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Efficacy and Outcomes of Primary Mediastinal B-Cell Lymphoma Patients Treated with DA-EPOCH-R Regimen: A Single-Centre Experience

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ABSTRACT

Introduction: Primary Mediastinal B-Cell Lymphoma (PMBCL) is an aggressive subtype of non-Hodgkin lymphoma (NHL). One of the current recommended first-line treatments for PMBCL is a dose-adjusted (DA)-EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) regimen. This study aimed to determine the outcome of PMBCL patients treated with DA-EPOCH-R.

Methods: We performed a retrospective, single-centre study of patients aged 18 years and above, diagnosed with PMBCL and treated with DA-EPOCH-R between January 2013 and December 2017. A total of seven patients were included in the analysis. The primary outcomes were progression-free survival (PFS) and overall survival (OS). Secondary outcomes were complete response (CR), overall response rate, and treatment-related neutropenia.

Results: The median progression-free survival (PFS) and overall survival (OS) were 5.5 months and 13.4 months, respectively. No patient achieved a complete response (CR). One patient underwent an autologous stem cell transplant, and one underwent consolidative radiotherapy.

Conclusion: The outcome of this study is inferior to the previous studies, possibly due to the lack of dose escalation of the DA-EPOCH-R regimen.

Keywords: PMBCL, DA-EPOCH-R, lymphoma

INTRODUCTION

Primary mediastinal B-cell lymphoma (PMBCL) is a rare, aggressive subtype of non-Hodgkin lymphoma (NHL) that is derived from medullary thymic B cells and has features that overlap with Hodgkin's lymphoma. PMBCL accounts for approximately 10.0% of all diffuse large B-cell lymphoma (DLBCL), with higher predominance in females and the median age at diagnosis of 30-40 years old (1,2).

PMBCL patients often presented with a bulky mediastinal mass with common features such as pleural and/or pericardial effusion, chest wall invasion, lung invasion, and nodal involvement at mediastinal, cervical, axillary, and paraaortic lymph nodes (3).

In 2006, Savage et al. retrospectively analysed the clinical outcomes of 153 newly diagnosed PMBCL patients treated in British Columbia between 1980 and 2003 (4). Patients were treated with MACOPB (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin)/VACOPB (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or R-CHOP (rituximab with CHOP). The study showed the dose-intensive regimens MACOPB/VACOPB has superior efficacy over CHOP in terms of overall survival (OS). On the other hand, consolidation with radiotherapy to the mediastinum failed to show significant effects in progression-free survival (PFS) or OS. The role of radiotherapy remains controversial today as it is associated with serious late complications (1,5). However, some studies suggested consolidative radiotherapy should be considered in R-CHOP-treated patients although there is a lack of strong evidence (6,7).

Optimal first-line therapy to treat PMBCL remains debatable. National Comprehensive Cancer Network (NCCN) recommends dose-adjusted (DA)-EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) as the preferred first-line therapy (8). Other first-line therapies include six cycles of R-CHOP with or without involved-site radiation therapy (ISRT) and four cycles of R-CHOP then three cycles of R-ICE (optional rituximab, ifosfamide, carboplatin, etoposide) with or without ISRT. In the National Cancer Institute (NCI) study, PMBCL patients treated with DA-EPOCH-R were able to achieve favourable survival without radiotherapy (5). Nevertheless, NCCN suggests ISRT to be added to treatment for the persistent focal disease (8).

DA-EPOCH-R consists of rituximab, etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone. The regimen was designed to administer cytotoxic agents as a continuous infusion over 96 hours, in contrast to the R-CHOP regimen that is administered as a slow bolus (15-30 minutes). Long-hour infusion ensures continuous exposure of tumour cells to the chemotherapy agents and simultaneously increases both the efficacy and toxicity of DA-EPOCH-R. Furthermore, in order to achieve maximum cytotoxicity, the dosage of DA-EPOCH-R can be adjusted based on the patient's nadir absolute neutrophil count (ANC) and platelet count after each cycle (5). A total of 6-8 cycles are targeted for each patient. For each cycle, doses of chemotherapy agents can be increased if the patient's nadir ANC > 500/mm^3 and platelet count > 25/mm^3. Supportive treatments should also be given e.g. granulocyte colony-stimulating factor to prevent common side effects such as neutropenic fever and to allow increment of dose level for the next cycle.

In Sarawak, we adopted DA-EPOCH-R as the first-line treatment for PMBCL patients since 2013. While most published studies showed favourable outcomes, real-world, clinical data in our local population is deficient. Therefore, this retrospective, single-centre study was conducted in Sarawak General Hospital, a tertiary government community hospital on Borneo Island, to determine the outcome of our PMBCL patients treated with DA-EPOCH-R.

METHODS

Study Settings and Participants

Data collection was done in June 2021 by retrospectively identifying all PMBCL patients treated under Haematology Department, Sarawak General Hospital between January 2013 and December 2017. Patients who fulfilled the following criteria were included in this study: (1) diagnosed with PMBCL, (2) treated with DA-EPOCH-R regimen as first-line treatment or as an escalated treatment from R-CHOP, (3) initiated from January 2013, and (4) aged 18 years and above. The data collected from clinical records included gender, age, tumour size, Ann Arbor stage of disease, serum lactate dehydrogenase level at diagnosis, number of extranodal sites, and performance status according to the Eastern Cooperative Oncology Group. Computerised tomography (CT) scans were done in all patients for initial disease staging and assessment of disease response after treatment. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan was not routinely available due to funding issues. All patients were hospitalised in the haematology ward to receive chemotherapy via intravenous infusion.

The primary endpoints were the patient's progression free-survival (PFS) and overall survival (OS). Secondary endpoints were complete response (CR), overall response rate (ORR), and treatment-related neutropenia.

Table 1: Lugano's CT-based response criteria

Treatment Response	CT-based response
Complete response (CR)	• Target lymph nodes < 1.5 cm in LDi • No extralymphatic sites of disease • Organ enlargement regress to normal • No new lesion
Partial response (PR)	• ≥ 50% decrease in SPD of up to 6 target measurable node and extranodal sites • Spleen must have regressed by >50% in length beyond normal • No new lesion
No response or stable disease	• < 50% decrease in SPD of up to 6 target measurable node and extranodal sites • No increase in organ enlargement • No new lesion
Progressive disease (PD)	One of the following: • Single node: LDi > 1.5 cm and PPD increases ≥50% and LDi or SDi increases 0.5cm for lesions ≤ 2cm or increases 1.0 cm for lesions > 2 cm • Splenic length increases by 50% of the extent of its prior increase beyond baseline; or, if no prior splenomegaly, increase by > 2cm from baseline. • New lesions (>1.5cm) or new extranodal sites

Abbreviations: LDi, longest transverse diameter of a lesion; SPD, sum of the product of the perpendicular diameters for multiple lesions; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi.

Statistical Analysis

Response assessment was done according to Lugano's CT-based response criteria for lymphoma as summarised in Table 1 (8). We calculated the duration of OS from the date of diagnosis until the time of death or last follow-up. The duration of PFS was calculated from the date of first treatment until the date of progression confirmed with a CT scan, or event defined as a treatment failure including initiation of the next line chemotherapy, time of death, or last follow-up. The overall response rate (ORR) was calculated as the sum total of CR and

partial response (PR). The Kaplan-Meier method was used to estimate the probability of OS and PFS. Median follow-up was calculated from the date of enrollment to June 2021, the date of the most recent update.

RESULTS

Patients' Baseline Characteristics

Among the seven patients included in the study, all received R-CHOP as the initial treatment, prior to receiving the DA-EPOCH-R regimen. The median number of cycles of R-CHOP received was 2 cycles (range 1-4 cycles) since they were deemed too ill for DA-EPOCH-R as induction therapy. The median time to initiation of the first chemotherapy was 20 days (range 2-72 days) from the day of diagnosis, while the median time to initiate DA-EPOCH-R was 92 days (range 30 -132 days) from the day of diagnosis.

Table 2: Baseline characteristic of the study patients

Characteristics	All Patients, (n=7)
Female sex - n (%)	3 (42.9)
Age - years Median Range	 28 20-40
Bulky tumor, >=10cm Patients - n (%) Maximal diameter range - cm	 5 (71.4) 7-16
Stage IV disease - n (%)	3 (42.9)
Elevated lactate dehydrogenase level - n (%)	4 (57.1)
Pleural effusion - n (%)	2 (28.6)
Extranodal sites - n (%)	3 (42.9) Note: Lung involvement in 2 patients Lungs, spleen, and renal involvement in 1 patient
Median number of cycles of R-CHOP given prior to DA-EPOCH-R	2 cycles (range 1-4 cycles)
Median number of cycles of DA-EPOCH-R given	2 cycles (range 2-5 cycles)

Treatment Tolerability and Dose Adjustment

The median number of DA-EPOCH-R was 2 cycles (range 2-5 cycles). None of the patients received 6 cycles. Cumulatively, 21 cycles of DA-EPOCH-R had been administered. Dose

escalations were done in two patients (dose escalation to level 4 in one patient and level 2 in one patient). Most of the patients (71.4%) were treated without any dose escalation.

Grade 3-4 neutropenia was the most common adverse effect in study patients (2 patients, 28.6%). Both patients required hospitalisation.

Response Assessment and Survival Analysis

The median follow-up duration was 13.4 months (range 5-61 months). The response assessment of the study patients showed 42.9% ORR (3 achieved PR and none achieved CR). Two patients with PR underwent consolidation: 1 (14.3%) with radiotherapy and 1 (14.3%) with autologous stem cell transplant (ASCT). The ASCT patient achieved stable disease after consolidation while the radiotherapy patient's disease progressed within 4 months and salvage therapy was then given. The other PR patient relapsed 3 months after the end of the last DA-EPOCH-R. Salvage therapy was also given.

Four patients (57.1%) had progressive disease, and none had stable disease after DA-EPOCH-R (Table 3). Amongst patients with progressive disease, three of them eventually received salvage chemotherapy. One patient received no further treatment due to the development of atrial fibrillation and severe hypotension at six months post-DA-EPOCH-R. The patient was later discharged and has opted for palliative care.

Table 3: Treatment response rate of the study patients (n=7)

Treatment Response	n (%)
Overall Response Rate (ORR)	
Complete Response (CR)	0 (0.0)
Partial Response (PR)	3 (42.9)
Consolidative Radiotherapy	1 (14.3)
Consolidative auto-HSCT	1 (14.3)
Disease recurrence	1 (14.3)
Stable Disease (SD)	0 (0.0)
Progressive Disease (PD)	4 (57.1)
Salvage treatment for PD patients	3 (42.9)
Death	1 (14.3)

Auto-HSCT: autologous hematopoietic stem cell transplantation

The 1-year PFS was 0.0% and the 3-year OS of study patients was 28.6% (2/7 patients) (Figure 1 and 2). Median PFS and OS were 5.5 and 13.4 months respectively.

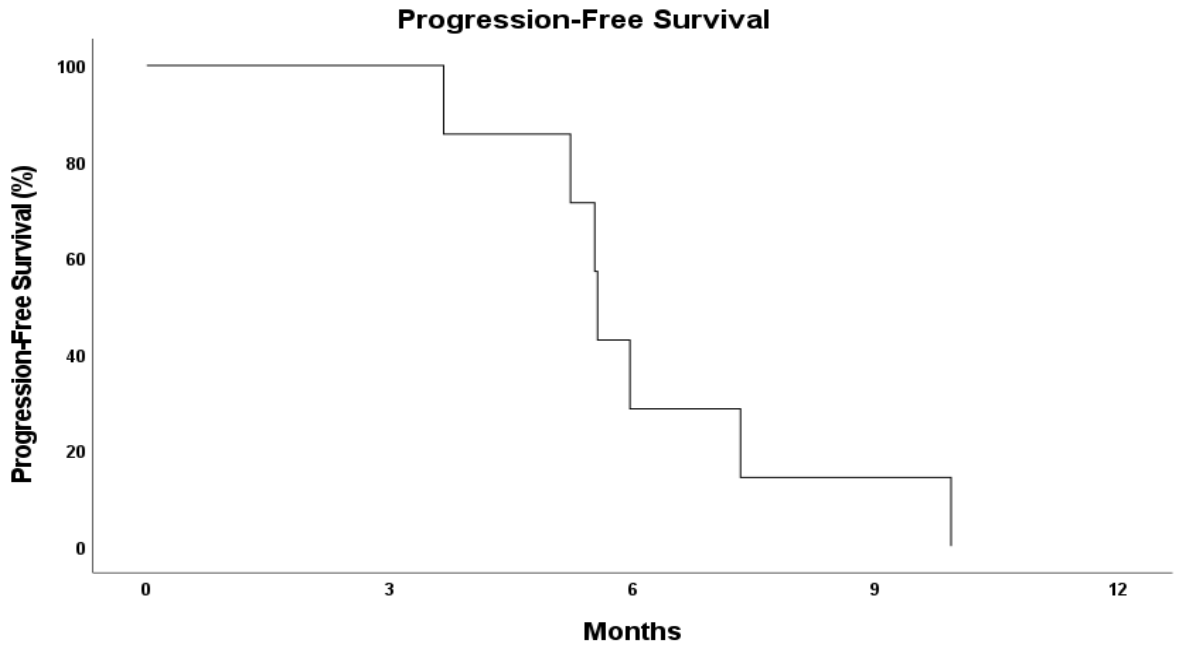

Figure 1: Progression-Free Survival over 12 months

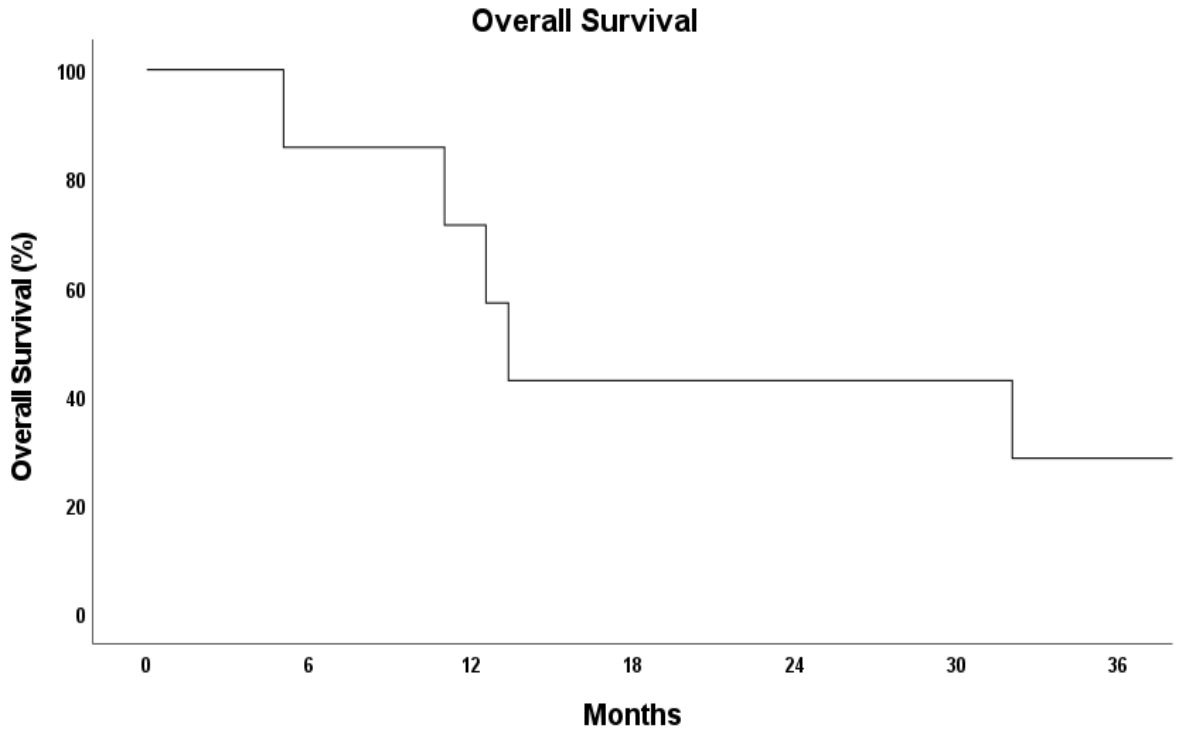

Figure 2: Overall survival over 36 months

DISCUSSION

Dunleavy et al. published a phase 2, prospective study that enrolled 51 untreated PMBCL patients to investigate the efficacy of DA-EPOCH-R in treating PMBCL without radiotherapy (5). 90.0% of the patients received 6 cycles of DA-EPOCH-R and 10.0% received 8 cycles. More than 50.0% of the patients had dose escalation to level 4 and above, and only a small portion (6.0%) did not have any dose escalation. On the other hand, Shah et al. conducted a retrospective, multi-centre study involving PMBCL patients diagnosed between 2011 and 2016 (6). The study compared the efficacy of R-CHOP and DA-EPOCH-R in 144 patients aged 18 years and above. The study population was similar to the study conducted by Dunleavy et al. Most patients (97.0%) received 6 cycles or more DA-EPOCH-R and dose escalations were done in 63.0% of all cycles.

In contrast, only a total of 21 cycles were administered in our study. There were 17 cycles where dose-escalation was indicated (absolute neutrophil count equal to or more than 500/mm^3) and none of the patients had thrombocytopenia. Despite so, dose escalation was only done in 4 cycles (19.0%). Doses of DA-EPOCH-R were not escalated due to fear of infection as many patients are staying in rural areas, far from the treating hospital. The absence of dose escalation for subsequent cycles of DA-EPOCH-R reduces the total dose administered which may impair the treatment outcomes.

Table 4: Comparison of DA-EPOCH-R cycles and dose escalation

Studies	Percentage of patients who received 6 or more cycles	Percentage of dose escalation done in all cycles
Dunleavy et al. (5)	90.0%	94.0%
Shah et al. (6)	97.0%	64.0%
Our results	0.0%	19.0%

Our results showed poorer outcomes when treating PMBCL patients with DA-EPOCH-R, with a median 1-year PFS of 0.0% and 3-year OS of 28.6%. Compared to Dunleavy et al., where a median follow-up of 63 months was done, the PFS and OS were 93.0% and 97.0% respectively. Of 294 cycles of DA-EPOCH, patients developed neutropenia (defined as absolute neutrophil count less than 500 cells per cubic milliliter) and thrombocytopenia (platelets less than 25,000 per cubic millimeter) were 50.0% and 6.0% respectively (5). Fever and neutropenia that requires hospitalisation account for 13.0% of the total cycles. Similarly, in Shah et al., at 24 months of median follow-up, the DA-EPOCH-R group has PFS and OS of 85.0% and 91.0%

respectively. Reported neutropenic fever and hospitalisation due to treatment complications were 33.0% and 34.0% respectively (6).

Nonetheless, in Dunleavy et al., ^{18}F-fluorodeoxyglucose–positron-emission tomography–CT (FDG-PET-CT) was used to assess disease response between cycles 4 and 6 to determine whether patients will receive a total of 6 cycles (those with a reduction of >20% in the greatest diameter of their tumour masses) or 8 cycles (those with a reduction < 20%). In contrast, our site only used CT scans as interim and end-of-treatment disease assessments. This may have contributed to the poor outcomes as CT scan is less sensitive than PET-CT, which leads to less accurately assessed disease response (9).

As aforementioned, the poorer outcomes in our setting were most likely due to the reduced number of cycles and lack of dose escalation in DA-EPOCH-R. As indicated in previous studies, regimens with increased dose intensity improve the survival of patients with PMBCL. DA-EPOCH-R was designed to deliver chemotherapy with increased intensity through a continuous infusion schedule which has shown promising outcomes without the need for radiotherapy (7). However, such improved outcomes have not been observed when DA-EPOCH-R was not delivered in sufficient doses and cycles. As a result, a patient might require radiotherapy at the end of treatment to achieve desired cure rate.

Several strategies should be considered to improve the current practice. R-CHOP followed by radiotherapy might be a feasible option to treat PMBCL patients with non-bulky disease (10). A single-centre retrospective study showed that there was no significant difference in OS between PMBCL patients with the non-bulky disease who received R-CHOP and DA-EPOCH-R (OS ranged 92-112 months vs 46-87 months, P=0.26) (11). For patients who received DA-EPOCH-R, dose escalation should be done if the patient's nadir ANC and platelet count are within the range as defined in the treatment protocol. Supportive care such as granulocyte colony-stimulating factor (GCSF) should be given as early as clinically feasible to reduce the rate and duration of neutropenia. Additionally, long-acting polyethylene glycol recombinant granulocyte colony-stimulating factor (peg-GCSF) might be considered as supportive management as it had been shown to reduce the incidence of febrile neutropenia (FN) and FN-related hospitalisation compared to conventional short-acting GCSF (10.4% vs 20.2%, P=0.038) (12).

CONCLUSION

The outcome of this study is inferior to the previous studies, possibly due to the lack of dose escalation of the DA-EPOCH-R regimen.

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REFERENCES

1. Nguyen LN, Ha CS, Hess M, Romaguerra JE, Manning JT, Cabanillas F, et al. The outcome of combined-modality treatments for stage I and II primary large B-cell lymphoma of the mediastinum. Int J Radiat Oncol Biol Phys. 2000;47:1281–1285.
2. Yang X, Laliberte F, Germain G, Raut M, Duh MS, Sen SS, et al. Treatment patterns, healthcare resource utilization, and costs of patients diagnosed with primary mediastinal B-cell lymphoma in the United States. Journal of Medical Economics. 2021; 24(1):469-478.
3. Müller NL, Tateishi U, Johkoh T, Onishi Y, Arai Y, Satake M, et al. Primary mediastinal lymphoma: characteristic features of the various histological subtypes on CT. J. Comput. Assist. Tomogr. 2004;28(6):782–789.
4. Savage KJ, Al-Rajhi N, Voss N, Paltiel C, Klasa R, Gascoyne RD, et al. Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience. Ann Oncol. 2006;17(1):123-130.
5. Dunleavy K, Pittaluga S, Maeda LS, Advani R, Chen CC, Hessler J, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med. 2013;368:1408-1416.
6. Shah NN, Szabo A, Huntington SF, Epperla N, Reddy N, Ganguly S. R-CHOP versus dose-adjusted R-EPOCH in frontline management of primary mediastinal B-cell lymphoma: a multi-centre analysis. Br J Haematol. 2018;180(4):534-544.

7. Wilson WH, Grossbard ML, Pittaluga S, Cole D, Pearson D, Drbohlav N, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood. 2001;99(8):2685-2693.
8. NCCN. Primary Mediastinal Large-B-cell lymphoma. In Zelenetz AD, Gordon LI, editors. NCCN Clinical Practice Guidelines in Oncology. B-Cell Lymphomas. 3rd ed.; 2021.
9. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwatz LH, Zucca E, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non Hodgkin Lymphoma: The Lugano Classification. Journal of Clinical Oncology. 2014;32(27):3059-3067.
10. Chen H, Pan T, He Y, Zeng R, Li Y, Yi L, et al. Primary Mediastinal B-cell Lymphoma: Novel Prevision Therapies and Future Directions. Frontiers in Oncology. 2021;11:ISSN 2234-943X.
11. Elhagracy R, Hamadah A, Pinto K, Hussain A, Osmani M, Alshemmari S. Primary mediastinal large B-cell lymphoma chemotherapy: Impact of chemotherapy choice. Hematol Oncol Stem Cell Ther. 2022;15(4):196-200.
12. Wei C, Zhang Y, Wang W, Zhang W. Optimizing Dose-Adjusted EPOCH Chemotherapy with Long-Acting Granulocyte Colony-Stimulating Factor During the COVID-19 Epidemic. Cancer Management and Research. 2021;13:3219-3225.