Bendamustine is effective in T-Cell prolymphocytic leukaemia

T-cell prolymphocytic leukaemia (T-PLL) is an aggressive T-cell neoplasm with a mature post-thymic T-cell phenotype. Most patients present with markedly elevated leucocyte counts, splenomegaly, lymphadenopathy, hepatomegaly, skin lesions, pleuropertitoneal effusions or central nervous system involvement (Matutes et al, 1991). The most frequent chromosome abnormalities in T-PLL are inv(14)(q11q32), t(14;14)(q11;q32) or the less common t(X;14)(q28;q11) (Maljaei et al, 1998). Activation of TCL1A or MTCP1 via the inv(14)/t(14;14) or t(X;14) respectively, are thought to be the primary genetic events in T-PLL. Frontline, high response rates have been reported with intra-venous alemtuzumab (Dearden et al, 2001). After 4 months of therapy, consolidation with stem cell auto- or even allo-transplantation is recommended whenever feasible. Various purine analogues have been used for front line therapy with limited efficacy (Mercierca et al, 1994). Sequential chemoimmunotherapy based on fludarabine, mitoxantrone and cyclophosphamide induction followed by alemtuzumab consolidation (FCM+A) also seems to offer an alternative to alemtuzumab alone (Hopfinger et al, 2013). Still, with current treatment options, outcomes remain poor, with early relapses and a median survival time of 20 months (Dearden, 2012). Bendamustine is an original alkylating agent that shows only partial cross-resistance with other DNA-binding anticancer agents and no cross-resistance with other alkylating agents. Bendamustine is widely used in the treatment of indolent B-cell lymphomas, including chronic lymphocytic leukaemia (CLL). Two studies have focused on the effect of bendamustine in refractory or relapsed mature T cell neoplasms (Damaj et al, 2013; Zaja et al, 2013) showing encouraging response rates and acceptable toxicity. To our knowledge, only three T-PLL treated by bendamustine have been reported to date. Here, we report the largest series of T-PLL managed with bendamustine in frontline and relapse settings.

In this multicentre retrospective study, 15 patients with a diagnosis of T-PLL according to World Health Organization criteria (Herling et al, 2004) were treated by bendamustine

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)*</th>
<th>Prior therapy</th>
<th>Best response to prior therapy</th>
<th>WCC* (CD4/CD8)**</th>
<th>Immunophenotype (x 10^9/l)</th>
<th>Dose (mg/m²)/cycle (n)</th>
<th>Response to Bendamustine</th>
<th>PFS (months)</th>
<th>Status, cause of death</th>
<th>OS (months)</th>
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<td>Alive</td>
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</table>

CD, cluster of differentiation; M, male; F, female; A, alemtuzumab; D, dexamethasone; R, revlimid; F, fludarabine; DHAC, dexamethasone cytarabine carboplatin; CR, complete response; PR, partial response; NR, no response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; WCC, white blood cell count; PD, progressive disease.

*At the time of bendamustine treatment.
†All patients were CD2^+, CD7^+, CD3^-.
between 2009 and 2013. Approval of this study was obtained from the local Institutional Review Board of the Regional Hospital and of Lille and was in accordance with the declaration of Helsinki. Seven patients received bendamustine after frontline alemtuzumab failure (three non-responders, four relapsed), two were treated after multiple therapies and six patients were treated by bendamustine frontline (after good response rates were observed prior to relapse). Table I summarizes baseline characteristics of the patients. Median age at T-PLL diagnosis was 62 (range: 45–86) years; 73% of patients were male. Thirteen patients had successful cytogenetic analysis, all karyotypes were complex (≥3 abnormalities). Seventy-nine percent of cases had chromosome 14 abnormalities (15% t(14q11)(14q32); 30% inv(14)(q11q32); 23% t(Xq28;14q11)). Del(11q) and del(17p) were found in 50% and 38%, respectively. Bendamustine was given intravenously (70–120 mg/m²/d over 30–60 min, days 1 and 2, every 3 weeks) for an intended total of six cycles. Prophylactic antibiotics (including anti-virals) were used in addition to bendamustine. Sixty percent of patients had received a prior therapy, which always included alemtuzumab (Table I). Responses to previous treatment were poor with a 5 months median (range 2–24) progression-free survival (PFS). Responses were evaluated on clinical and haematological data, including bone marrow aspiration. Detection of minimal residual disease by flow cytometry and polymerase chain reaction (PCR) was not included in the response criteria. PFS and overall survival (OS) were plotted according to Kaplan–Meier product-limit method and calculated from the beginning of bendamustine therapy to the occurrence of T-PLL relapse or death, respectively.

After bendamustine treatment, three patients (20%) achieved complete response (CR) and five patients (33.3%) partial response (PR), for an overall response rate (ORR) of 53.3%. The median PFS was 5 months (Fig 1A) and the median OS was 8.7 months (Fig 1B). PFS and OS were not correlated to alemtuzumab exposure, line of treatment (Fig 1C, D), karyotype or clinical features. The

Fig 1. Kaplan–Meier curve showing the PFS (A) and the OS (B) in 15 T-PLL patients treated with bendamustine. Patients’ status at bendamustine initiation (frontline or relapse) did not modify PFS (C) or OS (D), while response rate influenced both PFS (E) and OS (F). T-PLL, T-cell prolymphocytic leukaemia; PFS, progression-free survival; OS, overall survival.
patients with at least PR had a longer PFS (Fig 1E) and OS (Fig 1F) than those who did not respond (logrank \( P = 0.001 \) and \( P = 0.01 \) respectively). A trend toward a shorter PFS was found in patients with CD4+/CD8+ immunophenotype (logrank \( P = 0.07 \)). Two patients managed to proceed to autologous and two others to allogeneic bone marrow transplantation. Median daily bendamustine dosage was 100 (70–120) mg/m². Four out of six patients (67%) who received bendamustine 120 mg/m², responded. In contrast, only 4/9 (44%) patients who received bendamustine 100 mg/m² or less were responders. Interestingly, two of the three patients who were refractory to the last prior treatment regimen, responded to bendamustine (CR = 1, PR = 1) with a duration of response of 13 and 27 months, respectively. Among the six patients who received bendamustine as first line therapy, 4 (67%) responded (CR = 2, PR = 2) but response duration was short (2–10 months). The safety profile of bendamustine in these 15 patients appears similar to that in other studies in mature T cell neoplasms. Premature termination (<3 cycles) occurred in five patients due to progressive disease (PD), \( n = 3 \) or infections (\( n = 2 \)). Patient 2 died of infection (grade 5) related to bendamustine but also related to PD, in fourth line of treatment. Patient 8 developed a grade 2 infection related to bendamustine (neutropenia). The most frequent adverse events were haematological. Grade 3–4 neutropenia and thrombocytopenia were documented in three patients (20%) and two patients (13%), respectively.

Our results confirm the good ORR of single-agent bendamustine in mature T cell neoplasms. For those patients refractory to alemtuzumab or unsuitable for alemtuzumab retreatment, the recommendation is to use a purine analogue-based therapy (Dearden, 2012). Nolarabine and/or fludarabine are usually an alternative for which there is some evidence of activity. In a phase 1 study in 11 T-PLL patients (Gandhi et al, 2008), ORR was 20% for nelarabine as a single agent, rising to 63% (13% CR) for the combination with fludarabine, on a mixed population of T-PLL (three patients) and CLL (six patients). Furthermore, grade 3–4 neutropenia and thrombocytopenia complicated 38% and 36% of courses of nelarabine treatment in this study. Therefore, bendamustine seems to be a good alternative in this indication, with similar response rates and better safety.

In conclusion, our retrospective study in 15 patients showed that bendamustine is a valuable treatment option for T-PLL, particularly in patients who are refractory to alemtuzumab. Combinations with alemtuzumab or other new therapies effective in T-cell lymphomas (histone deacetylase inhibitors, pralatrexate) or targeting oncogenic pathways (phosphatidylinositol 3-kinase inhibitors) are warranted.

**Acknowledgements**

This work was partly supported by the CAPTOR project (Investissements d’avenir “ANR-11-PHUC-001”).

**Author contributions**

LY and BC designed the research, LY and CH wrote the manuscript, all authors performed the data collection, LY, GD and CH analysed data.

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**Keywords:** T-PLL, bendamustine, alemtuzumab, salvage therapy

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**References**


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