Original article

Retrospective Study of Efficacy and Safety of Various Salvage Chemotherapy Regimens in Relapsed or Refractory Lymphoma

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Abstract:

Background: *Relapsed or refractory lymphoma constitutes a poor prognosis. The standard of care involves salvage chemotherapy and autologous hematopoietic stem cell transplantation (ASCT). Choice of salvage chemotherapy depends on the experience and consideration of the physicians.* ***Objective:*** *The study aimed to compare salvage chemotherapy regimens' efficacy and side effects in relapsed or refractory lymphoma.* ***Method:*** *Medical records of patients with relapsed or refractory lymphoma receiving salvage chemotherapy in Srinagarind Hospital, Khon Kaen Province, Thailand from 1 January 2013 to 31 August 2018 were reviewed retrospectively.* ***Results:*** *Of all 55 patients with relapsed or refractory lymphoma, 23 patients received ESHAP regimen (41.8%), 26 patients received ICE regimen (47.3%), and 6 patients received R-ICE regimens (10.9%). The overall response rate (ORR) was 56.5% for ESHAP, 50% for ICE and 66.7% for R-ICE (p-value = 0.41). Males and normal serum LDH showed statistically significant better ORR (p-value = 0.015 both). No difference was found in adverse events rates. The 1-year overall survival rate (OS) did not differ among the three regimens. Patients with ASCT had significantly higher OS (p-value < 0.01).* ***Conclusion:*** *ESHAP, ICE and R-ICE regimens did not significantly differ in response rate, 1-year OS and adverse events. ASCT remains a key factor for long term survival among patients relapsed or refractory lymphoma.*

Keywords : ● *Relapse lymphoma* ● *Refractory lymphoma* ● *Salvage chemotherapy*

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นิพนธ์ต้นฉบับ

การศึกษาย้อนหลังของประสิทธิภาพและความปลอดภัยของการใช้เคมีบำบัดสูตร salvage regimen ต่างๆ ในผู้ป่วยมะเร็งต่อมน้ำเหลืองที่ไม่ตอบสนองต่อการรักษาหรือกลับมาเป็นซ้ำ

รณฤทธิ์ บุญรัตน์ กาญจนา จันทร์สูง จิตติมา ศิริจีระชัย และ ธีรินทร์ ลาน้ำเที่ยง
หน่วยโลหิตวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

บทคัดย่อ

บทนำ *มะเร็งต่อมน้ำเหลืองที่ไม่ตอบสนองต่อการรักษาหรือกลับเป็นซ้ำมีพยากรณ์โรคไม่ดี การให้เคมีบำบัดขนาดสูงตามด้วยการปลูกถ่ายไขกระดูกจากเซลล์ต้นกำเนิดตนเอง ถือเป็นการรักษามาตรฐาน สูตรเคมีบำบัดขนาดสูงที่ให้ขึ้นกับประสบการณ์และดุจพินิจของแพทย์* ***วัตถุประสงค์*** *เปรียบเทียบประสิทธิภาพและผลข้างเคียงของเคมีบำบัดขนาดสูงที่ใช้รักษาโรคมะเร็งต่อมน้ำเหลืองที่ไม่ตอบสนองต่อการรักษาหรือกลับเป็นซ้ำ* ***วิธีการศึกษา*** *ศึกษาข้อมูลเวชระเบียนย้อนหลัง ของผู้ที่รับการรักษาในโรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น ตั้งแต่วันที่ 1 มกราคม 2556 ถึง 31 สิงหาคม 2561* ***ผลการศึกษา*** *ผู้ป่วย 55 ราย ได้รับเคมีบำบัด ESHAP 23 ราย (41.8%), ICE 26 ราย (47.3%), R-ICE 6 ราย (10.9%) อัตราการตอบสนองโดยรวมเท่ากับ ESHAP: 56.5%, ICE: 50%, R-ICE: 66.67% (p-value = 0.41) เพศชายและค่า LDH ที่ปกติ มีความสัมพันธ์กับอัตราการตอบสนองโดยรวมที่ดีกว่า (p-value = 0.015 ทั้งสองปัจจัย) อัตรารอดชีวิตที่ 1 ปีและผลข้างเคียงไม่มีความแตกต่างกัน ผู้ที่ได้รับการปลูกถ่ายไขกระดูกจากเซลล์ต้นกำเนิดตนเอง มีอัตราการรอดชีวิตที่สูงกว่าอย่างมีนัยสำคัญทางสถิติ (p-value < 0.01)* ***สรุป*** *ESHAP, ICE และ R-ICE มีอัตราการตอบสนองโดยรวม อัตรารอดชีวิตและผลข้างเคียงไม่แตกต่างกัน การได้รับการปลูกถ่ายไขกระดูกฯ เป็นปัจจัยสำคัญสำหรับการรอดชีวิตในระยะยาวในผู้ป่วยมะเร็งต่อมน้ำเหลืองที่ไม่ตอบสนองต่อการรักษาหรือกลับเป็นซ้ำ*

คำสำคัญ : ● *มะเร็งต่อมน้ำเหลืองที่ไม่ตอบสนองต่อการรักษา* ● *มะเร็งต่อมน้ำเหลืองชนิดกลับเป็นซ้ำ* ● *เคมีบำบัด*
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Background

Approximately 10 to 13% of patients with lymphoma were found to have refractory disease, while 30 to 40% were found to involve relapsed disease[1,2]. Salvage chemotherapy and autologous hematopoietic stem cell transplantation (ASCT) are standard treatments for young and fit patients. The five-year survival rate was 53% among transplant eligible patients, but only 32% among transplant-ineligible patients[3]. Only chemosensitive patients can undergo ASCT, so salvage chemotherapy is crucial. Various salvage regimens have been used, such as ICE, R-ICE, DICE, DHAP, ESHAP, EPOCH, and MINE with quite similar outcomes. At Srinagarind Hospital in Khon Kaen, Thailand, 64 patients with relapsed or refractory lymphoma were retrospectively reviewed from 2013 to 2018. Salvage chemotherapy regimens included ESHAP, ICE, and R-ICE.

Limited information remains available about what should be the best regimen regarding treatment response, survival rate, success in stem cell collection and complications. This research aimed to determine the most suitable choice for second-line salvage chemotherapy regimens in refractory or relapsed lymphoma.

Materials and Methods

Those 18 years old or older with relapsed or refractory lymphoma receiving salvage chemotherapy as second-line treatment at Srinagarind Hospital, Khon Kaen University from January 2013 to August 2018 were reviewed retrospectively. Reviewed medical records were divided in three chemotherapy treatment groups: ESHAP, ICE, and R-ICE. The details of each regimen are shown in Table 1. Patients whose critical information was not fully recorded in their medical records or computerized databases were excluded.

All patients received G-CSF 24 hours after ending chemotherapy for at least seven days or until ANC > 1,000 cells/μL for three consecutive days. Acyclovir was administered to prevent reactivating the herpes zoster virus, and co-trimoxazole was administered to prevent *Pneumocystis jirovecii* pneumonia. Autologous hematopoietic stem cell transplantations were performed in eligible patients.

Refractory disease is defined as one that is unresponsive to therapy or increases in severity (progressive disease) based on Lugano criteria[4]. Relapsed disease means detecting new lesions among patients who previously had a complete response. This can be further subdivided by relapsing type: relapse within 12 months (early relapse) and relapse after 12 months (late relapse). Response to treatment was assessed after two cycles of chemotherapy.

The primary objective was to evaluate the overall response rate (ORR) in each regimen, which was counted for both complete remission (CR) and partial remission (PR). The secondary objective was to assess the side effects, factors affecting treatment results, overall survival (OS), and success rate in hematopoietic stem cell collection for ASCT.

Statistics and analysis were calculated in all three groups in terms of age, sex, disease stage, type of lymphoma, International Prognosis Index (IPI), pretreatment lactate dehydrogenase level (LDH), type of response to treatment after the first dose (refractory, early relapse, late relapse) and the number of chemotherapy cycles.

Table 1 Salvage chemotherapy details: ESHAP, ICE and R-ICE

ESHAP	**day**	**ICE**	**day**	**R-ICE**	**day**
interval 21-28 days		**interval 21-28 days**		**interval 21-28 days**	
Etoposide 40 mg/m^2	D1-4	Ifosfamide 5,000 mg/m^2 iv	D2	Rituximab 375 mg/m^2 iv	D1
Methylprednisolone 500 mg iv	D1-4	Carboplatin AUC = 5 (max 800 mg) iv	D2	Ifosfamide 5,000 mg/m^2 iv	D2
Cytarabine 2,000 mg/m^2	D5	Etoposide 100 mg/m^2 iv	D1-3	Carboplatin AUC = 5 (max 800 mg) iv	D2
Cisplatin 25 mg/m^2	D1-4			Etoposide 100 mg/m^2 iv	D1-3
16,030 THB		12,731 THB		45,218 THB	

The quantitative data are presented in mean and percentage data regarding treatment response. The differences in response to each treatment were statistically compared. The level of statistical significance was set at $\alpha = 0.05$. Overall survival was demonstrated using the Kaplan-Meier method, and groups were tested using log-rank analysis with a statistical significance level of $\alpha = 0.05$.

Results

Population characteristics and treatment

In all, 64 cases with relapsed or refractory lymphoma were reviewed, but only 55 patients with complete medical records were included. The median follow-up period was 11 months (5 to 30 months). The median age was 44.65 years (27 to 66.5 years), and 32 patients (58.18%) were men. Altogether 37 cases of diffuse large B-cell lymphoma (DLBCL) (67.3%), 9 cases of classical Hodgkin's lymphoma (16.4%), 5 cases of T-cell lymphoma (9.1%) and 4 cases of indolent lymphoma (7.3%) were found. Thirty-two cases involved refractory disease (58.2%), 11 cases late relapsed disease (20%), and 12 cases early relapsed disease (21.8%).

Twenty-three patients were treated using ESHAP chemotherapy, 26 patients for ICE, and 6 patients for R-ICE. Patients who were treated with the ICE regimen were younger, had more advanced staging, and had a higher proportion of refractory disease. The baseline characteristics are shown in Table 2.

Response to treatment

The overall response rate for the salvage chemotherapy regimen was 54.5%, with no significant differences among the three groups: ESHAP 56.5%, ICE 50%, and R-ICE 50% (n = 55, *p*-value = 0.41). The ICE regimen was more likely associated with a higher complete response rate but was not statistically significant, as shown in Table 3. The overall response rate for each lymphoma subtype from each regimen is shown in Table 4. Univariate analysis of factor-associated treatment response is demonstrated in Table 5, and multivariate analysis is demonstrated in Table 6.

Survival rate

At one-year follow-up, the number of survivors totaled 21 (ESHAP 7, ICE 12, and R-ICE 2). The total 1-year overall survival rate was 43.6% with 10±2.5 months median survival. No difference was found in the overall survival rate after one year (45.45% in ESHAP, 44.4% in ICE and 33.3% in R-ICE), as shown in Figure 1.

Table 2 Baseline characteristic data for each treatment population

Clinical characteristic	Number of patients		
	ESHAP (n = 23)	ICE (n = 26)	R-ICE (n = 6)
Median age (range)	51 (41-53)	39 (27-51.5)	60.5 (59-66.5)
Male	19	10	3
Female	4	16	3
Ann Arbor stage III-IV	14	19	3
Extra-nodal site >1	3	10	0
IPI 0-2	19	17	5
Refractory disease	13	19	0
Early relapse disease	6	4	2
Late relapse disease	4	3	4
DLBCL	13	18	6
Hodgkin lymphoma	4	5	0
T cell lymphoma	2	3	0
Indolent lymphoma	4	0	0
Median cycles (range)	4 (2-6)	4 (2-6)	4 (2-6)

Table 3 Response rate for each regimen

	Response			*p*-value
	ESHAP (n = 23)	ICE (n = 26)	R-ICE (n = 6)	
ORR	13 (56.5%)	13 (50%)	4 (66.67%)	0.41
CR	5 (21.7%)	11 (42.3%)	2 (33.3%)	0.13
PR	8 (34.8%)	2 (7.7%)	2 (33.3%)	
SD	4 (17.4%)	10 (38.5%)	0	
PD	6 (26.1%)	3 (11.5%)	2 (33.3%)	

Table 4 Overall response (complete and partial remission) of each regimen for each lymphoma subtype

Lymphoma subtype	Regimen	Overall response
DLBCL (n = 37)	ESHAP (n = 13)	7 (53.8%)
	ICE (n = 18)	8 (44.4%)
	R-ICE (n = 6)	4 (66.7%)
Hodgkin's lymphoma (n = 9)	ESHAP (n = 4)	2 (50%)
	ICE (n = 5)	3 (60%)
	R-ICE (n = 0)	-
T cell lymphoma (n = 5)	ESHAP (n = 2)	0
	ICE (n = 3)	2 (66.67%)
	R-ICE (n = 0)	-
Indolent lymphoma (n = 4)	ESHAP (n = 4)	4 (100%)
	ICE (n = 0)	-
	R-ICE (n = 0)	-

Table 5 Univariate analysis of factors associated treatment outcome for overall response rate

Factors	ORR (%)	Odd ratio	*p*-value (<0.05)	95% CI
Male (n = 32)	68.75	4.13	0.015	1.32-12.87
Normal LDH (n = 32)	68.75	4.13	0.015	1.32-12.87
ICE-based (n = 32)	53.13	0.87	0.803	0.29-2.56
Age < 60 year (n = 48)	52.08	0.44	0.347	0.08-2.46
Stages I-II (n = 19)	47.37	0.64	0.439	0.21-1.97
IPI 0-2 (n = 41)	56.09	1.28	0.693	0.38-4.31
Extranodal ≤ 1 (n = 42)	57.14	1.56	0.488	0.45-5.43
Bulky (n = 10)	40.00	2.05	0.313	0.51-8.29
Early relapse or refractory (n = 44)	52.27	0.63	0.501	0.16-2.45

Table 6 Multivariate analysis of factors associated treatment outcome for overall response rate

Factor	Odd ratio	*p*-value (< 0.05)	95%CI
Male (n = 32)	4.07	0.025	1.19-13.90
Normal LDH (n = 32)	4.84	0.029	1.17-19.85
IPI 0-2 (n = 41)	0.84	0.845	0.15-4.64
Stages I-II (n = 19)	0.59	0.474	0.15-2.46

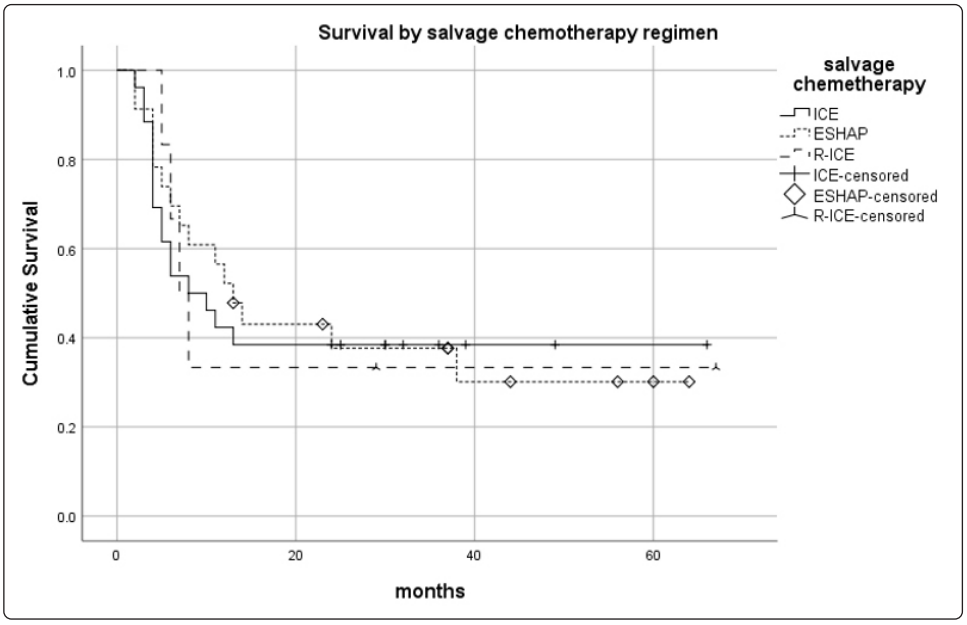

Figure 1 Overall survival rate of patients receiving each regimen of chemotherapy

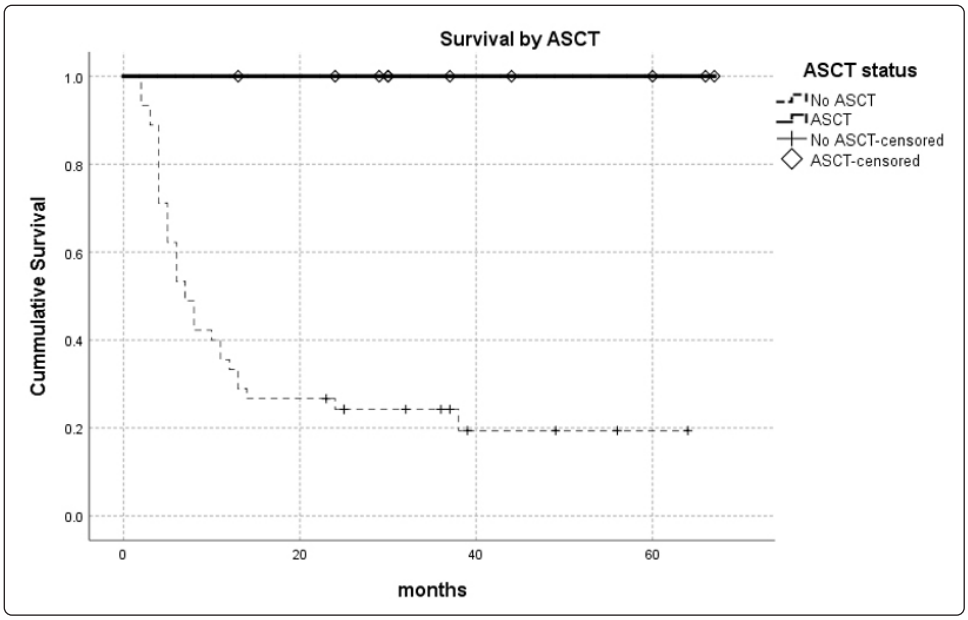

Figure 2 Significantly higher overall survival in the autologous stem cell transplant group (ASCT) compared with the nonrecipient group (p-value < 0.01).

Ten patients underwent a successful ASCT, 3 for ESHAP, 5 for ICE, and 2 for R-ICE. One patient, who was treated with six cycles of ICE, failed stem cell collection (stem cell collection < 2.0 x10^6 cell/kg). The patients with ASCT had significantly higher overall survival (p-value < 0.01), as shown in Figure 2. Among patients without ASCT, one year OS was only 24.4% and median survival was 6±1.4 months. Only eight patients who had complete remission response but did not receive ASCT remained alive with a median follow-up period of 36.5 months.

Safety and side effects of treatment

From the three treatment groups, 108 treatment-related side effects involved grades 3 and 4 severity from a total of 221 chemotherapy cycles (48.8%). The most common side effects included neutropenia (21.26%), thrombocytopenia (14%), and anemia (9.5%). No difference was observed in the incidence of side effects of the three chemotherapy regimens for hematologic and nonhematological conditions, as shown in Table 7.

Table 7 Adverse events of salvage chemotherapy

	ESHAP (N=94 cycles)		ICE (N=101 cycles)		R-ICE (N=26 cycles)	
Adverse event	all grades	Grade ≥3	all grades	Grade ≥3	all grades	Grade ≥3
Hematologic adverse event						
Anemia	19 (20.2%)	7 (7.4%)	24 (23.8%)	12 (11.9%)	3 (11.5%)	2 (7.7%)
Neutropenia	20 (21.3%)	20 (21.3%)	26 (25.7%)	23 (22.8%)	5 (19.2%)	4 (15.4%)
Thrombocytopenia	19 (20.2%)	12 (12.8%)	23 (22.8%)	17 (16.8%)	4 (15.4%)	2 (7.7%)
Nonhematologic adverse events						
Acute kidney injury	11 (11.7%)	0	17 (16.8%)	0	4 (15.4%)	1 (3.8%)
Nausea	18 (19.1%)	0	25 (24.8%)	0	3 (11.5%)	0
Febrile neutropenia	15 (16%)	3 (3.2%)	19 (18.8%)	3 (2.9%)	3 (11.5%)	0
Allergic reaction	0	0	0	0	1 (3.8%)	0
Liver enzyme elevation	2 (2.1%)	0	4 (3.9%)	1 (0.9%)	0	0
Venous thromboembolism	0	0	1 (0.9%)	1 (0.9%)	0	0

Discussion

Relapsed or refractory lymphoma is a poor prognostic disease. Currently, many drugs focus on targeted treatment, but not all patients have access to such treatments. Patients with relapsed or refractory lymphoma will receive high dose chemotherapy aiming for a complete or partial response, and then continue ASCT. This practice is crucial for a patient's long term survival.

Salvage chemotherapy comes in a variety of regimens. Treatment is mainly based on the physician's experience because the data from clinical research is relatively minimal, without head-to-head randomized controlled trials.

Our treatment response rates for ESHAP, ICE and R-ICE groups were similar. The average was 54.5%, similar to the result from the study of Ramzi M et al.[5], which found that ORR among 44 patients with relapsed or refractory Hodgkin's lymphoma using the ESHAP regimen was 50.0%. Norasetthada L et al.[6] found that 33 patients with relapsed or refractory peripheral T-cell lymphoma, receiving an ESHAP regimen had an ORR of 46%. Moreover, Gisselbrecht C et al.[7] found 202 of 396 patients with relapsed or refractory DLBCL, receiving RICE had an ORR of 63.5%, which differed from some studies with higher ORR. Kewalramani T et al.[8] found that 36 patients with relapsed or refractory DLBCL, receiving R-ICE had an ORR of 78%. A study by Hertzberg MS et al.[9] among 75 patients with Hodgkin's or non-Hodgkin's lymphoma found an ICE regimen efficacy of ORR 89%, but data could not be compared due to differences in population. Due to the limited access to anti-CD20 monoclonal antibody therapy (rituximab) in Thailand, only six patients received the drug, and only three patients were eligible to undergo ASCT.

Patients receiving rituximab exhibited a complete remission response rate of 66.7%. Habermann TM[10] found female patients had better overall responses, similar to Pfreundschuh M et al.[11] and Horesh N et al.[12] They explained that women had a lower clearance rate of some drugs in chemotherapy regimens than men, in contrast to our study, which found men had better overall responses than women. Nevertheless, we could not address the mechanism between sex-associated responses and salvage chemotherapy due to the small sample size. We also found that normal pretreatment serum LDH showed a better outcome than high level serum LDH because serum LDH indicated high tumor burden disease, correlating to the findings of Purnamasidhi CAW et al.[13], Ferraris AM et al.[14] and Schneider RJ et al.[15].

The side effects of each chemotherapy regimen did not differ for both hematologic and non-hematologic systems. The incidence of side effects was comparable to that of other studies[5-9].

All treatment regimens' survival rates were as follows: median survival = 10±2.5 months, 1 year OS = 43.6%. However, we found that one-year OS was only 24.4%, and median survival was 6±1.4 months for aggressive lymphoma groups not receiving ASCT. This study found that patients undergoing ASCT had better one-year OS. The PARMA study16 found that ASCT could improve five-year event-free survival and OS compared with conventional therapy. ASCT is considered whenever feasible.

Based on this study, ICE treatment might be associated with more complete remission than the ESHAP regimen. When combined rituximab was administered, it should improve the percentage of the best response. Due to the shorter duration of administration and lower cost compared with the ESHAP regimen (12,731 THB compared with 16,030 THB in 2019), ICE-based chemotherapy was more likely to be chosen than ESHAP to treat patients with relapsed or refractory lymphoma in our center.

The retrospective study design was a limitation, so we could not decide conclusively in selecting the most suitable regimen. Disease heterogenicity limited the interpretation of chemotherapy efficacy. In addition, inhomogeneous characteristics for each subtype of lymphoma may have influenced the outcome. For example, the CORAL study[7] found that the RDHAP regimen might improve outcome in DLBCL with the germinal center B-cell group. The quite smaller population in R-ICE compared with ESHAP and ICE constituted one limitation for interpreting differences among regimens. When a precise comparison between salvage regimens is necessary, prospective studies, using specific disease profile classification, should be performed to answer such a question.

Conclusion

ESHAP, ICE, and R-ICE chemotherapy regimens were not statistically significant in the response rate, one-year overall survival rate, success in stem cell collection or side effects. ICE-based regimen, especially combined with rituximab, possibly increased the likelihood of complete remission response. The limitations encountered in this research included its retrospective design, disease heterogenicity, and the rather smaller population in the R-ICE group. Salvage therapy and ASCT are crucial for the long term survival of those with relapsed or refractory lymphoma.

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