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Acta Haematologica Polonica

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DOI: 10.5603/ahp.99320

Article type: Review article

Submitted: 2024-02-11

Accepted: 2024-05-09

Published online: 2024-06-12

VIA MEDICA

REVIEW ARTICLE

Acta Haematologica Polonica 2024
Number 3, Volume 55, pages 137–144
DOI: 10.5603/ahp.99320
ISSN 0001–5814
e-ISSN 2300–7117

Current knowledge and management of primary mediastinal large B-cell lymphoma

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Abstract

Primary mediastinal large B-cell lymphoma (PMBCL) is a rare subtype of non-Hodgkin's lymphoma that predominantly affects young females. Despite advances in the understanding of its biology, there is still no consensus on the optimal treatment strategy. First-line regimens such as R-CHOP and DA-EPOCH-R result in 2-year progression-free survival (PFS) rates of c.80% and overall survival (OS) rates of c.90%. However, the role of radiotherapy as a consolidation treatment remains unclear, with some studies suggesting limited benefits for patients with negative PET scans at the end of treatment. In cases of relapse or refractoriness, second-line therapies are comparable to those employed in the treatment of diffuse large B-cell lymphoma. Autologous stem cell transplantation remains a crucial salvage option, with 3-year OS and PFS rates of c.65% and 60%, respectively. New treatment approaches, including immune checkpoint inhibitors (e.g. pembrolizumab and nivolumab), chimeric antigen receptor-T (CAR-T) cell therapy, and bispecific antibodies, have demonstrated promising results. Further research into novel molecular targets and treatment combinations is necessary to improve clinical outcomes and minimize treatment-related toxicities in PMBCL.

Key words: primary mediastinal large B-cell lymphoma, CAR-T, radiotherapy, refractory disease

Acta Haematologica Polonica 2024; 55, 3: 137–144

Introduction

Since 2008, primary mediastinal large B-cell lymphoma (PMBCL) has been recognized as a distinct entity in the World Health Organization (WHO) classification [1]. Despite sharing several features with classical Hodgkin's lymphoma (cHL) and gray zone lymphoma (GZL), PMBCL represents a separate clinicopathological entity that necessitates specific therapeutic approaches. [2] Despite increasing understanding of the disease's biology, there remains a lack of clear treatment guidelines [3–5]. This review aimed to summarize the current knowledge and therapeutic options for PMBCL.

Epidemiology

PMBCL accounts for c.2–4% of all non-Hodgkin's lymphoma cases, and 7% of diffuse large B-cell lymphoma (DLBCL), thus making it a relatively rare entity. The annual incidence of PMBCL is 0.4 per million, with a female/male ratio of 2:1. The median age at diagnosis is 35 years [6, 7].

Clinical features and risk stratification

The typical presentation of PMBCL is a large tumor in the anterior mediastinum. Due to compression caused by the rapid progressive mass, symptoms such as dyspnea, cough, dysphagia and obstruction of the airways or great

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Received: 11.02.2024 Accepted: 9.05.2024 Early publication: 12.06.2024

vessels can occur, resulting in superior vena cava syndrome. Approximately 50% of patients present with neck vein distension, facial edema, conjunctival swelling, and occasionally arm edema [8, 9]. Extrathoracic involvement at presentation is uncommon. 75% of patients present with stage I/II disease, and only 10% present with bone marrow infiltration [10].

Central nervous system (CNS) involvement is not a common feature, with a prevalence of 6% in the pre-rituximab era. It is currently not possible to accurately predict CNS relapses. However, multiple extranodal involvement, leukocytosis and elevated serum lactate dehydrogenase (LDH) levels have been linked to a higher probability of central nervous system (CNS) relapse. Therefore, routine CNS prophylaxis cannot be recommended in PMBCL [11].

For risk stratification, a standard international prognostic index (IPI) is used. But due to the fact that 2/5 risk factors are generally absent (i.e. stage III or IV and age over 60) the role of this index is limited [12]. A multicenter study in Japan demonstrated that pleural or pericardial effusion could be an adverse factor for PFS and the authors designed a novel prognostic score for PMBCL (the PMBL prognostic index — PMBIPI) which includes high/ /intermediate-risk IPI and effusions) [13]. The LYSA (Lymphoma Study Association) demonstrated that a baseline total metabolic tumor volume (TMTV) ≥360 cm^3 was associated with an unfavorable prognosis, independent of treatment [14].

Pathology and immunophenotype

PMBCL displays widespread growth and consists of large or medium-sized lymphoid cells, accompanied by varying levels of sclerosis. This sclerosis may encircle cell clusters and result in a compartmentalized or alveolar pattern. The cellular characteristics involve round to oval cells with transformed nuclei, similar to other centroblastic lymphomas. Immunoblasts and anaplastic cellular features can also be seen. Some PMBCLs contain Reed-Sternberg-like cells and their variants in certain microscopic fields [15].

PMBCL demonstrates the presence of pan-B cell antigens (CD19, CD20, CD22) and typically does not exhibit immunoglobulin expression, CD5 and CD10. In over 80% of cases, CD30 is positive, although the extent and intensity of the staining can vary. CD15 is generally negative. Tumor cells are usually positive for nuclear transcription regulators such as BOB1, PU.1, OCT2, PAX5 and MUM1/IRF4. Bcl-6 protein has been detected in over 50% of tumor cells and is considered to be a good prognostic factor [16]. PDL1, and PDL2 are positive in at least 70% of cases [17]. The presence of CD200, CD23, and MAL, along with TRAF1 and nuclear cREL, distinguishes PMBCL from DLBCL [18, 19].

Molecular pathogenesis

Oncogenic mutations in the JAK-STAT and NF-kB pathways are closely linked to immune evasion. Activation of the JAK-STAT pathway is achieved by IL-13R-mediated signaling, loss-of-function mutations in SOCS-1 and PTPN1, and gain-of-function mutations in STAT6 and IL4R [20, 21]. Gene expression profiles of oncogenic drivers in HL and PMBCL have indicated that PMBCL is one-third identical to NSHL.

The programmed death ligand-1 (PD-L1) locus (9p24.1) is frequently and specifically rearranged in PMBCL. Gene expression profiling studies have revealed that tumor necrosis factor (TNF) family members and TRAF1 are overexpressed in PMBCL. In PMBCL, this overactivation results in the activation of downstream anti-apoptotic genes, caspases, and cell cycle regulator transcription, which collectively lead to malignant proliferation. Two common genetic alterations in PMBCL are CIITA rearrangement and chromosome amplification of 9p24.1 (PDL1/PDL2) and 2p14 p16 [22, 23]. The presence of CIITA rearrangement has been demonstrated to be significantly associated with shorter disease-specific survival rates [24].

First line therapy

In the absence of large randomized controlled trials, there is no consensus on the first-line treatment of PMBCL. Current National Comprehensive Cancer Network (NCCN) guidelines recommend the R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) regimen with RT (radiotherapy) or consolidation with three cycles of R-ICE (rituximab, ifosfamide, carboplatin, etoposide). A parallel option is the DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) regimen with or without RT [25].

The European Society for Medical Oncology (ESMO) guidelines are similar: (R-CHOP, VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin); MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin); and R-V/ /MACOP-B, all with RT, plus other options such as dose-dense CHOP (R-CHOP14), and DA-EPOCH-R [26]. The British Society for Hematology guidelines include only two regimens: R-CHOPx6 + RT or DA-EPOCH-Rx6 without RT [27]. A comparison of the effectiveness of first-line treatment regimens is set out in Table I.

Studies comparing DA-EPOCH-R to R-CHOP are inconclusive. Zhou et al. demonstrated a higher ORR (overall response rate) i.e. 98% vs. 91% in patients treated with the DA-EPOCH-R protocol compared to the R-CHOP protocol. Also OS (overall survival) and PFS (progression-free survival) were better in the DA-EPOCH-R regimen [28]. In another study, 2-year survival was 89% in patients treated with R-CHOP compared to 91% in patients treated

Table I. Comparison of different treatment regimens for PMBCL

Reference	Treatment regimen	Number of patients	PFS	OS
Vassilakopoulos et al. [29]	R-CHOP	76	81% (5 years)	89% (5 years)
Lisenko et al. [30]	R-CHOP	45	95% (10 years)	92% (10 years)
Shah et al. [31]	R-CHOP	56	76% (2 years)	89% (2 years)
Shah et al. [31]	DA-EPOCH-R	76	85% (2 years)	91% (2 years)
Savage et al. [32]	M/VACOP-B	47	69% (5 years)	87% (5 years)
Zinzani et al. [33]	R-M/VACOP-B + RT	45	84% (5 years)	80% (5 years)

R-CHOP — rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; DA-EPOCH-R — dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab; M/VACOP-B — etoposide/methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; R-M/VACOP-B + RT — rituximab, etoposide/methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin with radiotherapy; PFS — progression-free survival; OS — overall survival

with DA-EPOCH-R. The aHR (adjusted hazard ratio) for OS and PFS was not statistically significant for DA-EPOCH-R vs. R-CHOP [OS, HR = 0.63 (0.19–2.15), *P* = 0.46; PFS, HR = 0.62 (0.24–1.47), *P* = 0.28]. The adjusted odds of CR were higher for patients treated with DA-R-EPOCH, but this was associated with a higher incidence of infection, neutropenic fever and hospitalization for acute toxicities [31].

Together, R-CHOP and R-CHOP-like regimens result in c.80% 2-year PFS and c.90% OS. The figures for DA-EPOCH--R are 81–93% 2-year PFS and 92–97% OS [34].

The role of radiotherapy as a consolidation treatment is also unclear. In 2013, Dunleavy et al. showed in a retrospective study of the DA-EPOCH-R regimen that of 51 patients included in the study, radiotherapy was deemed unnecessary in all but two (4%). Furthermore, during a median follow-up of more than 5 years (with a maximum of more than 13 years), no patient had recurrent disease [35].

A retrospective comparison of three regimens i.e. R--CHOP alone, R-CHOP + RT, and DA-EPOCH-R, showed that R-CHOP alone had a significantly inferior PFS, with projected 5-year PFS of 56.5% (95% CI 33.6%-74.1%), 88.5% (95% CI 74.5%-95.1%), and 90% (95% CI 72.1%-96.7%), for R-CHOP, DA-EPOCH-R, and R-CHOP + RT, respectively [36].

In patients with negative PET at end of treatment (EoT), the role of radiotherapy is limited. In a study of 268 patients with CMR (complete metabolic response) — defined as a Deauville score of 1 to 3 according to the Lugano classification — after treatment with rituximab and anthracycline-based therapy, and who were randomized to either OBS (observation) (n = 132) or RT (n = 136), PFS at 30 months was 96.2% vs. 98.5%. The 5-year overall survival was 99% in both arms [37].

In another study of 230 patients with PMBCL treated by immunochemotherapy, over 50% by R-CHOP, radiotherapy consolidation in the PET-negative subgroup led to a significant improvement (p = 0.039) in PFS at 6 years with 95% (n = 68) vs. 85.3% in the OBS group (n = 106). However, this was accompanied by a prolongation of OS (94.5% vs. 92.1%). In patients treated with R-CHOP, there was a trend towards a better probability of PFS in the RT group, but this was not statistically significant (HR 2.41, 95%CI 0.71–6.92, p = 0.17) and there was no difference in OS [38].

The role of RT after a DA-EPOCH-R regimen has also been evaluated. Patients with EoT-PET with a Deauville score of 1–3 should omit RT. However, a small group of patients with a Deauville-5 response, or high Deauville-4 uptake with SUVmax > 5, should undergo RT [39].

In summary, most patients treated with R-CHOP-like protocols can be effectively treated without radiotherapy. Nevertheless, RT is used more often in these regimens than in DA-EPOCH-R. Therefore, especially in younger patients with bulky disease, due to the risk of secondary tumors and cardiopulmonary toxicity of RT, DA-EPOCH-R may be preferred. EoT-PET can be a useful tool for further therapeutic decisions, regardless of the treatment regimen [22, 34].

Relapsed/refractory disease

In the rituximab era, treatment fails in 10–30% of cases, almost always within the first two years after diagnosis [40, 41]. Factors such as an IPI (International Prognostic Index) of 3 to 5, bulky disease, TMTV (total metabolic tumor volume) >360 cm^3, pericardial or pleural effusion and B symptoms have been associated with worse outcomes. If there is concern about disease progression, it is highly recommended that a tumor biopsy be performed to exclude a false positive PET result [42].

Second-line therapy in PMBCL is similar to that in DLBCL (diffuse large B cell lymphoma). Current NCCN guidelines recommend CAR-T therapy in the second-line in patients with primary refractory disease or relapse <12 months [25]. The UK guidelines recommend classical immunochemotherapy regimens (DHAP-R (dexamethasone, cytarabine, platinum, rituximab), GDP-R (gemcitabine, dexamethasone, cisplatin, rituximab), R-ICE (rituximab, ifosfamide, carboplatin, etoposide) for patients whose treatment intention is to proceed to transplantation [27].

In the MSKCC study of 60 patients receiving second-line therapy (SLT) for refractory (58%) or relapsed (42%) PMBCL, the overall response rate to SLT was 65%, with 40% achieving a complete response and 25% a partial response. Primary refractory disease was associated with a lower ORR than relapsed disease (54% vs. 80%, P = 0.02) and a much lower complete response rate (29% vs. 56%, P = 0.02). Patients with advanced disease had worse outcomes [43].

Autologous stem cell transplantation

Autologous stem cell transplantation (ASCT) remains an important option in the treatment of relapsed/refractory (R/R) disease. In some studies, transplantation in first remission has improved outcomes in patients with high-intermediate and high risk to the age-adjusted IPI or poor prognostic factors [44, 45]. However, other studies have shown contradictory results, and currently consolidation ASCT after first-line treatment is not recommended [46].

ASCT is a salvage therapy for patients who have achieved at least a partial response after subsequent chemotherapy. The overall response rate after ASCT was c.70%. The estimated 3-year OS and PFS of patients who proceeded to transplantation were 65% and 60%, respectively. Patients with chemo-refractory disease or relapse before 12 months had worse outcomes. Treatment-related mortality at 100 days was c.3% (neutropenic sepsis, disease progression) [40, 43].

Immune checkpoint inhibitors

Overexpression of PD1 in PMBCL may make it sensitive to PD1-blocking drugs such as pembrolizumab or nivolumab.

Pembrolizumab is a humanized, selective, IgG4/kappa monoclonal antibody directed against PD-1. In functional assays, pembrolizumab blocks PD-L1/2 and PD-1 interaction, and enhances T-cell activity for tumor regression and immune rejection [47]. In the KEYNOTE-170 trial, pembrolizumab was used in patients with R/R PMBCL after at least two lines of therapy. At a median follow-up of 48.7 months, the ORR was 41.4% (CR 20.8%), but the median DOR (duration of response) was not achieved. The 4-year PFS and OS were 33% and 45.3%, respectively. None of the patients who achieved CR progressed during follow-up. The most common adverse events were neutropenia (18.9%), asthenia (9.4%), and hypothyroidism (7.5%) [48].

Nivolumab is another PD1 blocker that has shown efficacy in PMBCL in combination with BV (brentuximab vedotin) — an anti-CD30 antibody conjugated to monomethyl auristatin E. The data came from the CheckMate 436 trial. 30 patients with R/R PMBCL after ≥ 2 lines of therapy were enrolled. The ORR was 73.3% (CR 40%) and the median time to response was 1.3 months. Median PFS and OS at 24 months were 55.5% and 75.5%, respectively. Consolidation HCT was received by 12 (40%) patients — 100% had a CR at 100 days post-transplant. The most common adverse events were neutropenia (40%), pyrexia (30%), and arthralgia (20%) [49].

CAR-T cell therapy

Chimeric antigen receptor-T (CAR-T) is a synthetic construct that can bind to target cell surface antigens via a single-chain variable fragment (scFv) recognition domain [50]. The US FDA (Food and Drug Administration) has approved two anti-CD19 CAR-T in PMBCL — axicabtagene ciloleucel (axi-cel) and lisocabtagene maraleucel (liso-cel) [51]. Currently, only liso-cel is registered by the European Medicines Agency (EMA) in second-line treatment. Axi-cel, due to a lack of trials (ZUMA-7 excluded patients with PMBL), is available after two lines of chemotherapy [52]. In the real-world results of axi-cel in PMBCL, the ORR was 76%, with a CR rate of 67%. The median time to best response was 29 days (range 20–492). The 24-month PFS and OS rates were 64% and 78%, respectively. Typical CAR-T complications such as cytokine-released syndrome (CRS) occurred in 88% of patients and neurological toxicity in 39% of patients. Grade 3 or higher CRS and neurological toxicity were observed in 6% and 27%, respectively [53].

The TRANSFORM clinical trial compared liso-cel to standard of care (SOC) with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment. The study included 17 patients with PMBCL. Results of the overall study showed that median event-free survival (EFS) was not reached (NR; 95% CI, 9.5 to NR) for liso-cel vs. 2.4 months (95% CI, 2.2–4.9) for SOC (HR, 0.356; 95% CI, 0.243–0.522). The complete response (CR) rate was 74% (95% CI, 63.7–82.5) for liso-cel vs. 43% (95% CI, 33.2–54.2) for SOC (P < 0.0001). Median PFS was NR (95% CI, 12.6 to NR) for liso-cel vs. 6.2 months (95% CI, 4.3–8.6) for SOC (HR, 0.400; 95% CI, 0.261–0.615; P < 0.0001) [54].

Risk factors identified for early progression after CAR-T therapy were extranodal involvement (≥2 sites) and lymphoma burden — elevated lactate dehydrogenase (LDH) and TMTV> 80mL [55].

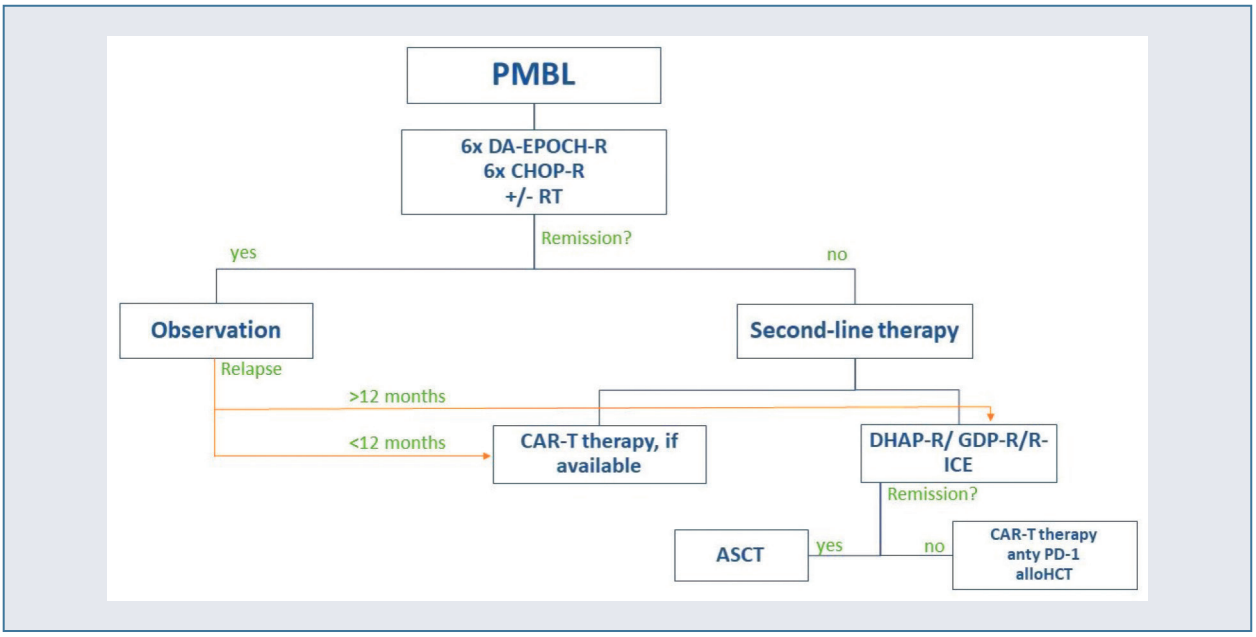

Figure 1. Treatment algorithm for primary mediastinal large B-cell lymphoma

Allogeneic hematopoetic cell transplantation

Until now, allogeneic hematopoietic cell transplantation (alloHCT) has been a therapeutic option for patients with R/R PMBCL who have progressive disease and who are ineligible for ASCT. In the CAR-T era, the role of allo-HCT has been limited. In the Lymphoma Study Association (LYSA) group trial, 33 patients with R/R PMBCL were enrolled to receive alloHCT. One patient received CAR-T prior to allo-HCT. At the time of transplantation, 50% of patients had a complete response, 40% had a partial response, and 10% had progressive disease. Median follow-up was 78 months. The 2-year OS, PFS and cumulative incidence of relapse were 48% (95%CI: 33–70), 47% (95%CI: 33–68), and 34% (95%CI: 18–50), respectively. Patients with progressive disease at transplantation had the worst 2-year PFS and OS (PFS: HR: 6.12, 95%CI: 1.32–28.31, p = 0.02 and OS: HR: 7.04, 95%CI: 1.52–32.75, p = 0.013) [56].

Data from allo-HCT post CAR-T therapy in large B-cell lymphoma shows that transplantation can provide durable remissions in a subset of patients. The median follow-up of survivors was 15 months. One-year OS, PFS and graft-versus-host disease-free survival were 59%, 45% and 39%, respectively. One-year non-relapse mortality and progression/relapse were 22% and 33%, respectively [57].

Bispecific antibodies

Bispecific antibodies (bsAbs) enable novel mechanisms of action and/or therapeutic applications that cannot be achieved with conventional IgG-based antibodies. Data from large clinical trials shows promising results in patients with R/R disease. For example, among 154 patients with large B-cell lymphoma treated with glofitamab (humanized anti-CD20/anti-CD3 bispecific monoclonal antibody), 39% achieved a complete response and 52% had an objective response [58]. In the pivotal trial of epcoritamab, the overall response rate was 63.1% (95% CI, 55.0–70.6) and the complete response rate was 38.9% (95% CI, 31.2–46.9) [59]. The trials also included patients after CAR-T therapy, which may be of interest for future therapeutic approaches. Both trials included several patients with PMBCL, but due to the small group size, further research into the efficacy of bsAbs is needed.

Role of ctDNA

Circulating tumor DNA (ctDNA) is an emerging biomarker in oncology, including lymphoma. Pre-treatment ctDNA levels and molecular responses are independently prognostic of outcome in aggressive lymphomas, including PMBCL. A 2-log decrease in ctDNA after one cycle of treatment (early molecular response [EMR]) and a 2.5-log decrease after two cycles (major molecular response [MMR]) stratify outcomes. In the first-line setting, patients achieving EMR or MMR had superior event-free survival (EFS) at 24 months (EMR: 83% vs. 50%; p = 0.0015; MMR: 82% vs. 46%; p< 0.001) [60]. Jimenez-Ubieto et al. showed that ctDNA was undetectable in patients with complete response. In terms of predicting relapse, the positive predictive value of ctDNA was 100% [61].

Conclusions

Despite the favorable results achieved with first-line treatment of primary mediastinal large B-cell lymphoma, the management of resistant and relapsed disease remains a challenge. Over the past two decades, considerable progress has been made in understanding the pathogenesis of this malignancy, leading to the introduction of novel therapeutic approaches. These range from the incorporation of rituximab to the use of PD1 inhibitors, CAR T-cell therapy, and bispecific antibodies. All of these agents have a place in the treatment algorithm (Figure 1). Ongoing investigations into innovative molecular targets, their synergistic effects with existing therapeutics, and the identification of determinants contributing to suboptimal treatment responses, have the potential to further improve clinical outcomes, making treatment more effective and less toxic.

Article information and declarations

Acknowledgments
None.

Authors' contributions
LG, SS — conceptualization; SS — formal research, writing original draft; LG, GD, AB — review and editing, supervision

Conflicts of interest
None.

Funding
None.

Supplementary material
None.

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