The impact of allogeneic stem cell transplantation on the natural course of poor-risk chronic lymphocytic leukemia as defined by the EBMT consensus criteria: a retrospective donor versus no donor comparison†

I. Herth1, S. Dietrich1, A. Benner2, U. Hegenbart1, M. Rieger1,3, P. Stadtherr1, A. Bondong1, T. H. Tran4, R. Weide5, M. Hensel1,6, W. Knauf7, J. Franz-Werner8, M. Welslau9, M. Procacciante10, M. Görner11, J. Meissner1, T. Luft1, S. Schönland1, M. Witzens-Harig1, T. Zenz1,12, A. D. Ho1 & P. Dreger1*

1Department Medicine V, University of Heidelberg, Heidelberg; 2Division of Biostatistics, German Cancer Research Center, Heidelberg; 3Private Hematology and Oncology Practice, Mannheim; 4Private Oncology Practice at the Agaplesion Hospital Bethanien, Frankfurt; 5Private Oncology Practice, Speyer; 6Private Practice for Hematology, Oncology and Diabetology, Aschaffenburg; 7Private Practice for Hematology, Oncology and Infectiology, Karlsruhe; 8Municipal Hospital and Private Oncology Practice, Bielefeld; 9Department of Translational Oncology, National Center for Tumor Diseases (NCT), University of Heidelberg and German Cancer Research Center (DKFZ), Heidelberg, Germany

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Background: In a single-center retrospective donor versus no-donor comparison, we investigated if allogeneic stem cell transplantation (alloSCT) can improve the dismal course of poor-risk chronic lymphocytic leukemia (CLL).

Patients and methods: All patients with CLL who were referred for evaluation of alloSCT within a 7-year time frame and had a donor search indication according to the EBMT criteria or because of Richter’s transformation were included. Patients for whom a matched donor could be found within 3 months (matches) were compared with patients without such a donor (controls). Primary end point was overall survival measured from the 3-month landmark after search initiation.

Results: Of 105 patients with donor search, 97 (matches 83; controls 14) were assessable at the 3-month landmark. Matches and controls were comparable for age, gender, time from diagnosis, number of previous regimens, and remission status. Disregarding if alloSCT was actually carried out or not, survival from the 3-month landmark was significantly better in matches versus controls [hazard ratio 0.38, 95% confidence interval (CI) 0.17–0.85; P = 0.014]. The survival benefit of matches remained significant on multivariate analysis.

Conclusion: This study provides first comparative evidence that alloSCT may have the potential to improve the natural course of poor-risk CLL as defined by the EBMT criteria.

Key words: CLL, alloSCT, donor

*Correspondence to: Dr Peter Dreger, Department of Medicine V, University of Heidelberg, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany. Tel: +49-6221/56-8008; E-mail: peter.dreger@med.uni-heidelberg.de
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introduction

There is accumulating evidence that allogeneic hematopoietic stem cell transplantation (alloSCT) with reduced-intensity conditioning (RIC) can be an effective treatment of chronic lymphocytic leukemia (CLL) and may provide long-term disease control in otherwise poor-risk disease as defined by clinical or biological indicators [1–6]. However, the information available to date about the efficacy of RIC alloSCT is entirely derived from uncontrolled phase II trials. Although the results of these trials are very suggestive, it is unclear to what extent alloSCT indeed can impact the natural history of the patient population with aggressive CLL, and what its overall clinical value for the treatment armory of CLL might be.

Comparative studies addressing this question are sparse. A small case–control series showed that survival from first treatment indication was significantly better in patients undergoing alloSCT during the course of their disease than in controls who were matched for age and time to first treatment but were not transplanted [7].

Here, we present the first donor versus no-donor comparison in CLL. Based on a patient sample meeting homogeneous criteria for high-risk disease, we analyzed if alloSCT can improve the outcome of poor-risk CLL if measured in a population with transplant indication rather than in patients who already have undergone transplantation. The results—albeit preliminary—suggest that alloSCT may prolong the survival of patients with aggressive CLL as defined by the European Group for Blood and Marrow Transplantation (EBMT) criteria [8, 9].

patients and methods

study design and patient eligibility

Included in this retrospective single-center analysis were consecutive patients who were referred to the University of Heidelberg for evaluation of alloSCT for treatment of CLL between June 2005 and June 2012. Patients were recommended to have a donor searched if they were 70 years or younger, otherwise eligible for alloSCT, and if they had a history of Richter’s transformation or met at least one of the three EBMT consensus criteria. The EBMT consensus criteria for poor-risk CLL justifying consideration of alloSCT include symptomatic disease with a p53 abnormality, fludarabine-refractory disease, and early relapse after intensive pretreatment [8]. The study population consisted of all patients who agreed to donor search, had a compatible donor found within 3 months, and were alive 3 months after start of donor search. A compatible donor was defined as a 10 of 10 or 9 of 10 high-resolution human leucocyte antigene (HLA-) matched related or unrelated donor. The control population consisted of all patients for whom no compatible donor was identified within 3 months after start of search (irrespective of a possible donor identification and alloSCT later on), and who were alive at the 3-month landmark.

Primary end point was overall survival (OS) calculated from the 3-month landmark after start of donor search. All patients gave written informed consent to donor search, the scientific evaluation of the data generated subsequently to donor search, and to alloSCT if applicable. Data analysis was approved by the Institutional Review Board.

definitions

Fludarabine-refractory disease was considered to be present in patients with nonresponse or relapse within 6 months after the last cycle. An early relapse was defined as relapse after intensive treatment such as fludarabine, rituximab (FR); fludarabine, cyclophosphamide, rituximab (FCR); pentostatin, cyclophosphamide, rituximab (PCR); bendamustine, rituximab (BR); or rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) later than 6 months but within 2 years. A p53 abnormality was defined by a deletion or mutation of the TP53 gene on chromosome 17 [10]. For HLA matching the HLA loci A, B, C, DRB1, and DQBI were analyzed. Both antigen and allele mismatches were counted against 10/10 identity.

statistical analysis

Kaplan–Meier product-limit estimates were used to assess the probability of OS and progression-free survival (PFS). Events for OS were defined as death from any cause. Events for PFS were defined as relapse, progression, or death from any cause, whatever came first. Median follow-up was estimated using the reverse Kaplan–Meier estimate [11]. Survival curves were compared using log-rank tests. Fisher’s exact test was used to compare categorical factors between groups of patients. For continuous variables, the Mann–Whitney test was applied. For multivariate analysis of OS from the 3-month landmark, a stratified Cox proportional hazard model was carried out using EBMT risk categories as strata. For multivariate analysis of OS of all patients with donor search, calculated from search initiation, a stratified Andersen–Gill model [12] was applied to account for alloSCT as time-dependent intervention, again using EBMT risk categories as strata. For assigning individual patients to an EBMT risk category, a hierarchical procedure was followed by giving p53 abnormalities priority over fludarabine refractoriness and early relapse after intensive therapy, and fludarabine refractoriness priority over early relapse after intensive therapy. If the patient had a history of Richter’s transformation, he was assigned to the Richter’s transformation category irrespective of the presence of the other three risk factors. Calculations were done using GraphPad Prism software (release 5.0; San Diego, CA), and the statistical computing language R (version 2.15.2: R Foundation for Statistical Computing, Vienna, Austria). Significance levels were set at 0.05. Data were analyzed as of 12 September 2012.

results

patient flow and donor search results

Altogether 137 patients met the eligibility criteria for this study. After exclusion of three patients in whom the diagnosis of CLL could not be confirmed, an indication for donor search initiation according to the EBMT consensus criteria was seen in 113 (84%) of the 134 remaining patients (Figure 1). Since five patients refused search, one turned out to have limiting comorbidities, and two patients were lost to follow-up at this stage, donor search was actually started in 105 patients. Within 3 months after start of donor search, six patients died because of progressive disease (PD), one patient refused alloSCT, and one additional patient was lost to follow-up, leaving 97 patients assessable for donor search results at the 3-month landmark. For 83 (86%) patients of these, donor search was successful, while for 14 (14%) patients, a compatible donor could not be found within 3 months. There were no significant differences between patients with and without a donor in terms of age, gender, stage, time from diagnosis, number of previous treatment regimens, and remission status at referral, but the proportion of patients...
Figure 1. Patient flow (alloSCT, allogeneic stem cell transplantation; f/u, follow-up; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, progressive disease).

Table 1. Patient characteristics at referral (N = 134)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Yes</th>
<th>No</th>
<th>Donor search indication (=EBMT risk or Richter’s)</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>113</td>
<td>21</td>
<td>83</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54 (37–70)</td>
<td>50 (38–67)</td>
<td>0.17</td>
<td>53 (39–69)</td>
<td>54 (37–64)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>83 (73)</td>
<td>16 (76)</td>
<td>0.80</td>
<td>60 (72)</td>
<td>12 (86)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (27)</td>
<td>5 (24)</td>
<td></td>
<td>23 (28)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Binet stage at diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>30 (34)</td>
<td>6 (35)</td>
<td>1.0 (A versus B+C)</td>
<td>20 (32)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>B</td>
<td>49 (56)</td>
<td>9 (53)</td>
<td></td>
<td>34 (55)</td>
<td>10 (77)</td>
</tr>
<tr>
<td>C</td>
<td>9 (10)</td>
<td>2 (12)</td>
<td></td>
<td>8 (13)</td>
<td>0</td>
</tr>
<tr>
<td>n.a.</td>
<td>25</td>
<td>4</td>
<td></td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Time from diagnosis (years)</td>
<td>4.0 (0.4–27.1)</td>
<td>5.4 (0.1–14.9)</td>
<td>0.68</td>
<td>3.7 (0.4–27.1)</td>
<td>3.2 (0.8–8.4)</td>
</tr>
<tr>
<td>Previous regimens, n</td>
<td>2 (0–8)</td>
<td>1 (0–4)</td>
<td>&lt;0.0001</td>
<td>2 (0–8)</td>
<td>2 (1–6)</td>
</tr>
<tr>
<td>Remission status at referral, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/PR</td>
<td>14 (12)</td>
<td>4 (19)</td>
<td>0.0002 (Refract. versus others)</td>
<td>12 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Untreated relapse</td>
<td>57 (50)</td>
<td>11 (52)</td>
<td></td>
<td>45 (54)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Refractory to last regimen</td>
<td>42 (37)</td>
<td>0</td>
<td></td>
<td>26 (31)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>No treatment ind. yet</td>
<td>0</td>
<td>6 (29)</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HCT-CI at referral, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>92 (81)</td>
<td>19 (90)</td>
<td>0.53 (0 versus &gt;0)</td>
<td>69 (83)</td>
<td>13 (93)</td>
</tr>
<tr>
<td>1</td>
<td>11 (10)</td>
<td>2 (10)</td>
<td></td>
<td>9 (11)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>4 (4)</td>
<td>0</td>
<td></td>
<td>2 (2.5)</td>
<td>0</td>
</tr>
<tr>
<td>&gt;2</td>
<td>6 (5)</td>
<td>0</td>
<td></td>
<td>3 (3.5)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>EBMT risk (hierarchic), n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Richter’s</td>
<td>6</td>
<td>0</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>p53 abnormality</td>
<td>40</td>
<td>0</td>
<td></td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Fludarabine refractory</td>
<td>42</td>
<td>0</td>
<td></td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>Early relapse</td>
<td>25</td>
<td>0</td>
<td></td>
<td>20</td>
<td>1</td>
</tr>
</tbody>
</table>

CR, complete remission; HCT-CI, hematopoietic cell transplantation comorbidity index; PR, partial remission.
meeting hierarchical risk category 3 (fludarabine refractory) was significantly higher in the no-donor group (Table 1).

Sixty-three of the 83 (76%) patients with positive donor search were actually transplanted (supplementary Table S1, available at Annals of Oncology online). Twenty patients (24%) did not proceed to transplantation because of disease progression (eight), refusal (five), donor health problems (three), emerging comorbidities (two), toxicity of the salvage therapy (one), or were waiting for transplant at the time of data cutoff for this analysis (one). On the other side, 6 of the 14 (43%) patients of the no-donor group were subsequently transplanted with donors identified later than 3 months (3) or donors with more than one mismatch (two donors with two mismatches and one donor with three mismatches). These six patients were counted for the no-donor group in all landmark evaluations.

outcome

No follow-up was available for three patients with search indication and five patients without indication. OS of the 110 patients with search indication for whom follow-up was available was 68% [95% confidence interval (CI) 59% to 78%) at 2 years from referral and, thus, inferior to the 93% (95% CI 82% to 100%) survival of the 16 assessable patients without search indication (hazard ratio 2.3, 95% CI 0.98–5.39; P = 0.054; supplementary Figure S1, available at Annals of Oncology online).

With a median follow-up of 28 months, 2-year survival of the 83 patients for whom a compatible donor could be identified within 3 months was 78% (95% CI 69% to 88%) compared with 55% (95% CI 34% to 90%) in the 14 patients without such a donor (Hazard ratio 0.38, 95% CI 0.17–0.85; P = 0.014; Figure 2A). Estimated median survival in the no-donor group was 30.6 months, but not reached in the donor group. There

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Figure 2. Survival from 3-month landmark (A) by donor availability; (B) by donor availability and actual transplantation status.
was no significant survival difference between the three EBMT risk categories, but patients with Richter's syndrome did significantly worse ($P = 0.046$). The survival benefit of patients with a donor remained significant after multivariate adjustment for possible prognostic covariates stratified for EBMT risk categories (Table 2). The only other variable significantly predicting (unfavorable) OS from the 3-month landmark was a high number of pretreatment lines, whereas age and remission status at referral had no significant impact. The risk reduction conferred by having a donor did not change when those four patients who had an indication but refused donor search and were followed up for three months or more were included in the donor group (hazard ratio 0.34, 95% CI 0.17–0.70; $P = 0.002$; supplementary Figure S2, available at *Annals of Oncology* online). Multivariate Andersen–Gill modeling to account for alloSCT as time-dependent intervention also confirmed the favorable effect of alloSCT in the donor group on OS (supplementary Table S2, available at *Annals of Oncology* online). Causes of death are summarized in (supplementary Table S3, available at *Annals of Oncology* online).

Two-year survival of those patients of the donor group who actually were transplanted was 88% (95% CI 80% to 97%; $n = 63$) and, thus, significantly superior over the 2-year survival of those patients who did not manage to proceed to alloSCT (38%, 95% CI 20% to 75%; $n = 20$). The hazard ratio was 0.12 (95% CI 0.04–0.32; $P < 0.0001$) (Figure 2B). Two-year PFS from the 3-month landmark of the 63 allografted patients of the donor group was 62% (95% CI 50% to 78%). In contrast, the six patients who subsequently underwent alloSCT in the no-donor group did not have a significantly different risk of dying compared with those eight patients who were not allografted (hazard ratio 0.79, 95% CI 0.21–2.99; $P = 0.72$).

### discussion

Although alloSCT is a recommended treatment option for eligible patients with poor-risk CLL [8, 9, 13], to date there is no evidence from comparative studies that alloSCT is indeed superior to alternative nontransplant treatments, and there is no information about the chances of proceeding to transplant once these poor-risk criteria are met. Apart from the case–control series already mentioned [7], a survival advantage of alloSCT over nontransplant strategies in patients with relapsed CLL was concluded from a systematic meta-analysis using a Markov decision model [14]. Owing to its virtual design, however, this type of study has substantial limitations.

Against this background, we aimed at providing comparative evidence for the potential superiority of alloSCT over alternative strategies in poor-risk CLL by performing a retrospective donor versus no-donor study. Similar to data obtained in other hematological malignancies [15, 16], the results consistently show that having an HLA-compatible related or unrelated donors indeed can at least halve the mortality of poor-risk CLL, and that the beneficial effect of having a donor is entirely due to the superior outcome of those patients who actually can undergo alloSCT (Figure 2B). The only other variable significantly affecting survival was extensive pretreatment (Table 2 and supplementary Table S2, available at *Annals of Oncology* online), highlighting the necessity of referring patients with transplant indication to specialized centers early.

However, this study has several limitations. Apart from the drawbacks of the retrospective design, the selection bias inherent to referral for transplant, and the fact that this is one single analysis from a single center, it is obvious that the ‘control arm’ is relatively small. Nevertheless, with a median OS of 30 months, the outcome of the no-donor group is within the range reported for pharmacological treatments in patients with poor-risk CLL [17–21]. Similar to some of these trials [18, 21], our no-donor group contained a proportion of patients who were finally transplanted with mismatched and/or ‘late’ grafts. However, this subset had no negative impact on the outcome of the no-donor group and actually contained the only long-term disease-free survivors in the control group. Accordingly, the significant survival difference between donor and no-donor group remained when the allografted subset was excluded from the no-donor group (supplementary Figure S3, available at *Annals of Oncology* online). Moreover, extending the control group to those patients who were otherwise eligible but refused donor search even strengthened the significance of the survival benefit of the donor group. Finally, multivariate Andersen–Gill modeling to account for alloSCT as time-dependent intervention also confirmed the favorable survival effect of alloSCT from a donor meeting the eligibility criteria of this study.

Another point to consider is that the outcome of the actually transplanted patients in the donor arm was relatively good with 2-year OS and PFS of 88% and 62%, respectively. An explanation for this may be a favorable patient selection because patients with higher comorbidity score were virtually absent from both the donor and the no-donor group. However, all other patient characteristics were not apparently different from those reported for the prospective studies [1–6]. Furthermore, besides a positive effect of center experience [22], disease control in the transplanted patients might have been improved by the aggressive MRD-driven immune modulation employed in our institution albeit this has not been investigated systematically yet [23]. Finally, the exclusion of potentially unfavorable mismatched or delayed donors caused by the landmark design of the present study could have contributed to the good results of our allografted patients.

On the other hand, strengths of our study are (i) the consistent use of the EBMT criteria as an accepted standard for poor-risk CLL defining the eligibility for inclusion, (ii) a valid control group restricted to transplant-eligible patients meeting these criteria, and (iii) the landmark approach for excluding deaths before donor search termination from the analysis in order to avoid imbalances disadvantaging the no-donor group. Moreover, another unique feature of the present study is its intent-to-treat

### Table 2. Multivariate Cox proportional hazards model of OS from the 3-month landmark stratified for EBMT risk category ($n = 97$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>Lower CL</th>
<th>Upper CL</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor (yes)</td>
<td>0.36</td>
<td>0.14</td>
<td>0.89</td>
<td>0.026</td>
</tr>
<tr>
<td>Previous therapies $&gt;2$</td>
<td>2.67</td>
<td>1.19</td>
<td>6.02</td>
<td>0.018</td>
</tr>
<tr>
<td>Age (10-year increment)</td>
<td>0.63</td>
<td>0.37</td>
<td>1.08</td>
<td>0.093</td>
</tr>
<tr>
<td>Refractory at referral</td>
<td>1.07</td>
<td>0.44</td>
<td>2.60</td>
<td>0.88</td>
</tr>
</tbody>
</table>
design, allowing for the first time to determine the proportion of patients with CLL in a defined high-risk setting who actually are capable of proceeding to alloSCT. This figure (which was exactly 60% here) has to be taken into account when the real effect of alloSCT on the prognosis of poor-risk CLL is calculated, implying that the survival probability of the 105 patients for whom search was started (and thus were intent-to-transplant) was 51% (95% CI 34% to 65%) at 5 years after start of search.

It is intriguing that the survival of the donor group was at no time inferior to that of the no-donor group, implying that the superior disease control provided by allografting is never counteracted by the NRM risk associated with alloSCT. This notion is further substantiated by the fact that mortality due to CLL progression before intended transplant was higher than transplant-related mortality in this high-risk selection.

In summary, this study provides the first comparative evidence that alloSCT indeed can significantly improve the prognosis of transplant-eligible patients with poor-risk CLL as defined by the EBMT criteria. Although limited by its retrospective character and the fact that this is just one single analysis from a single CLL-experienced transplant center, this study may serve as blueprint and rationale for validation in multicenter settings. Such efforts would be particularly important in the light of upcoming new treatment options for poor-risk CLL, namely novel agents targeting the B-cell signaling pathway [24]. Although B-cell receptor kinase inhibitors such as ibrutinib and idelalisib as well as BCL-2 antagonists show promising response rates in poor-risk CLL [24–26], it remains to be shown if these novel tools may alter the definition of high-risk CLL justifying alloSCT indication.

funding
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disclosure
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Final results of phase II trial of doxorubicin HCl liposome injection followed by bexarotene in advanced cutaneous T-cell lymphoma

D. J. Straus¹, M. Duvic², S. M. Horwitz¹, K. Hymes³, A. Goy⁴, F. J. Hernandez-Ilizaliturri⁵, T. Feldman⁴, B. Wegner¹ & P. L. Myskowski⁶

¹Department of Medicine, Division of Hematologic Oncology, Lymphoma Service, Memorial Sloan-Kettering Cancer Center, New York; ²Department of Dermatology, Division of Internal Medicine, M.D. Anderson Cancer Center, Houston; ³Department of Medicine, Division of Hematology, New York University Medical Center, New York; ⁴Division of Lymphoma, Hackensack University Medical Center, Hackensack; ⁵Department of Medicine, Roswell Park Cancer Institute, Buffalo; ⁶Department of Medicine, Dermatology Service, Memorial Sloan-Kettering Cancer Center, New York, USA

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Background: High response rates for doxorubicin HCl liposome injection (DLI) in cutaneous T-cell lymphoma (CTCL) have been reported with vague criteria until recently. Approximately 50% of CTCL patients respond to bexarotene (Bex).

Patients and methods: A phase II trial was carried out to clarify the true overall response rate (ORR) for DLI and to assess the role of sequential Bex. Patients were treated with DLI 20 mg/m² i.v. every 2 weeks for 16 weeks (8 doses) followed by 16 weeks with Bex 300 mg/m² orally. Response assessments were carried out after 16 weeks (DLI) and 32 weeks (Bex). Skin responses were measured by the modified Severity-Weighted Assessment Tool (mSWAT) and the Composite Assessment of Index Lesion Severity (CA).

Results: Thirty-seven patients were treated: stage IV (22, 8 with Sézary syndrome), IIB (10), earlier stage refractory to skin-directed therapies or radiation therapy (5). For 34 assessable patients: ORR 14/34 [41%: partial response (PR) 12, clinical complete response (CCR) 2]. Maximum responses were all seen after 16 weeks DLI. Median progression-free survival (PFS) was 5 months. There were 22 deaths: 21 of disease and 1 of heart failure. Twenty-seven grade 3 and 5 grade 4 toxic events were observed.

Conclusion(s): With strict criteria, DLI ORR is among the highest reported for single agents in CTCL. Sequential Bex did not increase the response rate or duration.

Clinical trial number: NCT00255801.

Key words: doxorubicin HCl liposome injection, bexarotene, cutaneous T-cell lymphoma

introduction

Cutaneous T-cell lymphoma (CTCL) is a rare heterogeneous group of non-Hodgkin lymphomas which respond to many systemic agents but are not curable. Most responses are partial and rarely continue after cessation of treatment.

Doxorubicin is one of many single chemotherapeutic agents active in CTCL [1]. Doxorubicin HCl liposome injection (DLI), which has reduced cardiac toxicity, is approved for treatment of AIDS-related Kaposi’s sarcoma and is highly concentrated in the skin [2]. Reported overall response rates (ORRs: complete response [CR] + partial response [PR]) for DLI as a single agent have ranged from 56% to 88% and CR rates from 20% to 44% without strictly defined response criteria [3–6]. Bexarotene (Bex) is a synthetic retinoid that targets the RXR receptor on CTCL cells [7]. The ORR for Bex in refractory early-stage [8] and late-stage [9] CTCL is ~50%, and it is approved in the United States for this indication.