Two decades of single-institution data reveal rare long-term survivors of relapsed/refractory Burkitt lymphoma

Burkitt lymphoma (BL) is a highly aggressive B-cell non-Hodgkin lymphoma, characterized by rapid disease progression driven by a high tumor proliferation rate.[1] While intensive front-line chemoimmunotherapy has achieved 3-year overall survival (OS) rate of over 80%, a subset of patients experience refractory or relapsed (R/R) disease associated with a poor prognosis.[2,3] Patients with the highest risk of relapse include those with central nervous system (CNS), marrow or peripheral blood BL, age ≥ 40, Eastern Cooperative Oncology Group score ≥ 2, and lactate dehydrogenase > 3× Upper Limit of Normal (ULN) as equally weighted independent factors.[4,5] Response rates to salvage therapies vary between 30-50%, with long-term survival rates below 20% and often approaching zero. Specifically, three studies reported long-term survival in 2 of 35 patients,[6] 0 of 9,[7] and 0 of 10,[8] although one study reported 11/74 survivors.[9]

To evaluate our own experience and ascertain clues for long-term survival, we conducted a retrospective review of Memorial Sloan Kettering Cancer Center patients with R/R BL using a database search from January 1st, 1988, to December 21st, 2021. This study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center and was conducted in accordance with the Declaration of Helsinki. We identified 276 patients with BL of whom 28 (10%) received second-line therapy for relapsed (N=8) or refractory (N=20) disease. Early and late relapse were defined as relapse <6 months and ≥6 months from the time of first remission, respectively. Overall response rate (ORR) was defined as the composite of complete remission (CR) and partial remission (PR). Relapse-free survival (RFS), and OS were calculated. RFS was defined as time from first remission or start of first-line treatment until relapse. OS was defined as time from first treatment failure or first relapse until death from any cause. Patients alive were censored at their last follow-up. Characteristics of the evaluable population are shown in *Online Supplementary Table S1*. The median age was 37 years (range: 21-69 years). High-risk baseline features include: stage IV disease (75%), leptomeningeal disease (LMD) (29%), bone marrow disease (25%). Six patients had HIV with 3 taking antiretroviral therapy at BL diagnosis. Six patients had Epstein-Barr virus (EBV)-positive disease, defined by EBER *in situ* hybridization positivity on tumor specimens; 12 were EBER-negative, and 10 had unknown EBV status. The vast majority received intensive first-line therapies, e.g., CODOX/IVAC (cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate alternating with ifosfamide, etoposide, and cytarabine), DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), and HyperCVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine), including 20 combined with received rituximab (R) not available in the first part of the study timeframe. Responses to first-line therapy included CR (29%), PR (36%), and progression of disease (POD) (36%). CR rates may reflect CT-defined response prior to the availability of positron emission tomography (PET). Among the 8 patients with CR, the median time to relapse was six months (95% Confidence Interval [CI]: 5-14). Second-line regimens included R-EPOCH (N=4), R+/- IVAC (N=6), R+/- ICE (ifosfamide, carboplatin, and etoposide) (N=4), high-dose methotrexate (MTX) +/-cytarabine (N=6), other (N=8). A patient flow diagram shows treatment overview (Figure 1). After second-line therapy, CR was 0%, partial response 25%, and POD 75%. The median OS for the entire cohort (measured from time of treatment failure or first relapse) was four months (95% CI: 3-8), with a 6-month OS rate of 43% (95% CI: 28-66), and 1-year OS rate of 11% (95% CI: 4-31) (Figure 2). Four patients achieved CR after additional lines of salvage chemotherapy regimens and one after radiation. All 5 patients had previously received first-line intensive treatment (R-CODOX-M/IVAC, R-EPOCH, R-HyperCVAD) along with CNS directed treatment (intrathecal (IT)/high-dose MTX +/- cytarabine). Two patients received allogeneic stem cell transplant (SCT); however, one died due to complications within a week of transplant and one had POD five months after SCT. The 3 remaining patients were long-term survivors, and all received consolidative autologous SCT after relapse. They were all male, one had EBV$^+$ BL, and they were the only patients to proceed to autologous SCT. At initial diagnosis, one had stage I and 2 had stage IV disease with bone marrow and leptomeningeal disease (LMD). Their unique treatment trajectories are described below.

The first patient had HIV with a normal CD4 count, undetectable HIV viral load, and stage I BL with a 10 cm axillary mass. He received 3 cycles of R-Hyper-CVAD (including 3 doses of IT MTX and 3 doses of HD-MTX) with biopsy proven PR, R-ICE for 1 cycle (and 3 additional doses of IT MTX) with no response, 30 Gy radiation with pathologic CR followed by consolidative autologous SCT. The patient remains in remission 12 years later.

The second patient had radiographic testicular involvement and LMD at diagnosis, and was treated with CODOX-M/IVAC-R (including 4 doses of IT MTX+ ARA-C and 2 doses of HD-MTX) followed by orchiectomy without evidence of

lymphoma. Five months post therapy a liver biopsy showed only necrotic cells, and a lung nodule showed BL with no other sites of disease. Salvage therapies over four months consisted of gemcitabine-oxaliplatin (1 cycle) without response; R-EPOCH x 2 cycles with initial POD, but while undergoing transplant evaluation, repeat imaging revealed response, followed by R-EPOCH x2 with further response, and radiation (30 cGy hyper fractionated IFRT to residual hilar LN), leading to CR, followed by consolidative autologous SCT. Patient developed secondary AML 31 months later, underwent a 10/10 MUD transplant and remains without evidence of disease after more than ten years.

The third surviving patient completed 5 cycles of front-line DA-EPOCH-R achieving control of stage IV disease except for progression in a single right level 2 cervical lymph node that was surgically resected showing lymphoma. For LMD at diagnosis, he received MTX/ARA-C via Ommaya twice weekly for four weeks with clearance, followed by maintenance weekly for six weeks and then monthly treatment (13 doses). After the cervical lymph node resection, he had 2 adjuvant cycles of HyperCVAD part B with MTX and high-dose cytarabine followed by consolidative autologous SCT and had no evidence of disease for almost ten years.

The ORR to all salvage chemotherapies in our series was 14% (CR, N=4; PR, N=0). Both early and late relapse patients had a median OS of four months. Despite advances in the molecular

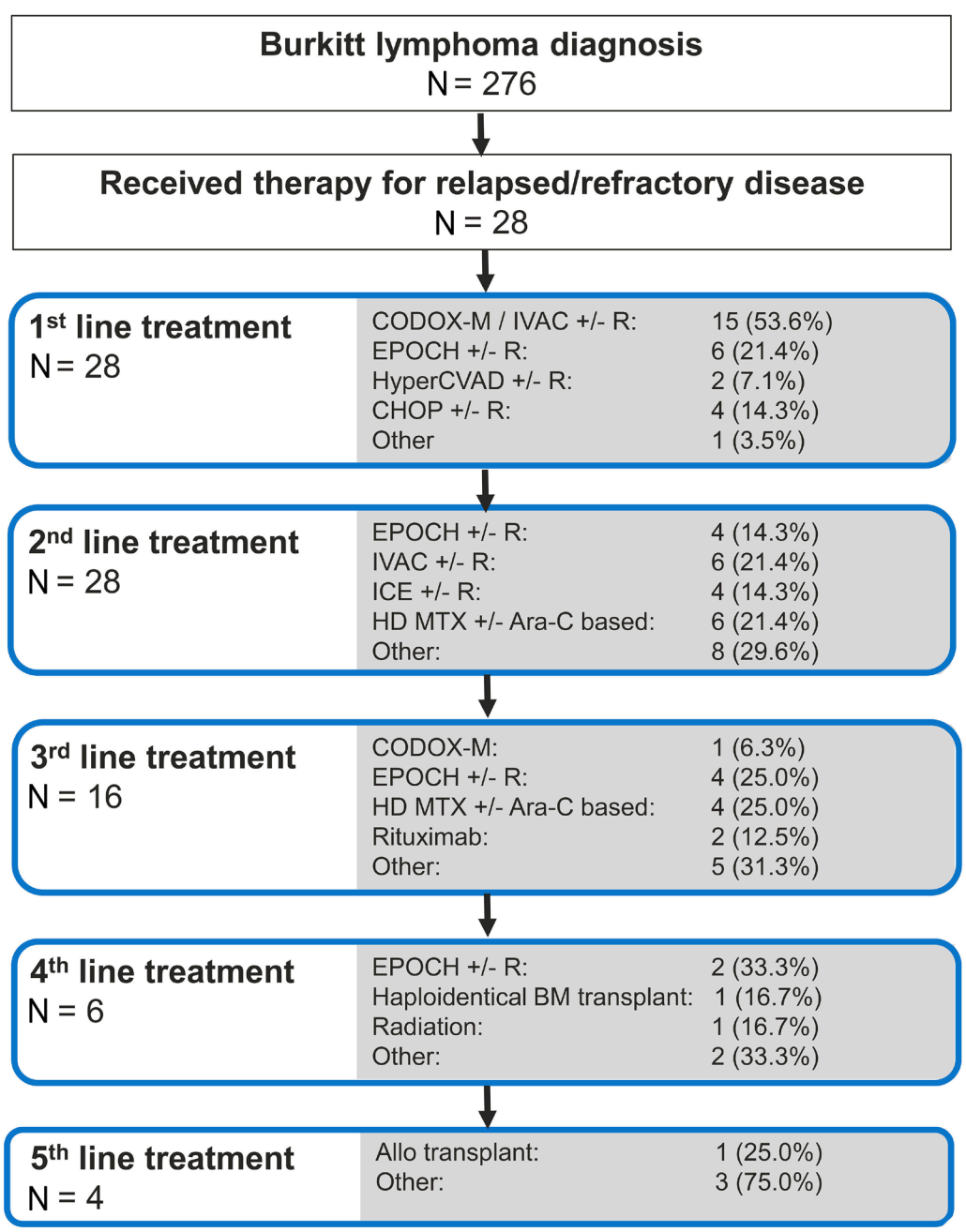

Figure 1. Patient flow diagram showing treatment overview. Allo: allogeneic; Ara-C: cytarabine; BM: bone marrow; CHOP: cyclophosphamide, doxorubicin, vincristine , and prednisone; CODOX/IVAC: cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate (MTX) alternating with ifosfamide, etoposide, and cytarabine; CR: complete remission; EPOCH: etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DA-EPOCH: dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; HD: high-dose; HyperCVAD: fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose MTX and cytarabine; N: number; R: rituximab.

understanding of BL, no targeted therapies have emerged in the salvage setting. Unfortunately, chimeric antigen receptor (CAR) T-cell receptor therapies have been largely unsuccessful in adults with Burkitt lymphoma, with a retrospective analysis of 31 patients reporting an ORR of nearly 60% at one month, but a median PFS of only 2.3 months, and just one survivor at 20 months.[10] All 3 patients bridged to allogeneic BMT experienced a relapse. Consequently, better front-line therapies for those with high-risk features will likely reduce the risk of R/R disease. In contrast in pediatrics, a sequential CAR-T approach in 23 patients targeting CD19, CD22, and CD20 if CR was not achieved resulted in an estimated 18-month 78% PFS and CR rate including 78% in patients with bulky disease and 60% in patients with CNS involvement.[11] Notably 9 patients received only a CD-19 directed CAR-T; 13 an anti-CD22; and 6 an anti-CD20. These remain investigational therapies and their broader applicability, particularly in adults, remains uncertain.

Regarding clinical trial participation, a total of 3 patients in our cohort were enrolled in clinical trials at some point during their therapy. One patient was enrolled in a first-line study evaluating R-CODOX-M/IVAC incorporating CNS penetration strategies and intensive intrathecal prophylaxis specifically for HIV-associated BL.[12] No patients were enrolled in trials during second-line therapy (1st salvage). One patient in the third-line (2nd salvage) participated in a phase I trial with an anti-CD47 monoclonal antibody. The third patient participated in phase I studies in the fourth and fifth lines of therapy, including trials of SGN-CD19A (denintuzumab mafodotin, an ADC) followed by fimepinostat (a PI3K/HDAC inhibitor) plus venetoclax. Challenges to trial enrollment in this population included the rarity and aggressive nature of R/R BL, limited trial options, as well as patients' rapidly deteriorating performance status. These barriers highlight the need for early-phase trial designs that accommodate patients with R/R BL, particularly those with high-risk features or rapidly progressive disease.

Importantly, this study was conducted prior to the implementation of comprehensive molecular profiling (such as the MSK-IMPACT testing, which screens for approximately 400 clinically relevant gene mutations) at our center. As a result, we unfortunately do not have detailed molecular data for these patients. In conclusion, we identified 28 patients over two decades with R/R BL of whom only 3 were long-term survivors. Our results are in keeping with other prior single-institution reports. Notably, 2 patients had LMD at first diagnosis and all 3 had very limited systemic disease at relapse, possibly all stage I. All 3 surviving patients underwent autologous SCT in second complete remission and remained BL free for ten years. Overall, long-

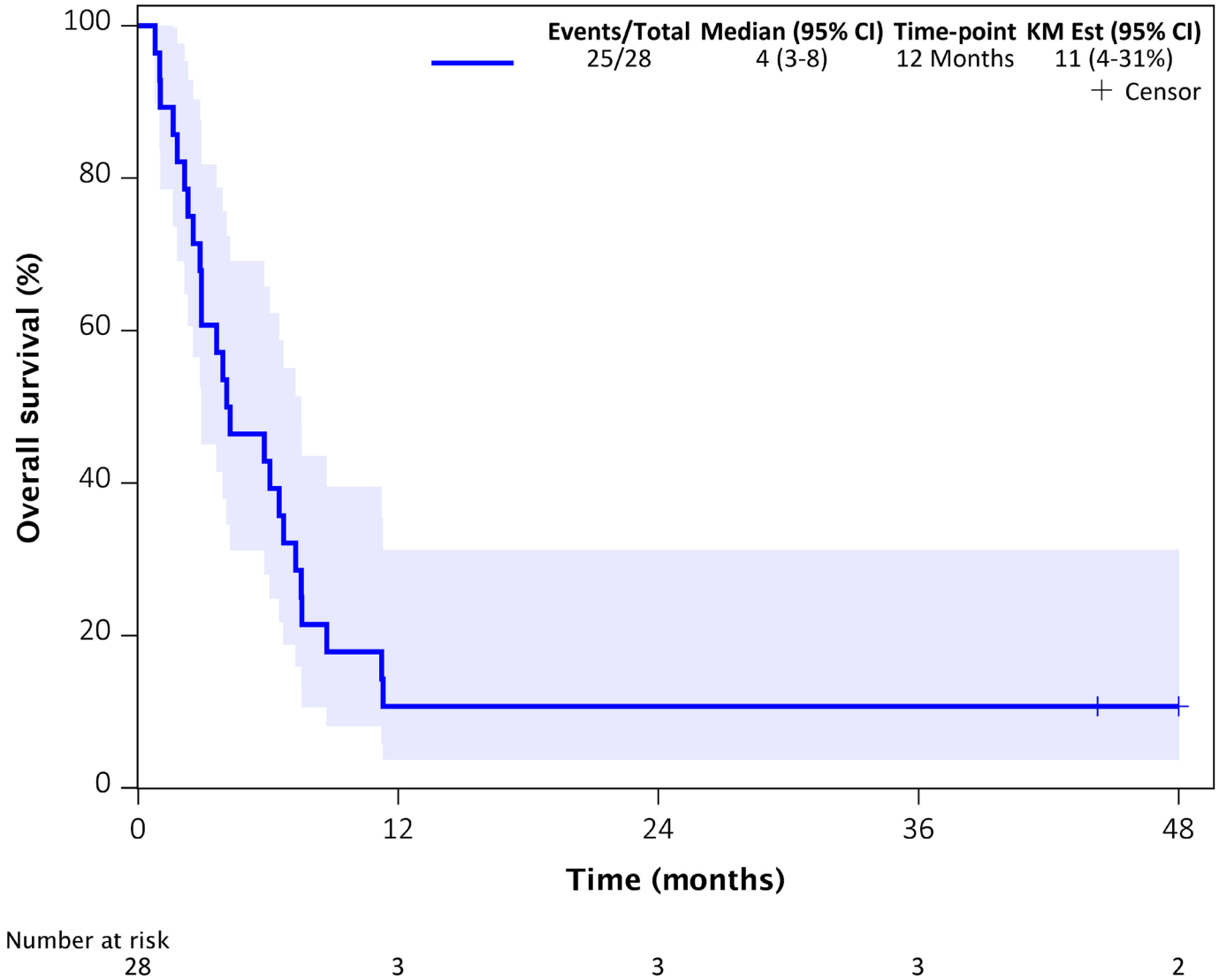

Figure 2. Overall survival measured from time of treatment failure or first relapse to death, or censored at last follow-up. CI: Confidence Interval; KM: Kaplan-Meier Estimate.

term survival is possible for only a minority with R/R BL, reinforcing the need for improved therapeutic strategies.

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Contributions

RM and AN wrote the letter. KB was the statistician. All other authors reviewed the letter prior to submission and managed patients included in study. All other authors have no conflicts of interest to disclose.

Data-sharing statement

The data that support the findings of this study are not publicly available due to institutional and patient privacy restrictions but may be shared by the corresponding author upon reasonable request.

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