Cancer Pathogenesis and Therapy 2 (2024) 62–64

Contents lists available at ScienceDirect

Cancer Pathogenesis and Therapy

journal homepage: www.journals.elsevier.com/cancer-pathogenesis-and-therapy

Letter

Clinical features and prognostic analysis of the blastoid variant of mantle cell lymphoma: An analysis of 20 patients from two centers

Sai Huang [a,b,1], Shaomei Liu [c,d,1], Hongmei Jing [e,1], Ping Chen [c], Lili Dong [c], Xiaoyu Hao [e], Jian Bo [a,b], Lu Sun [f], Yu Zhao [a,b,*]

[a] Department of Hematology, Senior Department of Hematology, The Fifth Medical Center of PLA General Hospital, Beijing 100039, China
[b] Department of Hematology, The First Medical Center of PLA General Hospital, Beijing 100853, China
[c] Medical School of Chinese PLA General Hospital, Beijing 100853, China
[d] Department of Clinical Laboratory, The First Medical Center of PLA General Hospital, Beijing 100853, China
[e] Department of Hematology, Lymphoma Research Center, Peking University Third Hospital, Beijing 100191, China
[f] Department of Pathology, The First Medical Center of PLA General Hospital, Beijing 100853, China

Managing Editor: Peng Lyu

Mantle cell lymphoma (MCL), a relatively uncommon subtype of non-Hodgkin's lymphoma (NHL), constitutes approximately 2 %–10 % of NHL cases. Characterized by its inertness, aggressiveness, and incurability, MCL has a median overall survival (OS) of approximately 3–5 years.[1] The blastoid variant of MCL (BV-MCL) is a less common variant, occurring in only 20 % of all patients with MCL. BV-MCL can be pathologically categorized into classical and pleomorphic BVs. Recent studies have illuminated the distinct clinical attributes of BV-MCL, notably marked by a more unfavorable prognosis compared to typical MCL.[2] BV-MCL has unique pathological features. Similar to classic MCL, CD20, and CyclinD1 are more likely to be positive in BV-MCL, with a higher Ki-67 proliferation index (Ki-67 $\geq$ 30 %) and increased c-MYC expression, yet rare in c-myc translocation.[3] Studies of BV-MCL in China are rare. In this study, we investigated the clinical and prognostic features of BV-MCL by retrospectively analyzing data from two centers to validate the clinical characteristics and prognosis of patients with BV-MCL.

This study included 20 patients diagnosed with primary BV-MCL who were admitted to The First Medical Center of the Chinese People's Liberation Army General Hospital and Peking University Third Hospital between 2012 and 2020. The inclusion criteria were as follows: (1) BV-MCL diagnosis by lymph node pathology and immunohistochemistry; and (2) first diagnosis with no relevant prior treatment. Pathological examination and immunohistochemistry encompassed markers, such as CD20, CD3, CD5, CD56, CD30, CD10, CD23, Ki-67, Bcl-2, Bcl- 6, MUM-1, and CyclinD1. All 20 patients with BV-MCLs received chemotherapy. Following the National Comprehensive Cancer Network (NCCN) guidelines, the initial treatment regimen included rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP) alternating with rituximab plus high-dose cytarabine as first-line therapy. Autohematopoietic stem cell transplantation (auto-HSCT) was performed on four young patients. After completing two treatment cycles, the patients were assessed for efficacy using the 2014 Cheson criteria to evaluate the effectiveness of treatment for malignant lymphomas. This evaluation encompassed categories such as complete remission (CR), partial remission (PR), persistent non-remission (NR), and the overall response rate (ORR), denoted as (CR + PR)/total number of patients $\times$ 100 %. The patients were followed up until August 16, 2022. In cases of relapse or refractory disease, second-line chemotherapy regimens such as rituximab + fludarabine + cyclophosphamide (R-FC) and rituximab + bendamustine (RB) were administered. Rituximab or rituximab combined with ibrutinib was administered as maintenance therapy. Statistical analyses were performed using SPSS version 22.0. The measurement data displayed a skewed distribution expressed as median (interquartile spacing), while the qualitative data were expressed using frequencies. The Kaplan–Meier method was used for survival analysis.

Twenty patients with BV-MCL presented with painless lymph node enlargement, abdominal pain, abdominal distension, a foreign body sensation in the pharynx, and fever. Upon initial diagnosis, 15 (75.0 %) patients had group B symptoms such as fever, night sweats, and weight loss. The median patient age was 61 years (range, 44–80 years), with a male-to-female ratio of 7:3. The MCL International Prognostic Index (MIPI) score was 0–3 in eight patients, 4–5 in six patients (30.0 %), and 6–11 in six patients (30.0 %). According to the International Prognostic Scoring System of MCL (MIPI-c) risk stratification, eight patients

* Corresponding author: Department of Hematology, Senior Department of Hematology, the Fifth Medical Center of PLA General Hospital, Beijing 100039, China.
E-mail address: zhaoyu301@126.com (Y. Zhao).
[1] Sai Huang, Shaomei Liu, and Hongmei Jing contributed equally to this work.

https://doi.org/10.1016/j.cpt.2023.10.007
Received 5 May 2023; Received in revised form 18 October 2023; Accepted 25 October 2023

Table 1
Characteristics of patients with blastoid variant of mantle cell lymphoma.

Characteristics	BV-MCL (n = 20)
Age (years), median (range)	61 (44–80)
Gender, *n* (%)	
Male	14.0 (70.0)
Female	6.0 (30.0)
Ann Arbor, *n* (%)	
I–II	2.0 (10.0)
III–IV	18.0 (90.0)
MIPI, *n* (%)	
0–3	8.0 (40.0)
4–5	6.0 (30.0)
6–11	6.0 (30.0)
MIPI-c, *n* (%)	
Low	0.0 (0.0)
Low-intermediate	8.0 (40.0)
High-intermediate	6.0 (30.0)
High	6.0 (30.0)
Cytomorphology, *n* (%)	
Blastoid	15.0 (75.0)
Pleomorphic	5.0 (25.0)
CD5, *n* (%)	
Positive	16.0 (80.0)
Negative	4.0 (20.0)
Ki-67, *n* (%)	
≥80 %	9.0 (45.0)
60–79 %	9.0 (45.0)
30–59 %	2.0 (10)
≤30 %	0.0 (0.0)
Other involvement, *n* (%)	
B symptoms	15.0 (75.0)
Bone marrow	10.0 (50.0)
Spleen	7.0 (35.0)
Gastrointestinal tract	3.0 (15.0)
Extranodal involvement, *n* (%)	
0–1	15.0 (75.0)
2–3	5.0 (25.0)
First-line therapy, *n* (%)	
CR	10.0 (50.0)
PR	6.0 (30.0)
Persistent disease	4.0 (20.0)
Relapse, *n* (%)	10.0 (50.0)
Early recurrence (≤12 months)	4.0 (20.0)
Late recurrence (>12 months)	6.0 (30.0)
OS	
Median OS (months)	24.0
2-year OS rate,%	55.0
PFS	
Median PFS (months)	20.6
2-year PFS rate,%	30.1
Follow-up time (months), median (range)	24.0 (11.6–93.2)

BV-MCL: Blastoid variant of mantle cell lymphoma; CD: Cluster of differentiation; CR: Complete remission; MIPI: Mantle Cell Lymphoma International Prognostic Index; MIPI-c: International Prognostic Scoring System of Mantle Cell Lymphoma; no.: Number; OS: Overall survival; PFS: Progression-free survival; PR: Partial remission.

(40.0 %) were classified as having low-intermediate risk, six patients (30.0 %) as having high-intermediate risk, and six patients (30.0 %) as having high-risk [Table 1].

The median white blood cell (WBC) count, hemoglobin (Hb), and platelet (Plt) count of 20 patients with BV-MCL at the time of diagnosis were 6.3 (range, 3.0–116.0 × 10^9/L), 119.0 (range, 63.0–157.0 g/L), and 194.5 (range, 35.0–505.0 × 10^9/L), respectively. The pathological characteristics of lymph nodes or tissue punctures in these 20 patients with BV-MCL revealed that 16 patients (80.0 %) were CD5 positive and four (20.0 %) were negative. Regarding the Ki-67 index, nine (45.0 %) patients had index values ≥ 80 %, nine (45.0 %) had values ranging between 60 % and 79 %, and two (10 %) had values within 30%–59 %. With respect to the pathological classification, 15 (75.0 %) patients were categorized as having classical disease and five (25.0 %) as having pleomorphic disease [Supplementary Table 1].

The median follow-up time was 24.0 months (range, 11.6–93.2 months). Among the patients who received first-line treatment with R-CHOP alternating with rituximab plus high-dose cytarabine, 10 (50.0 %) achieved CR, six (30.0 %) achieved PR, and four (20.0 %) sustained NR. The ORR for all patients was 80.0 %. At the last follow-up, five patients (25.0 %) achieved sustained remission, while 10 patients (50.0 %) experienced relapses, including four patients with early relapses (≤12 months) and six with late relapses (>12 months). All 10 patients who relapsed received second-line therapy, with only one patient eventually achieving CR and one patient achieving PR; by the last follow-up date, eight patients were dead. Among the four young patients who underwent auto-HSCT, two achieved sustained CR, whereas the other two experienced relapses. The median OS for all patients was 24.0 months, with a 2-year OS rate of 55.0 %. The median PFS for the 16 patients with evaluable PFS was 20.6 months, with a 2-year PFS rate of 30.1 %. No significant difference in PFS or OS was observed between the blastoid and pleomorphic variants, indicating a similarly poor prognosis for both subtypes of BV-MCL [Figure 1].

BV-MCL is a rare and highly aggressive hematological malignancy with a clinical presentation similar to that of classic MCL. BV-MCL predominantly affects males, with a median onset age of 61 years.[1] Our findings are consistent with those of previous studies, suggesting that the disease predominantly manifests in elderly males. The main symptoms were painless lymph node enlargement, abdominal pain, and abdominal distension, which were frequently accompanied by group B symptoms. In this study, we observed the prevalence of extranodal involvement in patients with BV-MCL, with 75.0 % of patients exhibiting engagement at more than one extranodal site, including bone marrow infiltration, spleen involvement, and gastrointestinal tract involvement. Notably, 90.0 % of patients were staged as III and IV according to the Ann Arbor classification, indicating a tendency for a high tumor burden at diagnosis in BV-MCL cases. The MIPI scores were evenly distributed among the 20 patients. In this study, similar to MCL, 20.0 % of patients were CD5 negative.

Several studies by the European Mantle Cell Lymphoma Network have confirmed the prognostic significance of the Ki-67 proliferation

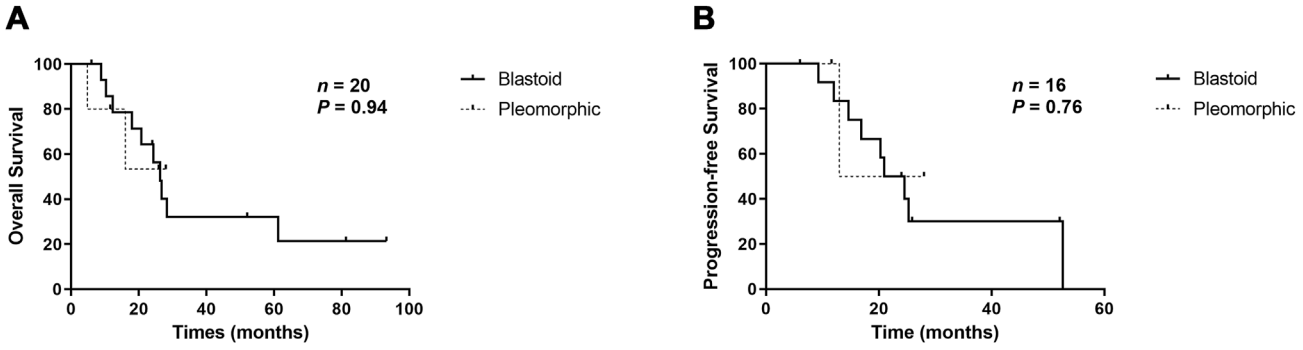

Figure 1. Prognosis of patients with BV-MCL. (A) Overall survival of 20 patients with BV-MCL. (B) Progression-free survival (PFS) curves of 16 patients with evaluable PFS with BV-MCL. BV-MCL: Blastoid variant of mantle cell lymphoma; PFS: Progression-free survival.

index in this disease.[4] In MCL prognostic evaluation, a cut-off Ki-67 proliferation index of 30 % is used as an indicator of poor prognosis. Our study observed that the Ki-67 proliferation index exceeded 30 % for all patients with BV-MCL, with over 60 % of the patients showing a Ki-67 proliferation index of up to 90.0 %. These findings suggest a more rapid proliferation of BV-MCL cells, indicating a heightened clinical malignancy and, ultimately, a poorer prognosis than that observed in classic MCL.

The prognosis of BV-MCL is extremely poor, making clinical observation unadvisable, even in cases of low tumor burden. The optimal regimen for BV-MCL is chemotherapy, with or without auto-HSCT consolidation. In the pre-rituximab era, patients with BV-MCL experienced a median OS of just 14.5 months under conventional-dose chemotherapy, primarily with cyclophosphamide + vincristine + prednisone (CVP) or the CHOP regimen. This outcome was considerably worse than the median OS of 53 months observed in patients with classical MCL. The advent of rituximab has improved the remission rate of MCL and prolonged the time to treatment failure (TTF) in patients; however, specific data regarding BV-MCL treatment are lacking.[3] The results of our study suggested that the CR rate after first-line therapy was only 50.0 %, with 20.0 % of patients experiencing early recurrence ($\leq$12 months) and 30.0 % having late recurrence (>12 months). The median OS and PFS times were 24.0 and 20.6 months, respectively. The 2-year OS and PFS rates were 55.0 % and 30.1 %, respectively, in all patients, which are better than those reported in previous studies. This may be attributed to the addition of rituximab. However, it was still significantly lower than the survival time associated with classic MCL. Therefore, new strategies should be developed to improve the prognosis of BV-MCL.

Allo-HSCT is a viable option for patients under 60 years of age. However, most patients with MCL are too frail for allo-HSCT. Therefore, in the current era of new drugs, BTK inhibitors (BTKi), BCL-2 inhibitors, immunomodulators, immune checkpoint inhibitors (ICPi), and CAR-T cells have potential therapeutic value. In a phase III clinical trial of BTKi ibrutinib monotherapy in MCL, BV-MCL showed an optimal response time similar to classic MCL (2.2 *vs.* 2.1 months); however, it was associated with a lower ORR (55 % *vs.* 72 %), shorter time to remission (8.6 *vs.* 18.8 months), and reduced PFS (5.1 *vs.* 14.6 months), as well as OS (12.8 months *vs.* not achieved). This implies that ibrutinib monotherapy for BV-MCL may be ineffective, and a combination with chemotherapy or other new drugs is essential for these patients.[5] The prognosis of relapsed/refractory BV-MCL is even poorer. A phase II clinical trial confirmed that the combination of a next-generation BTKi (LOXO-305), the BCL-2 inhibitor venetoclax, and anti-CD19 CAR-T has great potential to improve the poor prognosis of relapsed/refractory BV-MCL patients to some extent.[6]

In conclusion, BV-MCL is an aggressive type of MCL characterized by rapid development, a high recurrence rate, an elevated Ki-67 proliferation index, and an unfavorable prognosis. There are certain limitations, including a small patient cohort and a two-center nature of the study, which limit generalizability. The primary challenge in prognostic analysis is the limited sample size. Therefore, further validation in multicenter studies with larger sample sizes is necessary.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82200169).

Authors contribution

Sai Huang designed and performed the study and wrote the manuscript. Shaomei Liu and Ping Chen analyzed the data and revised the manuscript. Lili Dong, Xiaoyu Hao, Jian Bo, and Lu Sun collected data. Hongmei Jing and Yu Zhao designed and supervised this study. All authors reviewed the final manuscript.

Ethics statement

Our study followed the *Declaration of Helsinki*. Informed consent was obtained from all subjects. Ethical approval was granted by the ethical review boards of PLA General Hospital and Peking University Third Hospital (No. M2022564).

Data availability statement

The datasets generated and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Conflict of interest

None.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpt.2023.10.007.

References

1. Armitage JO, Longo DL. Mantle-cell lymphoma. *N Engl J Med*. 2022;386:2495–2506. https://doi.org/10.1056/NEJMra2202672.
2. Dreyling M, Klapper W, Rule S. Blastoid and pleomorphic mantle cell lymphoma: still a diagnostic and therapeutic challenge!. *Blood*. 2018;132:2722–2729. https://doi.org/10.1182/blood-2017-08-737502.
3. Jain P, Wang M. Blastoid mantle cell lymphoma. *Hematol Oncol Clin N Am*. 2020;34:941–956. https://doi.org/10.1016/j.hoc.2020.06.009.
4. Shrestha R, Bhatt VR, Guru Murthy GS, Armitage JO. Clinicopathologic features and management of blastoid variant of mantle cell lymphoma. *Leuk Lymphoma*. 2015;56:2759–2767. https://doi.org/10.3109/10428194.2015.1026902.
5. Rule S, Dreyling M, Goy A, et al. Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies. *Br J Haematol*. 2017;179:430–438. https://doi.org/10.1111/bjh.14870.
6. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020;382:1331–1342. https://doi.org/10.1056/NEJMoa1914347.