Review Article

Bendamustine in peripheral T-cell lymphoma

Emilie Reboursiere, Gandhi Damaj

Hematology Institute, School of Medicine and University Hospital of Caen, Caen University, Caen, France

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Correspondence to: Prof. Gandhi Damaj, MD, PhD. Hematology Institute, University Hospital, Avenue de la Côte de Nacre, 14033 Caen, France. Email: Gandhi.damaj@unicaen.fr.

Abstract: Peripheral T-cell lymphoma (PTCL) is a group of diseases with poor outcome and few therapeutic options. Three main studies described bendamustine in these patients: one prospective phase II study, Bently and two retrospectives Italian and French studies. Patients were mainly angioimmunoblastic, PTCL-not otherwise specified (PTCL-NOS) and anaplastic large cell lymphoma. The majority of patients had disseminated disease and extranodal localizations refractory or in relapsed with over one previous line therapy. Overall response rate (ORR) was 32% to 55% with complete response (CR) rate of 10% to 28%. Median progression free survival and overall survival (OS) were 3.1 to 3.6 and 4.4 to 6.2 months in different studies. Bendamustine as single agent could be considered as an accessible therapeutic option for relapsed or refractory PTCL (R/R PTCL). It can be a way to bring the eligible patients to transplant. In another way, this treatment could be administered for elderly patients. Combinations of bendamustine with other drugs warrant further evaluation.

Keywords: T cell lymphoma; bendamustine; chemotherapy

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Introduction

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of disease which represent 10–15% of non-Hodgkin lymphoma (NHL) with poor prognosis (1). As first line therapy, anthracycline based multi-agent chemotherapy protocols are most commonly used with a complete response (CR) rate of about 50% and 5 years overall survival (OS) of 37% (2). First line consolidation with autologous hematopoietic stem cell transplantation (HSCT) is recommended for eligible patients even there is no worldwide consensus on this strategy (3,4).

Relapsed or refractory PTCL (R/R PTCL) is a challenging situation. More than two-thirds of PTCL patients will met this category and the prognosis of patient with R/R PTCL is very poor. The 5-year OS rates after salvage autologous and allogeneic transplant were 32% and 52%, respectively; while the 5-year OS rates for patients who did not undergo transplant was 10% (5). In this setting, the goal is to obtain a good disease response, even CR, as a bridge for an intensive therapy followed by HSCT which could be attain in only a few subset of patients (6).

Results of conventional salvage therapies (often cytarabine or gemcitabine-based regimen) are disappointing. The median OS and progression-free survival (PFS) were 5.5 and 3.1 months, respectively as reported by the group from British Columbia (6). Great effort has been made in the last decade to improve our therapeutic strategies, but the obtained results did not meet our expectation.

That's said, several new agents, even not completely satisfactory, have been added to the armada of anti T-cell lymphoma such as brentuximab, pralatrexate, romidepsin, and bendamustine.

Bendamustine is a unique agent with structural similarities with both alkylating agents and purine analogs, without cross-resistance with other cytotoxic

Table 1 Patients' demographics, disease characteristics at Bendamustine and their response to bendamustine

Characteristics	Damaj *et al.* (n=60)	Zaja *et al.* (n=20)	Reboursiere *et al.* (n=138)
Age, median [range, years]	66 [43–87]	73 [31–83]	64 [28–89]
Sex, male/female	38/22	14/6	82/56
Histology, n [%]			
AITL	32 [53]	4 [20]	71 [51.4]
PTCL-NOS	23 [38]	8 [40]	40 [29.0]
ALCL	2 [3]	–	8 [5.8]
Ann Arbor stages III–IV, n [%]	52 [87]	–	127 [92.0]
IPI 3–5, n [%]	38 [63]		101 [73.2]
Previous lines of treatment, median [range]	1 [1–3]	2 [0–8]	2 [1–8]
Prior therapy, n [%]			
ASCT	7 [12]	1 [5]	16 [11.6]
CHOP/CHOP-like regimen	55 [92]	16 [80]	122 [88.4]
Cytarabine-based regimens	15 [25]	5 [25]	53 [38.4]
Median time "diagnosis-bendamustine", [range] months	11 [3–177]	18 [1–74]	12 [1.5–108]
Refractory to last prior therapy, n [%]	27 [45]	13 [65]	69 [50]
Bendamustine response, n [%]			
ORR	30 [50]	11 [55]	45 [32.6]
CR	17 [28]	2 [10]	34 [24.6]
Median bendamustine DOR, months [95% CI]	3.5 [1.0–20.7]	4 [2–12]	3.3 [1.0–38.8]
Median bendamustine OS, months [95% CI]	6.3 [5.1–9.6]	6 [1–18]	4.4 [0.2–55.4]
Median bendamustine PFS, months [95% CI]	3.6 [2.4–5.2]	3 [1–18]	3.1 [0.2–46.3]

AITL, angioimmunoblastic lymphoma; ALCL, anaplastic large-cell lymphoma; ASCT, autologous stem-cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; IPI, International Prognostic Index; PTCL-NOS, peripheral T cell lymphoma-not otherwise specified; CR, complete response; DOR, duration of response; OS, overall survival; PFS, progression free survival; ORR, overall response rate.

drugs. Bendamustine induce cell death by apoptosis by downregulating genes important in mitotic checkpoint regulation with mitotic catastrophe (7,8). Preclinical data have shown *in vitro* efficacy of bendamustine in lymphoma T-cell lines (9,10). Based on these data, bendamustine has been tested in PTCL patients.

Bendamustine activity in PTCL

Literature review showed three studies, which have been summarized in the *Table 1*.

The first one, is a prospective phase II, single arm study (the Bently study) (11) and the other two are retrospective (12,13) with included respectively 60, 20 and 138 patients. The patients' age varied between 64 to 73 years old. Most of the patients had angioimmunoblastic T-cell lymphoma (AITL) and PTCL-not otherwise specified (PTCL-NOS) histology. The majority of the patients had advanced diseases in relapse. A significant proportion of them had refractory disease at the beginning of bendamustine [45% (27/60) (11), 65% (13/20) (12) and 50% (69/138) (13) of patients, respectively] with a median prior line of previous chemotherapy of 2. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-like regimen (80%) as well as cytarabine-based (20%) chemotherapy were the most previous used

treatment before bendamustine. Ten percent of the patients have received high dose therapy followed by HSCT.

Bendamustine response

The Bently study described an overall response rate (ORR) in this highly aggressive form of PTCL good over 50%, and a CR rate of 28%. However, the median OS and PFS were 6.2 and 3.6 months, respectively (11). These results have been confirmed in the retrospective Italian study which found an ORR of 55%, a CR of 10% and 6 months OS and PFS of 57% and 44%, respectively (12) In the retrospective real life French study, bendamustine treatment demonstrated an ORR of 32.6%, CR of 24.6% and a median OS and PFS of 4.4 and 3.1 months, respectively (13).

The activity of bendamustine has been found across all age subgroups, disease characteristics as well as histological PTCL subtypes even there was a trend toward more efficacy in AITL. On multivariate analysis, only the ECOG (Eastern Cooperative Oncology Group) performance status adversely affected PFS (11). Disease status and extranodal localization have been found to adversely influenced ORR (13). Of note, elderly patients of >75 years old represented 17% of the cohort with similar efficacy and safety as reported in younger patients.

Nine patients (6.3%) could undergo intensive therapy and HSCT post bendamustine and obtain durable CR (13).

Administration schedule

In Bently study, bendamustine was administered in monotherapy at a dose of 120 mg/m² on days 1–2 every 3 weeks (11). The median administered dose was however, in the retrospective studies 90mg/m² on days 1–2, every 3 or 4 weeks (12,13). The maximal response rate was obtained at 4 cycles. Only one third of patients in partial response after 3 cycles converted their response to CR at 6 cycles (11,13). The optimal dose should not be less than 90 mg/m² on 2 successive days.

It's unclear if 6 cycles are better than four when patients obtain CR at 4 cycles. However, in the absence of grade 3–4 toxicities, we recommend to pursue bendamustine for a total of 6 cycles.

Safety

Hematological toxicity with severe neutropenia (56% and 16%) and thrombocytopenia (38% and 22%) was the most frequent side effects encountered (11,13). Grade 3–4 infections occurred in 56% and 22% of patients, respectively (11,13). Of note, we noticed some opportunistic infections in few patients (5% of Bently patients, 3/60) (11) [pneumocystis jiroveci pneumonia (one patient) (11,13), pulmonary aspergillosis (one patient), and cerebral toxoplasmosis (one patient) (11)] without prophylactic valacyclovir or sulfamethoxazole in Bently patients. A high incidence of CD4 lymphocytopenia (44% of Grade 4) and occasional observance of herpes viral infections in aggressive NHL patient (59 patients with B cell lymphoma) treated with bendamustine were reported (14). However, the nature of the disease and the degree of the immunosuppression of the patients included in the study do preclude any firm conclusions on the relation with the treatment.

Conclusions

Bendamustine is a relatively effective molecule in PTCL, with about 50% of ORR and a quart of patients in CR. It represents a possible and accessible therapeutic option for R/R PTCL patients. Despite its short duration of action, it can be a way to bring the eligible patients to transplant. In another way, this treatment could be administered for elderly patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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