Brief Report

CLINICAL TRIALS AND OBSERVATIONS

The impact of health care settings on survival time of patients with chronic myeloid leukemia

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Key Points

- CML patients enjoyed superior survival chances when treated in THs.
- Treatment centers having less experience with CML patients did not affect the patient's survival chances.

With the introduction of tyrosine kinase inhibitors, the treatment of chronic myeloid leukemia (CML) patients has migrated extensively to municipal hospitals (MHs) and office-based physicians (OBPs). Thus, we wanted to check whether the health care setting has an impact on outcome. Based on 1491 patients of the German CML Study IV, we compared the outcomes of patients from teaching hospitals (THs) with those from MHs and OBPs. Adjusting for age, European Treatment and Outcome Study (EUTOS) score, Karnofsky performance status, year of diagnosis, and experience with CML, a significant survival advantage for TH patients (hazard ratio: 0.632 respectively 0.609) was found. In particular, when treated in THs, patients with blast crisis showed a superior outcome (2-year survival rate: 47.7% vs 22.3% vs 25.0%). Because the impact of the health care setting on the outcome of CML patients has not been reported before, these findings need confirmation by other study groups. This trial was registered at www.clinicaltrials.gov as #NCT00055874. (*Blood*. 2014;123(16):2494-2496)

Introduction

With the advent of tyrosine kinase inhibitors (TKIs), the treatment of chronic myeloid leukemia (CML) has profoundly changed. Not only have prognosis and quality of life of CML patients improved remarkably, but treatment is widely considered to be less complex. As a consequence, medical treatment of CML patients has migrated steadily from teaching hospitals (THs) to municipal hospitals (MHs) and especially to office-based physicians (OBPs). Although the proportion of the first has declined from 50% in earlier studies to 36%, the percentage of the latter has increased from 6% to 23%. Although this closer-to-home care may be considerably more convenient for the patients, it may be accompanied by therapeutic disadvantages too. The question of whether academic medicine brings an added value has already been the topic of debates in the past,[1] but to our knowledge, it has never been investigated for CML. Thus, the aim of this work was to analyze if patients at THs have a survival advantage in comparison with patients that are treated in MHs or at OBPs.

Study design

The study sample consisted of the patients from the German CML Study IV.[2] The study is conducted in agreement with the Declaration of Helsinki and has been approved by the Medizinische Fakultät Mannheim der Universität Heidelberg and by local ethics committees of participating centers. Out of 1551 patients randomized, 13 did not match the inclusion criteria, 2 withdrew informed consent during the first days, and 45 could not be considered because of missing covariates. Thus, 1491 patients were evaluable. For details on study design, patients' characteristics, and outcomes, see previous work by Hehlmann et al.[3]

Every study center was classified into 1 of 3 categories: TH, MH, or OBP. In Germany, the treatment is either hospital based (either THs or MHs) or office based. THs are run directly by universities. All THs and most MHs have a specialized hematologic or oncological unit, but at least a division of internal medicine. The OBPs in this study are either hematologists or oncologists too. The number of patients enrolled in the CML Study IV was used as a proxy measure for experience with CML patients with 3 categories: 1-9, 10-19, and 20 or more patients recruited.

Survival times were calculated starting with the date of diagnosis. Patients were censored at the date of last observation unless they had already died. Cox models were estimated to assess the impact of study center type and experience with CML. The models were adjusted for the following covariates: European Treatment and Outcome Study (EUTOS) score prognostic group,[4] calendar year of diagnosis, age at diagnosis, and Karnofsky performance status (KS). The frequencies of the covariates are shown in Table 1 (second column). Additionally, a random center effect was included (frailty model), and the models were stratified according to randomized treatment.

Results and discussion

The proportion of high-risk patients was fairly similar in the 3 groups (13% at THs, 12% at MHs, and 10% at OBPs), but OBP patients had a significantly better KS. TH patients were significantly younger

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Table 1. Multivariate Cox model for survival

Variable	n (%)	HR	95% CI	P
Institution				
TH	532 (35.7%)	0.633	0.414-0.966	.034
MH	618 (41.4%)	1		
OBP	341 (22.9%)	1.038	0.691-1.560	.857
Experience				
1-9 patients	561 (37.6%)	0.788	0.505-1.230	.293
10-19 patients	424 (28.4%)	0.809	0.521-1.255	.343
20+ patients	506 (33.9%)	1		
EUTOS				
Low risk	1312 (88.0%)	1		
High risk	179 (12.0%)	1.854	1.190-2.889	.006
Age at diagnosis	median: 52 (range: 16-88)	1.044	1.030-1.058	<.001
Year of diagnosis		0.954	0.876-1.039	.277
KS				
0-80	280 (18.8%)	1		
>80 to <100	421 (28.2%)	1.194	0.775-1.838	.421
100	790 (53.0%)	0.735	0.475-1.135	.165

Frequencies (second column) and results of the multivariate Cox model (third to fifth columns). The reference categories were MH, 20+ patients, EUTOS low risk, and KS 0-80.

CI, confidence interval; HR, hazard ratio.

(median age at diagnosis: 50) than MH patients (median: 53) and OBP patients (median: 54; both P values <.001).

When considering experience, no noteworthy differences were seen with regard to KS and EUTOS score. Patients at the most experienced hospitals were younger (median: 51) than patients at medium and less experienced hospitals (median: 53, both).

The overall survival of our sample is shown in Figure 1a. After a median observation time of 5.6 years, there were 149 deaths. As expected, age was the most important predictor in the multivariate Cox model for survival. EUTOS high-risk patients had a significantly higher mortality than low-risk patients (HR: 1.854). However, because patients treated at a TH had a lower risk of death, the type of the study center was important too. The HR of TH patients was 0.633 (95% CI: 0.414, 0.966; P = .034) when compared with MH and 0.609 (95% CI: 0.363, 1.024; P = .060) when compared with OBP. We could not find a significant influence on survival for either experience or year of diagnosis. The results of the model are summarized in Table 1 (third to fifth columns).

When the model was stratified for treatment, only minor changes were observed. A random center effect was not significant and thus was omitted.

Based on 73 patients who had suffered from a blast crisis (see Figure 1b), there were hints that survival after blast crisis was much better when the patient had been originally treated at a TH (p[TH vs MH] = 0.015; p[TH vs OBP] = 0.012). After 2 years, survival was 47.7% (95% CI: 28.4% to 67.4%), whereas for the MH and the OBP patients it was 22.3% (8.9% to 39.7%) respectively 25.0% (7.6% to 48.3%).

We could not find significant differences concerning the use of second-generation TKIs, although THs seemed to treat patients slightly more frequently with second-generation TKIs. After 5 years, the cumulative incidences of being treated with a second-generation TKI were 18.6% (95% CI: 15.2% to 22.3%), 14.3% (11.5% to 17.4%) respectively 14.1% (10.5% to 18.4%).

During the first year, TH patients had significantly more molecular evaluations (mean: 2.71) than MH (2.50, P = .033) and OBP (2.3, P = .001) patients.

We found a tendency for more reported adverse events (AEs) in TH patients. In a Cox model for the time to first AE while still under imatinib treatment, HR for MH vs TH was 0.958 (0.822-1.116), whereas it was 0.860 (95% CI: 0.715-1.035) for OBP vs TH. It may be that this finding is just attributable to better reporting because the average numbers of documented AE forms per year were somewhat higher for TH with 3.5 vs 3.3 vs 2.8.

Our data indicate a survival advantage for CML patients treated initially at a TH compared with those that were treated at an MH or OBP. This finding even held when adjustments for age, KS and EUTOS score, and year of diagnosis were considered. In contrast, we could not find any hint that more experience with CML patients led to better survival probabilities. It may be argued that the number of patients enrolled by a center was not a suitable marker for its experience because centers may gain experience during a study and may rather be inexperienced when treating the first patients. However, results were fairly similar when the center experience was judged with the data of earlier studies of our study group (CML III and IIIA). Besides, numbers of patients in the current and in earlier studies were highly correlated. Furthermore, year of diagnosis was included in the model to take this potential bias into account.

Usually, TH patients are overrepresented in clinical trials, whereas OBP patients are underrepresented compared with standard care, which limits the generalizability of the results of clinical trials. Given the results of our study and assuming that <50% of all CML patients in Germany are treated within clinical trials, the outcome of
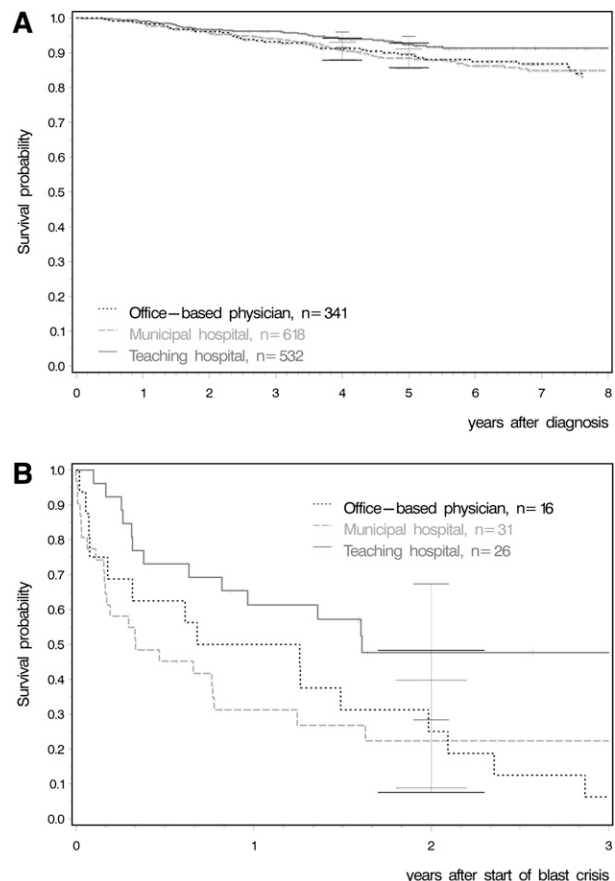
Figure 1. Survival according to institution type after diagnosis (A) and start of blast crisis (B).

CML treatment on a population level may be considerably compromised. There might be a slight bias in favor of OBPs because it is probable that these investigator physicians were a positive selection by being more interested in CML. The patients' choice of being treated in a TH might be a manifestation of their more serious attitude toward the disease. Thus, it cannot be ruled out that these patients might, for example, be more compliant.

Papanikolaou et al,[5] who conducted a systematic review of 132 studies on the impact of health care settings, did not report an overall impact on outcome. Considering breast cancer, however, they reported a significantly better survival for TH patients. In Germany, Klimm et al[6] analyzed center effects in the treatment of Hodgkin lymphoma but found no influence of the type of hospital or of the treatment experience.

Our analyses had not been planned a priori in the study protocol, so the results have to be interpreted with caution. In addition, the sample size did not allow splitting our data set into learning and validation samples. Because the differences in the outcomes seen here are not negligible, further research should try to replicate such an analysis in an independent data set and explore potential reasons for the observed differences.

Authorship

Contribution: R.H. collected the data; M.L. performed the analysis; J.H. designed the research; and all authors analyzed and contributed to the interpretation of the results and wrote the paper.

Conflict-of-interest disclosure: All authors work in the medical faculty of a university. R.H. has received research funding from Novartis and has a consultancy with Bristol-Myers Squibb.

For a complete list of German CML Study Group participants, see the supplemental Appendix available on the *Blood* Web site.

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