freiburg, Germany, which waived the need for informed patient consent, and is registered in the German Clinical Trial Register (ID DRKS00000331).

Statistical analysis

Figure 1 illustrates the competing risks situation [7]. Patients enter state 0 (see Fig. 1) after transplantation, i.e. become neutropenic. The aim of the analysis is to investigate the time until subsequent BSI during neutropenia. Patients who acquire BSI during neutropenia make a $0\rightarrow1$ transition at the time of infection. Patients who leave neutropenia without prior infection make a $0\rightarrow2$ transition when neutropenia ends. Patients who die during neutropenia without

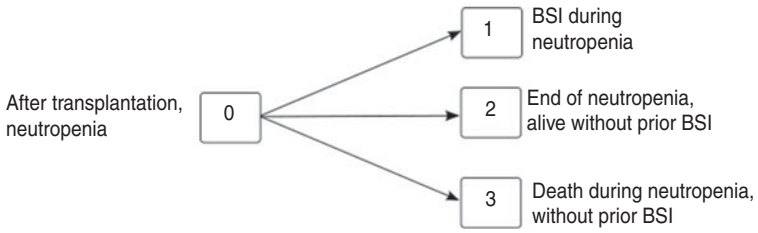

Fig. 1. Competing risks multistate model for the occurrence of bloodstream infection (BSI) during neutropenia.

prior infection make a 0→3 transition at the time of death.

Let T denote the waiting time a patient spends in the initial state 0. That means T is the time until BSI, until the end of neutropenia without prior infection, or until death during neutropenia without prior infection, whichever occurs first. Let ε denote the type of that first event, i.e. the competing risks. The occurrence of BSI is denoted by $\varepsilon = 1$, end of neutropenia without prior BSI is denoted by $\varepsilon = 2$, and death during neutropenia without prior BSI is denoted by $\varepsilon = 3$.

We note that our model does not make any assumption about independence or dependence of the competing risks [8, 20]. As the aim is to investigate the cumulative BSI probability, end of neutropenia without prior BSI, and death during neutropenia without prior BSI (event types 2 and 3) may – technically – be combined into one single endpoint. This is further justified as follows: only 1·2% of the patients were observed to die during neutropenia without prior BSI, as reported above. As a consequence, the interpretation of preceding analyses focused on the endpoints BSI and end of neutropenia [10, 14, 16].

The target statistical quantity of our analysis is the cumulative incidence function (CIF) of BSI. The CIF of BSI denotes the expected proportion of patients at time t who acquired BSI during neutropenia.

The aim is to compare the CIFs of the transplant groups. More specifically, we wish to investigate whether the CIF for allo-HCTs runs below the CIF for auto-HCTs for early days of neutropenia.

We employed a generalization of the Kaplan–Meier estimator to multiple states (see Figure 1), i.e. the so-called Aalen–Johansen estimator for estimating the CIF within transplant groups [21]. Log-log transformed 95% confidence intervals can be constructed for the Aalen–Johansen estimator of the CIF based on approximate normality of the estimator, but these confidence intervals are only pointwise. This means that if we consider two (or even more) time points, there is no guarantee that both confidence intervals cover the true quantities with an overall probability of 95%. This is a multiplicity problem and in general the overall coverage probability will be less than 95%.

The present analysis has a more challenging aim. We wish to find a region, a so-called band, over a prespecified time interval with the following property: the difference of the CIFs of the two transplant types lies within this region with a probability of 95%. This question is not addressed by pointwise confidence intervals but by simultaneous confidence bands.

Analytical solutions for calculating confidence bands are only available in the absence of competing risks [22]. We therefore employed a simulation technique developed for the competing risks situation [17]. We considered the time interval from days 1 to 20 in neutropenia. As illustrated in previous analyses [14], the infection CIFs reached a plateau after day 20. The difference between the CIFs was weighted as in the standard log-rank test [22]. That is, for each day the weight was the product of the risk sets in each group divided by the sum of these risk sets.

For illustration, we supplemented the primary analysis using confidence bands for the difference of the CIFs between transplant group with univariate and multivariate Cox models for the so-called cause-specific hazards [22]. The cause-specific hazards can be thought of as momentary forces of transition moving along the arrows in Figure 1.

Following Meyer *et al.* [14], the multivariate analyses included as additional risk factors female gender, early or late stage of acute myeloid leukaemia (AML), early or late stage of myelodysplastic syndrome (MDS), and early or late stage of Non-Hodgkin's lymphoma (NHL). Results of these analyses for transplant status were illustrated using Nelson–Aalen estimates of the cumulative cause-specific hazards [22].

RESULTS

Previous analyses [16] of the ONKO-KISS data suggested that a major side-effect of allo-HCTs is prolonged duration of neutropenia and

Table 1. *Cox analyses of the cause-specific hazards*

Risk factor	Cause-specific hazard ratios with pointwise 95% confidence intervals for endpoints	
	BSI ($n=319$)	No BSI during neutropenia ($n=1280$)
Univariate analysis		
Allogenic-HCT	0·79 (0·62–0·99)	0·28 (0·25–0·31)
Multivariate analysis		
Allogenic-HCT	0·70 (0·54–0·91)	0·28 (0·25–0·32)
Female gender	0·71 (0·56–0·90)	1·08 (0·97–1·21)
AML (early stage)	1·14 (0·82–1·57)	0·93 (0·79–1·10)
AML (late stage)	1·56 (1·15–2·13)	0·74 (0·61–0·88)
MDS (early stage)	0·41 (0·13–1·30)	1·20 (0·85–1·69)
MDS (late stage)	0·56 (0·14–2·26)	0·90 (0·53–1·53)
NHL (early stage)	0·93 (0·57–1·52)	1·00 (0·80–1·27)
NHL (late stage)	0·62 (0·40–0·95)	0·86 (0·72–1·02)

BSI, Bloodstream infection; HCT, haematopoietic cell transplantation; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; NHL, Non-Hodgkin's lymphoma.

immunosuppression. During the prolonged neutropenia, patients are exposed to an only slightly reduced BSI hazard. This is confirmed in Table 1 and Figure 2. Table 1 lists cause-specific hazard ratios for the two endpoints BSI and end of neutropenia, respectively, and the corresponding pointwise 95% confidence intervals. The effect of allo-HCTs found in the univariate analysis is similar to those of the multivariate analysis. The univariate analysis is illustrated in Figure 2 using cumulative cause-specific hazard plots estimated by the Nelson–Aalen estimator.

Figure 3 depicts the CIF for patients with allo-HCTs and auto-HCTs for BSI together with their pointwise 95% confidence intervals (95% CI). The estimated cumulative incidences for BSI at day 20 were 0·198 (95% CI 0·173–0·225) and 0·175 (95% CI 0·149–0·206) for allo-HCT and auto-HCT patients, respectively. The median time from transplantation to any first event, i.e. BSI during neutropenia or end of neutropenia without prior BSI, or death during neutropenia without prior BSI, whichever occurs first, was 14 days (95% CI 14–15) for patients with allo-HCTs and 8 days (95% CI 8-8) for patients with auto-HCTs, respectively. Figure 3 shows that during an initial time (days 0–14) the CIF of BSI of the allo-HCT group increases later than the CIF of BSI of the auto-HCT group. By the time the CIFs have reached their plateaus (day 20), the CIF of BSI of the allo-HCT group lies above the CIF for the auto-HCT group, i.e. indicates eventually more cases of BSI in allo-HCT patients compared to auto-HCT patients with. Figures 2 and 3 are confined for the time interval (0–20 days) because the estimated CIFs for BSI reach a plateau after day 20 [16].

The primary aim of the present analysis is to answer the question whether there is significant evidence in the ONKO-KISS data that allo-HCT initially leads to a smaller number of patients with BSI. This research question must be addressed by simultaneous confidence bands.

Figure 4 displays the estimated CIF for BSI in the autologous group minus the estimated CIF for BSI in the allogeneic group together with a simultaneous 95% confidence band. Figure 4 is the final analysis. The band confines a region over the time interval from 1 to 20 days within which the difference of the CIFs lies with a probability of 95%. This region is strictly positive for days 5–9 which verifies our original objective: the ONKO-KISS data provides significant evidence that allo-HCTs initially lead to fewer BSI. We note that the absolute differences of Figure 4 are at most 0·044, but interpretation of these numbers must bear in mind that the probabilities in Figure 3 are at most 0·021.

However, Figure 4 also illustrates that the confidence band becomes rather wide after day 10. This pattern, which is a result of the ambitious aim of a confidence band analysis, implies that the present analysis does not yield significant evidence that the CIFs for BSI cross.

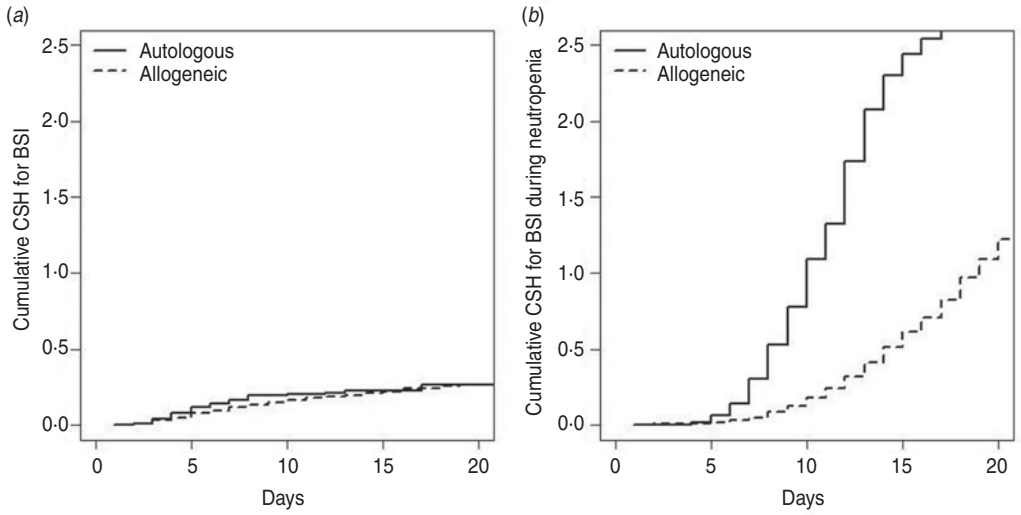

Fig. 2. Nelson–Aalen estimates of the cumulative cause-specific hazards (CSH) within the transplant group. BSI, Bloodstream infection.

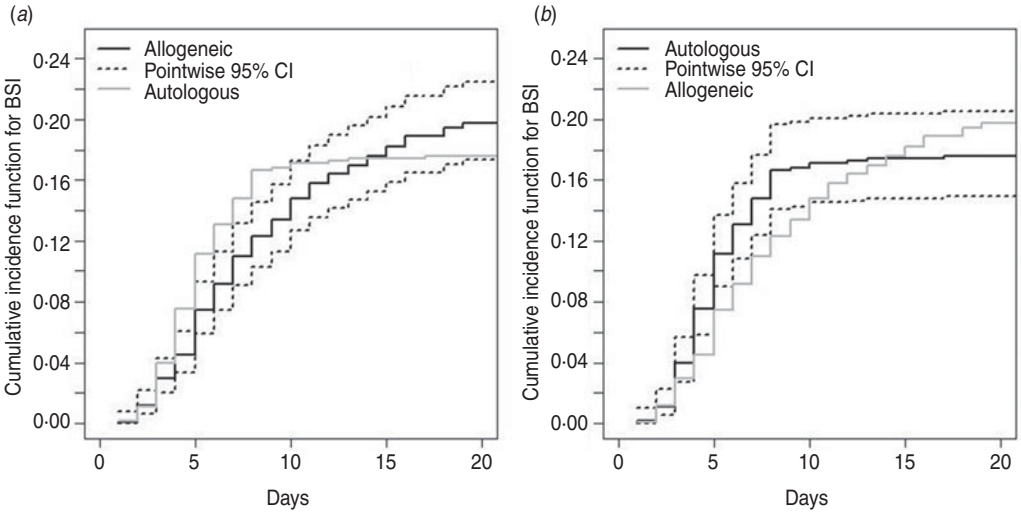

Fig. 3. Aalen–Johansen estimates and pointwise 95 % confidence intervals (CI) of the cumulative bloodstream infection (BSI) probabilities within the transplant group.

DISCUSSION

Allo-HCTs are generally considered to lead to more BSI cases in patients undergoing peripheral blood stem-cell transplantation [4]. For the data in the present paper it appears that an unfavourable infection outcome was mainly mediated via prolonged neutropenia in the presence of a slightly reduced infection hazard. Our retrospective analysis, based on simultaneous confidence bands, shows that an increased probability of BSI with allo-HCT was not uniform in time, but that allo-HCT patients displayed fewer BSI cases than auto-HCT patients in early days of neutropenia. That is, we found significantly fewer BSI cases for allo-HCTs during days 5–9 as shown Figure 4. However, the approach using simultaneous confidence bands did not yield significant evidence that the CIFs for the two transplant groups cross as the confidence band becomes rather wide after day 10. This pattern is a result of the ambitious aim of a confidence band analysis. In other words, our approach was successful in answering the medical research question at hand, but it was not successful in re-establishing the otherwise well acknowledged fact that allo-HCT leads to (eventually) more BSIs.

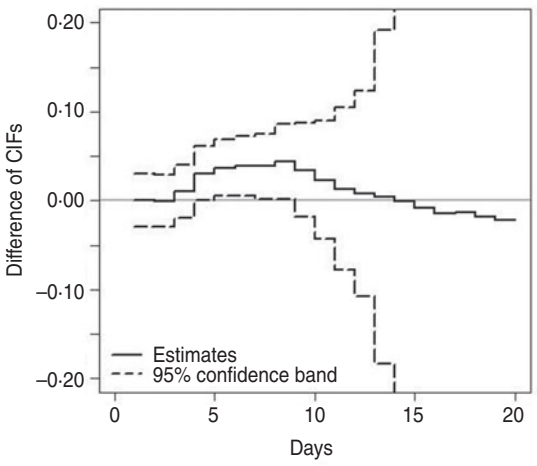

Fig. 4. Difference of the Aalen–Johansen estimates of the cumulative bloodstream infection probabilities between the autologous and allogeneic groups and simultaneous 95% confidence band. CIF, Cumulative incidence function.

Patients with allo-HCTs are routinely subject to antibiotic prophylaxis but this is not necessarily the case for patients with auto-HCTs. It is therefore a logical question to ask whether there is an interaction between auto-HCTs and the policy of antibiotic prophylaxis. Unfortunately, we had only partial knowledge about whether this policy was adhered to in the participating centres and about the timespans that each centre had contributed to the study. We performed a preliminary analysis of the cause-specific hazards in which we also included an interaction term 'auto-HCT' × 'no prophylaxis'. This preliminary analysis indicated that part of the reducing effect of allo-HCTs on the BSI hazard may be due to the routine antibiotic prophylaxis. Although this is preliminary and uses only partial information, this analysis aims to motivate future prospective collection of data on antibiotic prophylaxis. This would allow refining of the supplementary Cox analyses in Table 1, which, in turn, would be useful for discussing a future policy of antibiotic prophylaxis in auto-HCT patients.

A further restriction of the present analysis is its retrospective nature. While ONKO-KISS is a prospective cohort study, the preceding analyses [14, 16] used more standard proportional hazard-type analyses [15]. It was precisely through these analyses that the current investigation based on confidence bands was motivated. We also note that Figure 2*b* suggests a non-proportional effect of allogeneic transplantation on the cause-specific hazard for end of neutropenia. As a consequence, the hazard ratio in Table 1 describes an average effect. However, it must be emphasized that the crossing cumulative BSI probabilities are not a consequence of a violation of the proportional hazards assumption, but due to the different magnitudes of the cause-specific hazards in Figure 2(*a*, *b*) and the different effect sizes of the transplant type within these panels.

It is the aim of future research to evaluate the findings of the present paper in a prospective study. Such a study may use new data from ONKO-KISS, which is part of an ongoing infection surveillance programme. A crucial issue in planning such an analysis is calculating the sample size [23, 24]. A further limitation of the study is the fact that only limited and partial data were available on death after BSI and were therefore not further analysed. It is conceivable that not all BSIs carry the same mortality risk, and therefore it would be worthwhile to further study mortality after BSI. Unfortunately, the present database does not provide this information. However, the aim of ONKO-KISS is to provide reference data and to assess risk factors for the occurrence of BSI during neutropenia – the study does not aim to investigate mortality during neutropenia. ONKO-KISS is an ongoing project and it currently collects information on mortality after BSI which we plan to analyse in a future report.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S0950268812000283.

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DECLARATION OF INTEREST

None.

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