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EFFICACY OF AUTOLOGOUS STEM CELL TRANSPLANTATION IN ADULT BURKITT/BURKITT-LIKE LYMPHOMA: A SYSTEMATIC REVIEW

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***Background*: Burkitt and Burkitt like lymphoma (BL/BLL) are highly proliferative germinal or post-germinal B cell tumors. Few studies have evaluated the impact of autologous stem cell transplantation (ASCT) on disease outcomes. *Aim*: We performed a systematic review to analyze the efficacy of ASCT as frontline consolidation and for treatment of relapsed/refractory cases in adult BL/BLL. *Materials and Methods*: Eligible studies with clear outcome measures on the efficacy of ASCT in adult patients with BL/BLL were identified through systematic search. The overall survival (OS), progression-free survival (PFS), complete response (CR), partial response (PR), and progression/relapse were used to assess the efficacy. *Results*: For patients who underwent ASCT in first CR, 5-year PFS and OS ranged between 70–78% and 70–83% respectively. For relapsed/refractory disease, 5-year PFS and OS were 27% and 31%, respectively. Patients undergoing ASCT for chemoresistant disease fared poorly with 3-year OS of 7% *vs* 37% for chemosensitive disease ($p \leqslant 0.00001$). The overall response rate to ASCT for patients transplanted in first CR ranged between 71% and 93% and was 37% for patients who were transplanted in disease status other than first CR. Disease progression/relapse was observed in 16–29% of the patients transplanted in first CR, and 55% to 60% in relapsed disease. *Conclusion*: We found insufficient evidence to support ASCT over chemotherapy alone in the first remission for adult BL/BLL. Evidence supports guidelines recommending ASCT for chemosensitive disease but suggests there is no benefit to ASCT for chemoresistant disease.**

***Key Words*: Burkitt lymphoma, chemotherapy, hematopoietic stem cell transplantation, autologous, survival outcome.**

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Adult Burkitt lymphoma (BL) is a rare and highly aggressive form of non-Hodgkin's lymphoma [1]. A new provisional entity, Burkitt-like lymphoma (BLL) with 11q aberration, displays a similar phenotype with lower MYC expression and lacks *MYC* translocation [2]. According to the 2016 World Health Organization (WHO) classification of hematologic malignancies, BL and BLL are now viewed upon as two different manifestations of the same disease spectrum [2, 3]. The 2-year and 5-year overall survival (OS) ranges from 50% to 65%, and decreases to less than 30% with bone marrow or central nervous system (CNS) involvement [4].

Patients with BL require intensive multidrug therapy and adequate CNS prophylaxis. Common regimens used for adult BL patients include short, sequential chemotherapy (CT) like CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ ifosfamide, etoposide, high-dose cytarabine), or other similar high-intensity regimens featuring multiple chemotherapeutic agents with high degrees of CNS activity [5–10]. Alternatively, the less-intensive DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) is also an active and reasonable option particularly for older or more frail patients [5, 6]. CT regimens like CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) are inferior and associated with frequent relapse in BL [5]. Different studies using high or low dose

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Abbreviations used: ASCT – autologous stem cell transplantation; BACT – bischloroethyl nitrosourea, cytosine arabinoside, cyclophosphamide, 6-thioguanine; BEAM – carmustine, etoposide, cytarabine, melphalan; BFM – Berlin – Frankfurt – Munster; BL/BLL – Burkitt and Burkitt-like lymphoma; CBV – cyclophosphamide, bischloroethyl nitrosourea, etoposide; CHOP – cyclophosphamide, doxorubicin, vincristine, prednisone; CI – confidence interval; CNS – central nervous system; CODOX-M/IVAC – cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, high-dose cytarabine; CR – complete response; CT – chemotherapy; DA-EPOCH – dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; DHAP – dexamethasone, high-dose cytarabine, cisplatin; HDT – high-dose therapy; MACOP-B – methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; NCCN – National Comprehensive Cancer Center Network; ORR – overall response rate; OS – overall survival; PACEBOM – prednisolone, doxorubicin, cyclophosphamide, etoposide, bleomycin, vincristine, methotrexate; PFS – progression-free survival; PICO – Population, Intervention, Comparison/control, and Outcome; PR – partial response; PRISMA – preferred Reporting Items for Systematic Review and Meta-analysis; WHO – World Health Organization.

CT regimens, with or without radiation treatment, and CNS prophylaxis have demonstrated a varying degree of complete response (CR) rate, progression-free survival (PFS) and OS in adults [7–14].

Although these regimens are active, OS ranges from 56% to 95% and is heavily impacted by age, performance status, and other disease factors [15]. To improve these outcomes, high-dose CT followed by autologous hematopoietic stem cell transplantation (ASCT) may be considered especially for those with relapsed disease. Unfortunately, the role of ASCT is not well defined, particularly in the era of modern chemoimmunotherapy incorporating agents like rituximab.

Recognizing this important limitation in the available literature, we performed a systematic review to analyze the efficacy of ASCT as frontline consolidation and for treatment of relapsed/refractory cases in adult BL/BLL.

METHODS

We analyzed the role of ASCT in adult patients with BL/BLL according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) statement [16]. We used the PICO (Population, Intervention, Comparison/control, and Outcome) format to formulate our research question: population — BL/BLL in adult patients, intervention — ASCT, comparison — with or without control group, and outcome — efficacy endpoints.

Literature search. An extensive search of PubMed, Google Scholar, Cochrane, and EMBASE databases until March 2021 was done, with no restriction to country of origin. We used these keywords in different combinations for the literature search: "Burkitt lymphoma", "Stem cell transplantation", "autologous", "Burkitt", and "Burkitt-like lymphoma". We used the following as one of the search strategies without any automatic filters for PubMed: (Stem Cell Transplantation [MeSH Terms]) AND (autologous [All Fields]) AND (Burkitt [MeSH Major Topic]) OR (Burkitt like [All Fields] OR (Burkitt-like [All Fields]) AND (Lymphoma [MeSH Terms]). The reviewers independently screened the title and abstract of the articles identified during the initial search. After excluding duplicates, articles that did not study BL/BLL or ASCT, preclinical studies, and pediatric studies, we studied the full texts of the potentially relevant articles in greater detail. For each study chosen for the systematic review, we screened the references and checked the citing articles to identify other eligible studies not found in the prior database searches. Whenever there was any confusion regarding the data or inadequacy in the data existed, we contacted the corresponding author of the study for clarification.

Eligibility criteria. The inclusion criteria for our analysis were: 1) clinical trials, prospective studies, or retrospective studies published in English language; 2) studies involving patients with BL/BLL; 3) patients' age $\geqslant$ 15 years; 4) studies reporting treatment with ASCT; and 5) data on efficacy or safety endpoints.

The exclusion criteria for our analysis were: 1) review articles, meeting or conference abstracts, posters, editorials, pre-clinical studies, case reports; 2) studies with no data on outcome measures. We excluded the meeting or conference abstracts with no published full-text articles to ensure we only include studies of highest quality and rigorous peer review.

Data extraction. Reviewers (UJ, RS, GN, and SG) extracted the relevant data from the included studies independently and entered the data into a standardized spreadsheet. The following data were collected: 1) name of the first author; year of publication; study identification number; country/region where the study was conducted; type of study; study period; study design; sample size; number of transplanted patients; age, gender, and racial features of the study population; performance status; tumor type and stage; prior CT lines, disease status before transplant; follow-up duration; 2) OS, PFS, CR, partial response (PR), progression or relapse; overall response rate (ORR), time to recovery; and 3) adverse events or toxicity to the treatment regimen. Once data entry was completed, the lead author rechecked, verified, and corrected the entered data wherever necessary.

Outcome measures. The primary outcome measures of our study were OS and PFS. The secondary outcome measures of our study were CR, PR, progression or relapse, ORR, and toxicity or adverse events related to the treatment regimen. OS refers to the time from the start of the treatment to the time of death from any cause. PFS refers to the time from the start of the treatment to either objective tumor progression, relapse, or death. ORR is defined as the proportion of patients who had either a CR or a PR [17, 18].

RESULTS

Study selection. A total of 206 articles were identified from the database search. After the removal of duplicates and screening of the remaining articles, 27 full-text articles were evaluated for further review. Of these, only 5 articles met the inclusion criteria. A manual search of the references and citations of these included articles yielded no additional eligible articles. We show this entire process in the PRISMA diagram as shown in the Figure.

Study characteristics. We reviewed five retrospective and prospective studies that evaluated the efficacy of ASCT in adult patients with BL/BLL [19–23]. Due to their common immunophenotypic and cytogenetic features, BL and BLL have been evaluated as a combined group in most of the studies, and hence analysis of the BL population as a separate entity remains difficult. Our systematic review included adult patients with both newly diagnosed and relapsed/refractory BL/BLL originating from multiple countries across Europe and North America. One of the studies was a phase II multicenter study, three of them used a lymphoma registry to evaluate the outcome measures, and one was a prospective cohort study. The lymphoma registries used were the European Group for Blood and Marrow Transplantation registry, the Center for International Blood and Marrow Transplant Research registry, and

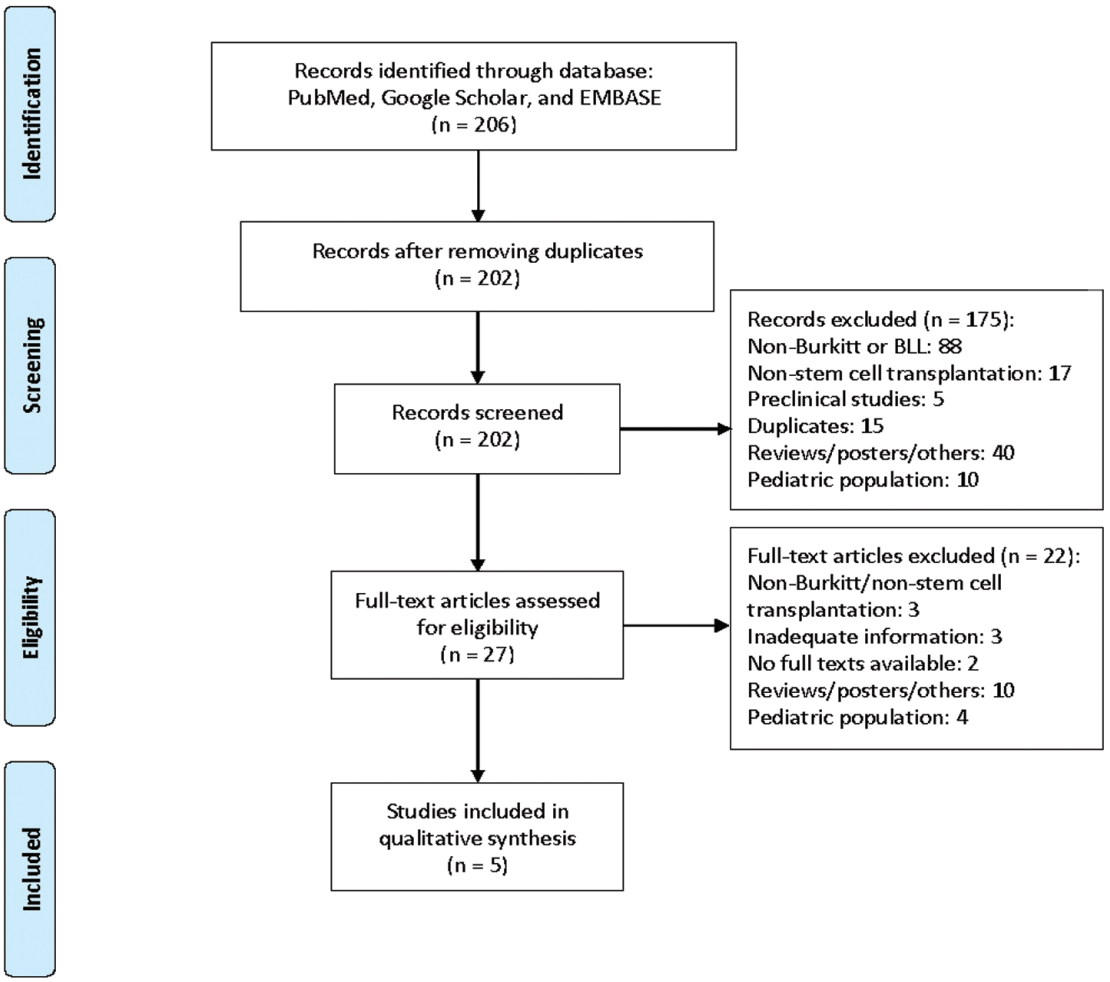

Figure. PRISMA flow diagram for selection of included studies

the Norwegian Radium Hospital lymphoma database. All the patients included in the studies were aged > 15 years. However, Maramattom *et al.* [19] evaluated patients of all age groups, and attempts to extract data separately for patients aged > 15 years were unsuccessful. With a disease as rare as BL/BLL, it was not practical to exclude a study that still comprised more than 75% of the patients older than 15 years. Maramattom *et al.* [19] and Appelbaum *et al.* [20] included patients who had undergone treatment with various combination CT and had either relapsed or were refractory to the regimen prior to initiating ASCT. Data on performance status of the patients were only available for two studies (WHO score in van Imhoff *et al.* [21] and Karnofsky score in Maramattom *et al.* [19]). Median time to cell line recovery (white blood cells, platelets) was presented in two studies [21, 22]. The additional characteristics of the studies are shown in Table 1. Treatment regimens used in these studies are presented in supplementary table (available at https://www.researchgate.net/ profile/Utsav-Joshi-2).

***Efficacy of transplant*.** The efficacy end points reported in the form of OS, PFS, progression/relapse, CR, PR, and ORR in the included studies are presented in Table 2.

ASCT after first CR/PR. Van Imhoff *et al.* [21] treated 27 newly diagnosed BL or BLL patients with two consecutive induction CT courses (induction I — cyclophosphamide, doxorubicin, prednisolone; induction II — etoposide, mitoxantrone, prednisolone), followed by high-dose therapy with BEAM (carmustine, etoposide, cytarabine, melphalan) and ASCT. Treatment per protocol including ASCT was completed by 23 patients. With a median follow-up of 61 months, OS at 5 years was 81% (95% confidence interval (CI), 61–92), and PFS at 5 years was estimated at 73% (95% CI, 51–86). The overall response (CR and PR) of the study population to the treatment protocol stood at 93% (25/27). Disease progression (including relapse) was observed in 8/27 (30%) of the subjects, of which 7/27 (26%) progressed following ASCT.

Sweetenham *et al*. [23] studied the outcomes of a variety of high-dose CT regimens (including those used for treatment of acute lymphoblastic leukemia, CHOP regimen, MACOP-B (methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) regimen, PACEBOM (prednisolone, doxorubicin, cyclophosphamide, etoposide, bleomycin, vincristine, methotrexate) regimen, BEAM regimen, CBV (cyclophosphamide, bischloroethyl nitrosourea, etoposide) regimen) followed by ASCT in 117 patients with BL or BLL. Seventy patients, who underwent high-dose therapy (HDT)/ASCT in first CR, were followed for a median duration of 23 months, and

Table 1. Baseline characteristics of included studies

Author, year	Study type, period	Number of transplant patients	Median age in years (range)	Sex (M/F)	Tumor stage	Disease status before transplant	Median follow-up duration in months (range)
Van Imhoff, 2005	Prospective, 1994–2003	27	36 (15–64)	21/6	I(E): 5 II: 10 III: 2 IV: 10	Upfront	61
Smeland, 2004	Retrospective, 1981–2001	14			I: 12 II: 11 III: 2 IV: 24	Upfront	
	Three cohorts:						
	MmCHOP:	0	30 (15–44)	9/4			218 (190–247)
	MmCHOP+HDT:	12	31 (15–56)	11/ 6			127 (71–179)
	BFM:	2	36 (17–69)	13/6			49 (13–80)
Maramattom, 2013	Longitudinal, 1985–2007	113	31 (5–76)	79/34	I–II: 34 III–IV: 76 Unknown: 3	PIF sensitive: 13 (12) PIF resistant: 5 (4) CR1: 48 (42) REL sensitive: 17 (15) REL resistant: 3 (3) CR2 or beyond: 19 (17) Unknown: 8 (7)	79 (9–222)
Sweetenham, 1996	Retrospective, 1984–1994	117	32 (17–58)	81/36	I: 18 II: 14 III:34 IV: 40 Unknown: 11	CR1: 70 (60) CR2: 12 (10) > CR2: 3 (3) PR: 10 (9) Responding relapse: 7 (6) Untested relapse: 1 (1) Resistant relapse/primary refractory: 14 (12)	26 (1–126)
Appelbaum, 1978	Prospective, NA	5	17 (16–33)	3/2	NA	Relapse: 3 PR: 1 Primary refractory: 1	1–29

Table 2. Efficacy of ASCT from included studies

Author, year	N	Cohort	OS (95% CI)	PFS(95% CI)	Progression/relapse[$]	PR	CR	ORR (%)
Van Imhoff, 2005	27	Upfront	5 yr: 81% (61–92)	5 yr: 73% (51–86)	8*	3	22	93
Smeland, 2004[#]	17	Upfront	5 yr: 70.6% (NA)	5 yr: 70.6% (NA)	5	0	12	71
Maramattom, 2013	48	Upfront	1 yr: 85% (72–93) 5 yr: 83% (69–91)	1 yr: 85% (71-93) 5 yr: 78% (63-88)	5 yr: 18% (8-30)[&]	NA	NA	NA
	57	Relapsed/refractory	1 yr:42% (29–54) 5 yr: 31% (19–44)	1 yr: 40% (27–52) 5 yr: 27% (16–40)	5 yr: 61% (47–73)[&]	NA	NA	NA
Sweetenham, 1996	70	Upfront	3 yr: 72% (NA)	3 yr: 73% (NA)	11	0	57	84%
	47	Relapsed/refractory	Chemosensitive: 37% (NA) Chemoresistant: 7% (NA)	NA	24	3	14	37%
Appelbaum, 1978	5	Relapsed	NA	NA	3	0	2	NA

Notes: *includes 1 patient who had already progressed prior to ASCT; [#]only patients who underwent MmCHOP + HDT/ASCT are included in the table; [&]5 year probability of progression/relapse with 95% CI in brackets. Absolute value is not reported in the article; [$]progression/relapse includes treatment-related deaths; NA – not available.

the 3-year OS and PFS rates were 72% and 73%, respectively. Two patients had insufficient follow-up data to be included in the final analysis. Within the same cohort, 57/68 maintained CR after a median follow-up of 26 months, whereas 11/68 had disease progression, relapse, or treatment-related death.

In the same study, 15 patients were treated with HDT/ASCT in their subsequent CR and 10 in PR. Seventy patients transplanted in first CR were followed for a median duration of 26 months (range, 1–126). The 3-year OS and PFS for the entire ASCT cohort (including those transplanted at first remission *vs* later) stood at 53% and 54%, respectively. Data for the cohort with subsequent CR and PR subjects were not analyzed separately in the study, and hence could not be presented here in the review.

Smeland *et al.* [22] retrospectively analyzed the clinical and histological data of 49 patients diagnosed with BL/BLL during 1981–2001; thirteen patients received MmCHOP therapy (intravenous

and intrathecal methotrexate, cyclophosphamide, doxorubicin, vincristine, prednisone), 17 received MmCHOP +/- HDT (cyclophosphamide and total body irradiation) and ASCT, and 19 received therapy as per Berlin — Frankfurt — Munster (BFM) protocol. Twelve out of 17 patients who achieved CR on MmCHOP eventually received HDT/ASCT and both the 5-year OS and PFS for the group was projected at 71%. On evaluation of the Kaplan — Meier plot for the other two groups, the projected 5-year OS and PFS for MmCHOP was 23% and 31%, respectively, and for BFM was 65% and 73%, respectively. The comparison of the survival plot among 3 groups shows a higher rate of OS and PFS in HDT/ASCT and BFM groups, although no statistical testing was reported to examine differences. Five of the 17 patients who did not achieve CR demonstrated tumor progression and eventual death from BL/BLL.

Maramattom *et al.* [19] studied the outcomes of autologous and allogeneic SCT in 241 patients of BL/BLL. Of these, 113 patients underwent autologous SCT, and 48 were transplanted in the first CR. The 5-year probability of progression or relapse in the total cohort was 44% (95% CI, 35–53) and 18% (95% CI, 8–30) in the first CR. PFS at 1- and 5- year was estimated to be 60% (95% CI, 51-69) and 48% (95% CI, 39–58), respectively. For patients transplanted in the first CR, PFS at 1- and 5- year was 85% (95% CI, 71–93) and 78% (95% CI, 63–88), respectively. OS at 1- and 5- year was 85% (95% CI, 72–93) and 83% (95% CI, 69–91), respectively. For the whole cohort, OS at 1- and 5- year was 62% (95% CI, 53–71) and 54% (95% CI, 44–63), respectively.

ASCT for relapse/refractory disease. In the study by Sweetenham *et al*. [23], the actuarial 3-year OS rate for patients in chemo sensitive relapse was 37%, whereas this was only 7% for chemo resistant relapse. Of the 47 patients who underwent ASCT at various disease stages (second or subsequent CR, PR, relapse, refractory), the study noted that 14 (30%) had a CR and 3 (7%) achieved PR after 26 months. Twenty one (46%) had relapse or disease progression, 5 (11%) did not show any response, and 3 (7%) died early due to treatment-related complications. The data for PR were presented together with disease stages other than first CR, and hence could not be further distinguished.

Maramattom *et al.* [19] noted a significant difference in the 1- and 5-year probability of PFS and OS in patients with subsequent CR/relapse as compared to first CR. PFS at 1- and 5- year was estimated to be 40% (95% CI, 27–52) and 27% (95% CI, 16–40), respectively. OS at 1- and 5-year was found to be 42% (95% CI, 29–54) and 31% (95% CI, 19–44), respectively. The progression rate was 61% (95% CI, 47–73) at 5 years.

Appelbaum *et al.* [20] studied the effects of high-dose CT with BACT regimen (bischloroethyl nitrosourea, cytosine arabinoside, cyclophosphamide, 6-thioguanine) in a group of 14 patients. Eight of these included patients were adult BL patients who had to have failed initial induction therapy, relapsed and failed re-induction, or relapsed within 2 months of prior induction for treatment with HDT/ASCT. Five patients underwent ASCT following HDT, of which one patient achieved CR for > 29 months and the other for >2 months since the completion of BACT within the study period. Three patients receiving ASCT died of complications following initiation of CT.

Safety/adverse events. Several toxicities were observed as a result of HDT/ASCT in the studies included in our analysis. In the study by van Imhoff *et al.* [21], reported toxic side effects of the treatment included mucositis, liver derangements, diarrhea, neurotoxicity, bone pain, and hemorrhage. No treatment-related mortality was reported in the study. 50% of the patients developed WHO grade 2–3 infections following ASCT. The only grade 4 toxicity seen with the treatment course was severe mucositis, with 17% developing this after ASCT. However, this data on toxicity were presented together for the entire cohort of BL/BLL and lymphoblastic lymphoma, and therefore does not represent the safety profile solely for BL/BLL.

Of the 113 patients in the ASCT cohort, Maramattom *et al.* [19] reported 56 deaths, 79% of which was attributed to relapsed BL. This was similar to reported deaths due to relapsed BL in human leukocyte antigen identical allogeneic SCT cohort (72%). Causes of non-relapse mortality included infection (n = 2; 4%), graft versus host disease (n = 1; 2%), and other causes (n = 9, 16%). Other reported causes were new malignancy, hemorrhage, spongiform disorder of the brain, and bilateral pneumonia with respiratory distress syndrome.

Of the 114 evaluable patients, Sweetenham *et al.* [23] reported 5 treatment-related deaths within 3 months and 5 deaths within 4 to 9 months of ASCT. Four patients died of infection (including cytomegalovirus and systemic fungal), and one patient died from thrombotic complication (hepatic veno-occlusive disease).

Of the 14 patients who underwent HDT/ASCT, there were no treatment-related deaths in the study by Smeland *et al.* [22].

Of the 5 adult patients who underwent ASCT, Appelbaum *et al.* [20] reported 3 deaths within 2 weeks of initiation of HDT/ASCT; two of them died because of acute carditis, and the other patient developed multiorgan failure and septicemia.

DISCUSSION

The rarity of adult BL/BLL leads to a challenge in designing research studies to improve outcomes or even establish a standard of care. To address limitations in the literature, we performed the first systematic review to explore the role of ASCT in the treatment of adult BL/BLL. Here, we found that adult patients who received ASCT had a 5-year OS ranging between 54% and 81% and a 5-year PFS stretching from 48% to 73%. The median ORR from the available data stood at 71%. Disease progression post-ASCT was found to be considerably lower in patients who underwent ASCT at first CR. We reviewed the available evidence on the role of ASCT in frontline consolidation in patients in the first remission. In the study by Smeland *et al.* [22], survival outcomes were comparable between MmCHOP + HDT/

ASCT group and BFM group (no ASCT) (5-year OS, 71% *vs* 65% and 5-year PFS, 71% *vs* 73%, respectively). Multiple other studies demonstrate measures of survival outcomes with CT alone for upfront consolidation which are comparable with the outcome measures of the studies using HDT/ASCT [10, 11, 15, 24]. For example, Mead *et al*. [10, 11] evaluated CODOX-M/IVAC regimen in adult BL, and calculated the event-free survival at 2 years to be 50–60% in high-risk patients. Evens *et al.* [15] examined the survival outcomes in newly diagnosed adult BL managed with CT and found the 3-year PFS and OS to be 64% and 70%, respectively after a median follow-up of 45 months. Based on the available evidence, ASCT in first remission may not offer benefit over CT alone. Further randomized controlled trials will be required to draw definite conclusions.

Patients who received ASCT in their first CR had better OS, PFS, and ORR than patients who were transplanted in subsequent remission or relapse or those who were refractory. Within the relapsed cohort, patients with chemosensitive relapse had better outcome measures with ASCT than chemoresistant relapse. A study from MD Anderson Cancer Center on 35 patients with relapsed or refractory BL or high-grade B-cell lymphoma also reported better median OS with chemosensitive relapse than those with chemoresistant relapse (7.5 months *vs* 1.7 months) [25]. The poor outcomes post-ASCT in chemoresistant disease suggests there is no benefit to transplant in this population.

Our systematic review found that ASCT appears to be effective in chemosensitive relapsed BL. The actuarial OS for patients with chemo sensitive relapse was found to be better with HDT/ASCT than those reported for conventional-dose salvage CT. Similar evidence was presented in a multicenter trial (PARMA) that compared ASCT with consolidation CT alone in chemo sensitive relapsed non-Hodgkin's lymphoma [26]. Even though this trial predominantly evaluated patients with diffuse large B-cell lymphoma, we can gain some valuable insight into the nature of chemosensitive relapsed aggressive B-cell lymphoma. Compared with DHAP (dexamethasone, high-dose cytarabine, cisplatin) alone, ASCT achieved better response rates (84% *vs* 44%), PFS (46% *vs* 12%), and OS (53% *vs* 32%) [26]. These data support the approach of ASCT in selected patients with chemosensitive disease.

Our review suggesting a benefit for ASCT in patients with chemosensitive relapse is aligned with the current National Comprehensive Cancer Center Network (NCCN) guidelines for ASCT in BL/BLL [6]. Currently, HDT with autologous stem cell rescue is recommended by NCCN guidelines as a consolidation/additional therapy for relapsed/refractory BL/BLL following CR or PR to second line therapy. NCCN guidelines do not suggest ASCT as a consolidative therapy in patients with no disease response or progressive disease, which is also supported by our review describing very poor outcomes (OS 7%) for patients undergoing ASCT for chemoresistant disease.

This review highlights the overall poor outcomes associated with relapsed or refractory BL. Studies in the pediatric population have also shown poor survival outcomes, with 5-year PFS and OS reported at 27%, and 25%, respectively [27, 28]. Further research is required to improve these outcomes, where novel antibody-drug conjugates, T-cell activating therapies, or CD19-directed chimeric antigen receptor T-cell therapies may have activity. Evaluating these therapies for relapsed BL against ASCT in a randomized controlled trial setting could provide critical information to guide treatment decisions.

Our study has several limitations. First, the majority of our included studies featured retrospective or prospective cohort methodologies. Many of these studies used cancer registries to quantitatively assess and draw a conclusion on the role of HDT and ASCT. Registry-based studies may have limited availability of treatment data, and outcomes may be underreported if there is premature loss to follow-up or inadequate follow-up [29]. The heterogeneity in subjects undergoing various induction regimens and high-dose conditioning protocols prior to ASCT in our studies limits our ability to make definitive conclusions.

To sum up, our systematic review found insufficient evidence to support ASCT over CT alone in first remission for adult BL/BLL. There is evidence to support the use of ASCT in chemosensitive relapse. There is insufficient evidence to support the efficacy of ASCT in chemoresistant disease. There is a lack of sufficient data and research on treatment-related mortality after ASCT. Further studies may be needed to draw definite conclusions.

STATEMENT OF ETHICS

An ethics statement is not applicable because this study is based exclusively on published literature.

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CONFLICTS OF INTEREST

Vijaya Raj Bhatt reports receiving consulting fees from Genentech, Rigel, Incyte, Servier Pharmaceuticals LLC, Partnership for health analytic research, LLC (which in turn, receives funds from Jazz Pharmaceuticals) and Abbvie, research funding (institutional) from Abbvie, Pfizer, Incyte, Jazz, Tolero Pharmaceuticals, Inc, and National Marrow Donor Program, and drug support (institutional) from Oncoceutics for a trial.

AUTHOR CONTRIBUTIONS

UJ: Conception and design, acquisition of data, analysis and interpretation of data, drafting the article, and final approval of the manuscript. RS: Acquisition of data, analysis and interpretation of data, and final approval of the manuscript. GN, SG: Acquisition of data, drafting the article, and final approval of the manuscript. VA: Analysis and interpretation of data, referencing, critical revision and final approval of the manuscript. BSP, VRB, CD: Conception of the study, analysis and interpretation of data, critical revision and final approval of the manuscript.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article or its supplementary material files. Supplementary table is freely available at https://www.researchgate.net/ profile/Utsav-Joshi-2. Further enquiries can be directed to the corresponding author.

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ЕФЕКТИВНІСТЬ АВТОЛОГІЧНОЇ ТРАНСПЛАНТАЦІЇ СТОВБУРОВИХ КЛІТИН У ДОРОСЛИХ ІЗ ЛІМФОМОЮ БЕРКІТТА АБО БЕРКІТТ-ПОДІБНОЮ ЛІМФОМОЮ: СИСТЕМАТИЧНИЙ ОГЛЯД

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Вступ: Лімфома Беркітта та Беркітт-подібна лімфома (ЛБ/БПЛ) є новоутвореннями з В-клітин гермінальних або постгермінальних етапів диференціювання з високою проліферативною активністю. З огляду на нечисленну кількість досліджень, присвячених вивченню впливу автологічної трансплантації стовбурових клітин (АТСК) на результати терапії нами було проведено систематичний огляд та проаналізовано ефективність застосування АТСК для лікування дорослих з рецидивами/рефрактерними випадками ЛБ/БПЛ. ***Матеріали та методи:*** За допомогою систематичного пошуку було визначено дослідження з чіткими результатами щодо ефективності АТСК у пацієнтів з ЛБ/БПЛ. Для оцінки ефективності використовували показники загальної виживаності (ЗВ), виживаності без прогресування (ВБП), повної відповіді (ПВ), часткової відповіді (ЧВ) і прогресування/рецидиву. ***Результати:*** Для пацієнтів, які пройшли АТСК та характеризувалися ПВ, 5-річна ВБП та ЗВ коливалися в межах 70–78% та 70–83% відповідно. У разі рецидивних або рефрактерних форм ЛБ/БПЛ 5-річна ВБП і ЗВ становили 27% і 31% відповідно. Пацієнти, які проходили АТСК при хіміорезистентних формах ЛБ/БПЛ, мали нижчі показники 3-річної ЗВ (7% проти 37%) у порівнянні із хіміочутливими формами захворювань ($p \leqslant 0{,}00001$). Загальний рівень відповіді на АТСК у пацієнтів з первинною ПВ, коливався в межах 71–93%, тоді як для пацієнтів, яким АТСК проводили за іншого статусу, ніж первинна ПВ, цей показник становив 37%. Прогресування/рецидив захворювання спостерігався у 16–29% пацієнтів, яким проводили трансплантацію після першої ПВ, і у 55–60% при рецидиві захворювання. ***Висновок:*** Не встановлено достатніх доказів на користь вищої ефективності АТСК з хіміотерапією після першої ремісії ЛБ/БПЛ у дорослих в порівнянні із самою лише хіміотерапією. Підтверджено ефективність АТСК при хіміочутливих, але не резистентних формах ЛБ/БПЛ.

Ключові слова: лімфома Беркітта, хіміотерапія, трансплантація гемопоетичних стовбурових клітин аутологічна, виживаність.