Quantitative evaluation of therapy options for relapsed/refractory diffuse large B-cell lymphoma

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Abstract

Background

The prognosis of patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) is still poor, and their treatment options are limited, which highlights the need for new treatments. This study aimed to quantitatively evaluate the efficacy, safety, and related factors of various therapeutic options for patients with r/r DLBCL to provide necessary quantitative information for clinical practice.

Methods

A literature search was conducted using public databases. The parametric survival function was used to describe the time course of overall survival (OS) and progression-free survival (PFS) in patients with r/r DLBCL receiving various treatment regimens. A random-effects model in a single-arm meta-analysis was used to analyze the objective response rate (ORR) and grade 3–5 adverse event rates based on various treatment regimens.

Results

A total of 58 studies including 3124 subjects were included. Combination therapy had a significant benefit in terms of OS, PFS, and ORR compared with monotherapy. ORR and PFS were significantly improved in the treatment regimen, including chemotherapy, but OS did not improve, and grade 3–5 adverse events significantly increased. In terms of treatment strategy, the efficacy of chemotherapy combined with immunotherapy sequential autologous stem cell transplantation (ASCT), immunotherapy combined with immunotherapy, chemotherapy sequential ASCT, chemotherapy combined with immunotherapy, and chemotherapy combined with two types of immunotherapy is better. Specific to each treatment regimen, R-inotuzumab ozogamicin, R-BEAM + ASCT, R-ESHAP-L, iodine-131 tositumomab + BEAM + ASCT, and chemotherapy + CAR-T had better efficacy, with median OS of 48.2, 34.2, 27.8, 25.8, and 25 months, respectively. Moreover, there was a strong correlation between the 6-month PFS and 2-year OS in the combination therapy.

Conclusions

Combination therapy and chemotherapy can significantly improve the efficacy of r/r DLBCL treatment. The 6-month PFS can be used as a surrogate endpoint for the 2-year OS. This study provides the necessary quantitative information for clinical practice and clinical trial design of r/r DLBCL.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive (fast-growing) B-cell non-Hodgkin lymphoma (NHL)[1]. It is the most common subtype of NHL, with an estimated incidence rate of 4.68 cases per 100,000 person-years[2,3]. Although rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is the standard treatment for patients with DLBCL[4–7], approximately 33% of patients are refractory to or that relapse after frontline therapy, and the prognosis is usually poor[8,9].

Autologous stem cell transplantation (ASCT) consolidation remains the treatment of choice for patients with DLBCL. However, it can only be recommended to young, relatively healthy patients who respond to chemotherapy, with a long-term survival rate of only 40%[10–13]. Chemosensitivity is a major factor that determines the benefits of ASCT. Therefore, refractory patients who do not respond to chemotherapy benefit little from ASCT and have a poor prognosis[14]. For patients who are ineligible for ASCT or relapse within 12 months after ASCT and for refractory patients who do not respond to chemotherapy, treatment options are limited, and the efficacy is poor[15–18]. Therefore, it is crucial to explore and evaluate new therapeutic strategies for relapsed/refractory (r/r) DLBCL treatment[19–21].

Various novel therapies are currently used to treat r/r DLBCL, including chimeric antigen receptor T cells, bispecific T-cell engagers, immunomodulatory drugs, immune checkpoint inhibitors, monoclonal antibodies, and antibody–drug conjugates[22]. A combination of drugs with different targets among chemotherapy, targeted therapy, and immunotherapy may produce synergistic effects to improve the poor efficacy in patients with r/r DLBCL. However, no studies have systematically compared the efficacy of different regimens, and published meta-analyses have only evaluated the efficacy of a single regimen[23–25]. Furthermore, although the NCCN guidelines provide medication guidance for r/r DLBCL, they are only qualitative descriptions, lack quantitative comparison of the efficacy of different treatment regimens, and cannot fully guide clinical medication[26].

A model-based meta-analysis (MBMA) is a quantitative analysis method that combines mathematical modeling and meta-analysis. By establishing a time course model and covariate model, MBMA can deduce the influence of heterogeneity among different studies, thereby quantifying the time effect and influencing factors of drugs, and has become an important method in model-informed drug development strategies[27,28]. This study quantitatively analyzed the efficacy characteristics (including overall survival [OS] and progression-free survival [PFS]) and influencing factors of all current treatment regimens (single and combination therapies) for the treatment of patients with r/r DLBCL through MBMA based on extensive literature data. This study aimed to clarify the differences in the efficacy of different treatment regimens and analyze the incidence of adverse events, which can provide necessary quantitative information for the clinical use of r/r DLBCL and development of new drugs.

Methods

Search strategy

A comprehensive literature search was performed in the public databases of PubMed, Embase, and the Cochrane Library for clinical trials of drug therapy in r/r DLBCL published between January 1, 2010, and January 25, 2021. The search keywords included “relapsed,” “refractory,” and “diffuse large B-cell lymphoma.” Only clinical trials were included, and the language was restricted to English. The detailed search strategies are described in the Supplementary Material.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) diagnosis of relapsed/refractory DLBCL; (2) report on least one of the efficacy indicators of OS, PFS, or objective response rate [ORR]; and (3) interventions that include chemotherapy, targeted therapy, and immunotherapy used alone or in combination.

The exclusion criteria were as follows: (1) other subtypes, DLBCL transformed from other subtypes, or high-risk disease with undiagnosed r/r DLBCL and (2) sample size of < 10 per arm in order to reduce sampling error.

Data extraction

Microsoft Excel (version 16.0.12130.20232) was used to categorize the relevant information from the included studies. The collected information included literature characteristics (author, publication year, clinical trial registration number), trial design (group, dose, administration frequency, administration period, and sample size), participant characteristics (age, sex ratio, race, ECOG score, Ann Arbor stage, IPI score, proportion of relapsed or refractory patients, time since diagnosis, medication history, percentage of patients previously treated with rituximab, etc.), efficacy outcomes (OS, PFS, ORR, and safety outcomes (incidence of grade 3–5 hematologic and non-hematologic toxicities).

The abovementioned information was independently extracted by two researchers, and inconsistencies were determined by a third researcher through consultation. When the data in the literature were presented graphically, the data in the figure were extracted using the Engauge Digitizer (version 4.1) software.

OS and PFS analysis

Parametric survival models were used to analyze the OS and PFS data. The survival model is related to hazard function h(t), which can be interpreted as an instantaneous hazard at time t. The relationship between the survival model and hazard function was determined as follows[29]:

Survival model $\mathrm{S(t)} = \exp(-\int_0^t h(t)\,dt)$ (1)

Four different hazard functions were evaluated, including the constant, Gompertz, Weibull, and lognormal models (Equations 2–5):

Constant $h(t) = \lambda$ (2)

Gompertz $h(t) = \lambda \cdot \exp(\beta \bullet t)$ (3)

Weibull $h(t) = \lambda \bullet \exp(\beta \bullet \ln(t))$ (4)

Lognormal $h(t) = \frac{\left(\sigma t\sqrt{2\pi}\right)^{-1} e\left(-\frac{1}{2}z^2\right)}{1-\emptyset(Z)}$, (5)

In Equations 2–5, λ and β denote the hazard rate at time 0 and change in the regression coefficient of the hazard rate over time, respectively. h(t) in Eq. 5 conforms to a log-normal distribution, where μ and σ are the median and standard deviation of the log-normal distribution, respectively. The best hazard model was selected based on the minimum value of the objective function (OFV), standard error of the model parameter estimation, and goodness-of-fit of the model.

The inter-trial variation (Eq. 6) and residuals (Eq. 7) were added to the model parameters to account for the differences between the observed and model-predicted values. The inter-study variability (η) was introduced into the model parameters in an exponential form, and the residual variability (ε) was defined by an additive model:

$$P_i = P_{pop} \times e^{\eta_i}$$

6

$$Obs_{j,i} = Pred_{j,i} + \mathrm{SE}_{j,i} \times \epsilon_{j,i}$$

7

$$SE_{j,i} = \sqrt{\frac{Obs_{j,i} \times (1 - Obs_{j,i})}{N_{j,i}}}$$

8

In Eq. 6, $\mathrm{P_i}$ is the individual value of the model parameter for study i, and $\mathrm{P_{pop}}$ is the typical population value of the model parameter. η_i is the inter-study variability of the model parameter, which conforms to a normal distribution with a mean of 0 and variance of ω_i^2. In Eq. 7, $\mathrm{Obs_{j,i}}$ is the measured survival data at time j in study i. $\mathrm{Pred_{j,i}}$ is the predicted survival data at time j of study i. $\epsilon_{\mathrm{j,i}}$ is the residual error of time j of study i, which conforms to a normal distribution with a mean of 0 and variance of σ^2. $\epsilon_{\mathrm{j,i}}$ is weighed by the standard error of the survival data at time j of study i ($SE_{j,i}$), which can be acquired by Eq. 8, where $N_{j,i}$ is the sample size of time j in study i.

Covariate models were used to examine potential factors affecting the model parameters. The examined continuous covariates included age, sex ratio, race ratio, ECOG score, Ann Arbor stage, IPI score, number of treatments received since diagnosis, and proportion of relapsed or refractory patients. The examined

categorical covariates included whether patients received chemotherapy or whether patients received combination therapy. Missing covariate information was imputed using the median value of the entire study population. Missing covariate proportions of > 30% were not tested. Continuous variables were introduced using Equations 9–10, and categorical variables were introduced using Eq. 11:

$$P_{pop} = P_{typical} + \left(COV - COV_{median}\right) \times \theta_{cov}$$

9

$$P_{pop} = P_{typical} \times \left(\frac{COV}{COV_{median}}\right)^{\theta_{cov}}$$

10

$$P_{pop} = P_{typical} + COV \times \theta_{cov}$$

11

In Equations 9–11, P_{pop} is the model parameter at different covariable levels, and $P_{typical}$ is the typical population value of the model parameter when the categorical covariate is equal to 0 or continuous covariate is equal to COV_{median}. COV is the covariate value, COV_{median} is the median value of this covariable in the analysis dataset, and θ_{COV} is the correction coefficient of the covariable for the model parameters.

Forward inclusion and backward elimination methods were used for covariate screening. The bound of OFV decrease in the forward method was set at 3.84 ($P < 0.05$), while, in the backward method, the bound was set at 6.63 ($P < 0.01$).

Model evaluation

The goodness of fit of the proposed model was assessed using the model diagnostic plot. Model diagnostic plots included scatter plots of observed values versus population predicted values (PRED) and individual predicted values, conditional weighted residuals versus time, and PRED. A visual predictive check (VPC) was used to evaluate the predictive performance of the model by comparing the 95% confidence interval (CI) of the model predictions with the observed values. The bootstrap method was used to assess the robustness of the model; that is, 1,000 new datasets were acquired from the original dataset to obtain the median of the model parameter distribution and its 95% CI and compared with the estimated values of the model parameters obtained from the original dataset; if they were closer, it indicated that the model was robust and less influenced by individual studies[30].

Model prediction

After the final model was established, Bayesian feedback was used to obtain model parameters and their standard errors for each trial. A random-effects model in a one-arm meta-analysis was used to

summarize the model parameters under different treatment regimens. Finally, Monte Carlo simulations (10,000 times) were used to obtain the typical OS and PFS time curves and their 95% CIs for each treatment regimen[31].

ORR and grade 3–5 adverse events

The ORR and incidence of common grade 3–5 adverse events were pooled using a random-effects model in a single-arm meta-analysis to obtain the characteristics of ORR and safety under different treatment regimens.

Correlation between ORR, PFS, and OS

Weighted linear regression analysis was used to evaluate the correlation among the efficacy indicators: (1) 6-month PFS and 2-year OS, (2) 1-year PFS and 2-year OS, (3) ORR and 6-month OS or PFS, (4) ORR and 1-year PFS, and (5) ORR and 2-year OS. The Pearson correlation coefficient (R^2) was used to measure the correlation between efficacy indicators. $R^2 \geq 0.8$ was predetermined as a strong correlation, 0.6–0.8 as a moderate correlation, and < 0.6 as a weak correlation[32].

Software

Model building and simulations were performed using NONMEM 7.3 (Level 1.0, Icon Development Solutions, New York, USA), and model parameters were estimated using first-order condition estimates. Meta-analysis and graphical visualization were performed using the R software (version 4.0.3, The R Foundation of Statistical Computing, Vienna, Austria). Weighted linear regression analysis was performed using SPSS (IBM SPSS Statistics 23).

Results

Characteristics of the included studies

Finally, 58 articles were included in the study (Supplementary Figure S1), with 68 trials and a total sample size of 3124. Eleven types of treatment strategies are involved, including monotherapy (chemotherapy, targeted therapy, and immunotherapy) and combination therapy (chemotherapy + immunotherapy, chemotherapy + ASCT, targeted therapy + targeted therapy, immunotherapy + immunotherapy, targeted therapy + immunotherapy, chemotherapy + targeted therapy + immunotherapy, chemotherapy + immunotherapy + immunotherapy, and chemotherapy + immunotherapy + ASCT). A total of 63 specific treatment regimens were used in this study. The number of studies, number of trials, and sample size for each treatment regimen and the reported percentages of the three efficacy indicators of OS, PFS, and ORR for each treatment regimen are shown in Supplementary Figure S2. The median age of the included studies was 66 years, the median male percentage was 61%, and the median number of treatments received since diagnosis was 2.3 times. Details of the included trials are provided in Supplementary Table S1.

Model establishment and evaluation

The results show that the lognormal model can better describe the characteristics of PFS and OS data than the other three hazard functions; the OFV is the smallest, and the relative standard error (RSE) % of the model parameters is also smaller. Therefore, a lognormal hazard model was selected to fit the OS and PFS data.

The model parameters are presented in Table 1. The results showed that the RSE% of the final model parameters of OS and PFS were both within 30%, indicating that the estimated values of the model parameters were relatively stable. The 1,000-time bootstrap-replaceable repeated sampling method successfully converged 997 times and 962 times, respectively, with 95% CIs that are extremely close to the parameter estimates of the final models of OS and PFS, indicating that the final models are robust and relatively less affected by individual study data (Table 1). The goodness-of-fit plots and individual fit plots of the final model showed that the model fits the measured data well (Supplementary Figure S3) and no systematic bias was observed. The VPC chart of the final model shows that the measured data generally fell within the 95% CI predicted by the model, indicating that the model had good predictability (Figure 1).

The results of the covariate analysis showed that patients who received monotherapy or combination therapy had a significant impact on OS. Combination therapy was associated with a 1.67-fold reduction in the 1-year risk of death for OS compared to monotherapy. Furthermore, combination therapy and chemotherapy had a significant impact on PFS. The 1-year PFS risk of combination therapy was 2.56 times lower than that of monotherapy, and the 1-year PFS risk of patients who received chemotherapy was 2.34 times lower than that of patients who did not receive chemotherapy.

Typical value of OS

Based on the final model, the effects of monotherapy or combination therapy on OS were simulated. The results showed that the typical median OS rates were 8.8 (95% CI, 6.9, 11.4) months and 14 (95% CI, 10.6, 19.6) months for monotherapy and combination therapy, respectively (Figure 2A). The 1-year OS for monotherapy and combination therapy were 38.5% (95% CI, 29.9%, 47.9%) and 57.2% (95% CI, 44.9%, 65.9%), respectively.

The typical OS curves for each type of treatment strategy are shown in Figure 3A. Among them, chemotherapy + immunotherapy + ASCT, immunotherapy + immunotherapy, chemotherapy + ASCT, chemotherapy + immunotherapy and chemotherapy + immunotherapy + immunotherapy have better efficacy, and the median OS were 28.5, 16.5, 15.5, 14 and 13.9 months, respectively (Figure 4).

Specific to each treatment regimen, R-inotuzumab ozogamicin, R-BEAM+ASCT, R-ESHAP-L, iodine-131 tositumomab + BEAM + ASCT, and chemotherapy + CAR-T had the best efficacy on OS, and the median OS was > 2 years, and 1-year OS rate was > 80% (Figure 5).

Moreover, we summarized the median OS of the different targets of targeted therapy and immunotherapy, and the results are shown in Supplementary Figure S5.

Typical value of PFS

Based on the final model, PFS can be simulated in four scenarios depending on whether patients received combination therapy and whether patients received chemotherapy. Since there were only two studies on chemotherapy used alone, it simulates only three scenarios: monotherapy without chemotherapy, combination therapy and chemotherapy, and combination therapy without chemotherapy. The results (Figure 2B) showed that the median PFS were 2.7 (95% CI, 2.3, 3.3) months, 7.3 (95% CI, 4.4, 12.4) months and 5.0 (95% CI, 3.3, 7.7) months for monotherapy without chemotherapy, combination therapy and chemotherapy, and combination therapy without chemotherapy, respectively. The 1-year PFS were 3.4% (95% CI, 1.64%, 6%) months, 35.6% (95% CI, 22.3%, 51.8%) months, and 21.5% (95% CI, 11.7%, 34.5%) months for monotherapy without chemotherapy, combination therapy and chemotherapy, and combination therapy without chemotherapy, respectively.

The typical PFS curves for each treatment strategy are shown in Figure 3B. Among them, chemotherapy + immunotherapy + ASCT, chemotherapy + immunotherapy + immunotherapy, immunotherapy + immunotherapy, chemotherapy + ASCT, and chemotherapy + immunotherapy have better efficacy, with median PFS of 23, 9, 6.5, 5.9 and 4.9 months, respectively (Figure 4).

Specific to each treatment regimen, yttrium-90 ibritumomab tiuxetan + BEAM + ASCT, R-ESHAP-lenalidomide, R-BEAM + ASCT, iodine-131 tositumomab + BEAM + ASCT, and tafasitamab + lenalidomide had the best efficacy, and the median PFS was > 10 months (Figure 5).

Furthermore, we summarized the median PFS rates for different targets of targeted therapy and immunotherapy, and the results are shown in Supplementary Figure S5.

ORR

The ORR of combination therapy was significantly higher than that of monotherapy, which were 49% (95% CI, 41%, 58%) and 23% (95% CI, 17%, 29%), respectively (Supplementary Figure S4). The efficacy of different types of treatment strategies can be roughly divided into three categories, among which chemotherapy + immunotherapy + ASCT, chemotherapy + ASCT, and chemotherapy + immunotherapy + immunotherapy have higher ORR, which was > 70%; chemotherapy + immunotherapy, chemotherapy used alone, chemotherapy + immunotherapy + targeted therapy, and immunotherapy + immunotherapy have moderate ORR, which range from 41% to 58%; immunotherapy used alone, targeted therapy + targeted therapy, targeted therapy + immunotherapy, and targeted therapy used alone have lower ORR, which range from 15% to 20%. These results suggest that chemotherapy is involved in two categories with better efficacy, indicating that the ORR is higher in regimens with chemotherapy than in those without chemotherapy.

Specific to novel treatment options, such as CAR-T cell therapy, HDC+ASCT, R+ADC, CD3/CD19-targeting bispecific antibodies, and ADCs, the ORR were 82% (95% CI, 75%, 89%), 70% (95% CI, 60%, 79%), 48% (95% CI, 32%, 67%), 43% (95% CI, 22%, 64%), and 33% (95% CI, 19%, 46%), respectively.

Moreover, we summarized the ORR of different targets of targeted therapy and immunotherapy, and the results are shown in Supplementary Figure S5.

Grade 3–5 adverse events

A total of 25 trials reported the incidence of grade 3–5 adverse events, and the results showed that the incidence of grade 3–5 neutropenia, leukopenia, and thrombocytopenia was higher in chemotherapy used alone, chemotherapy + immunotherapy, chemotherapy + immunotherapy + immunotherapy, and chemotherapy + targeted therapy + immunotherapy and the incidence rate was > 30%. (Figure 4).

Correlation between ORR, PFS, and OS

The correlations between the ORR, PFS, and OS are shown in Figure 6. The results showed that 6-month PFS was moderately correlated with 2-year OS (R^2 = 0.746), and the equations were as follows: y = 0.8005x + 0.0192; that is, for every 10% increase in 6-month PFS, 2-year OS would increase by 8.0%. Subgroup analysis showed a strong correlation between the 6-month PFS and 2-year OS with combination therapy (R^2 = 0.948).

Moderate correlations were found between 1-year PFS and 2-year OS (R^2 = 0.743) and between ORR and 2-year OS (R^2 = 0.754). Moreover, weaker associations were found between ORR and 6-month PFS (R^2 = 0.684) and between ORR and 1-year PFS (R^2 = 0.623).

Discussion

r/r DLBCL remains an unmet medical field[33,34]. New therapies have emerged recently; however, there has been no comprehensive quantitative comparison of the efficacy of current emerging therapies for r/r DLBCL. This study comprehensively analyzed 11 types of treatment strategies and 63 treatment regimens under three efficacy indicators (PFS, OS, and ORR) to determine the most effective types of treatment strategies and treatment regimens and the factors influencing their efficacy, providing key quantitative information for clinical medication guidelines.

This study shows that combination therapy has a significant benefit in OS, PFS, and ORR compared with monotherapy, suggesting that multiple-drug therapy has a multi-target coordination effect, which is the general trend of the current r/r DLBCL treatment. In addition, patients who received chemotherapy had significantly improved ORR and PFS compared to patients who did not receive chemotherapy, but there was no apparent benefit in OS. For example, the median survival times under chemotherapy + immunotherapy + immunotherapy and immunotherapy + immunotherapy treatment regimens were 16.8 months and 16.5 months, respectively; the former was only 0.3 months longer than the latter. However, in terms of safety, the incidence of grade 3–5 neutropenia, leukopenia, and thrombocytopenia was > 30% in combination therapies containing chemotherapy, such as chemotherapy + immunotherapy, chemotherapy + immunotherapy + immunotherapy, and chemotherapy + targeted therapy + immunotherapy. However, grade 3–5 adverse events of combination therapy without chemotherapy, such

as targeted therapy + targeted therapy, immunotherapy + immunotherapy, and targeted therapy + immunotherapy, were mainly neutropenia, with a low incidence of < 27.1%. These results suggest the need for careful evaluation of the benefit-to-risk ratio of combination therapy with or without chemotherapy. Previous studies have shown a synergistic effect of rituximab, gemcitabine, and oxaliplatin. Furthermore, gemcitabine and oxaliplatin also showed synergistic effects in human colon cancer cell lines, and the feasibility and safety of this combination have been demonstrated in various solid tumors and lymphoma[35].

In terms of the type of treatment strategy, we found that chemotherapy + immunotherapy + ASCT had the best efficacy, with the best performance in ORR, PFS, and OS. Since the publication of PARMA trial results, ASCT has become the gold standard for r/r DLBCL treatment[36]. However, the population receiving this therapy must be chemosensitive and aged < 60 years and have no comorbidities. Many studies have shown that chemo-insensitive patients treated with ASCT tend to have poor efficacy and prognosis[37]. It was also found that, compared with chemotherapy + ASCT, chemotherapy + immunity + ASCT had significantly prolonged PFS and OS, with a median PFS of 5.9 months and 23 months, respectively, and a median OS of 15.5 months and 28.5 months, respectively. In terms of safety, the incidence of grade 3–5 adverse events was similar between the chemotherapy + ASCT and chemotherapy + immunotherapy + ASCT groups. The abovementioned results suggest that immunotherapy before chemotherapy + ASCT can achieve a better benefit-to-risk ratio. In contrast to traditional treatment methods, immunotherapy, such as PD-1 and PD-L1, can restore the immunity of patients with immune deficiency by mobilizing the natural antitumor ability of the human body and preventing immune suppression caused by surgery, radiotherapy, or chemotherapy[38]. In addition, after entering the body, monoclonal antibodies targeting B cells can bind to antigen targets, such as CD20 and CD19, resulting in the specific death of tumor cells. Therefore, immunotherapy before chemotherapy + ASCT can achieve better remission for patients so that more patients can receive ASCT.

In terms of specific treatment regimens, we found that yttrium-90 ibritumomab tiuxetan + BEAM + ASCT, R + BEAM + ASCT, R-ESHAP-lenalidomide, and R-inotuzumab ozogamicin had outstanding efficacy. Among them, yttrium-90 ibritumomab tiuxetan + BEAM + ASCT showed the longest PFS. A meta-analysis showed that yttrium-90 ibritumomab tiuxetan + chemotherapy + ASCT was more effective in r/r DLBCL treatment, which is consistent with the results of our study[23]. In addition, some studies have shown that preconditioning regimens containing radioimmunotherapy are safer than conventional regimens containing whole-body radiotherapy or chemotherapy alone and may be superior to conventional regimens in patients with multiple relapses or drug resistance[39]. However, this study showed that, in terms of OS, the median OS of yttrium-90 ibritumomab tiuxetan + BEAM + ASCT was even lower than that of R + BEAM + ASCT, with median OS of 12.2 months and 34.2 months, respectively. These results suggest that a preconditioning regimen containing radioimmunotherapy may effectively control disease progression but has no significant effect on OS. Lenalidomide, an immunomodulatory agent, has been shown to have various effects on the immune system and alters the tumor microenvironment by affecting the production and activity of cytokines involved in the maintenance of tumor growth and

survival. In terms of the mechanism of action, the combination of lenalidomide and rituximab can have a synergistic effect, such as sensitizing tumor cells to rituximab and enhancing NK cell-mediated ADCC[40,41]. This study showed that the ORR of R-ESHAP-lenalidomide regimen was 79%, the median PFS was 21.6 months, and the median OS was 27.8 months, which was close to the efficacy of regimen containing ASCT. Inotuzumab ozogamicin (INO) is an antibody-targeted chemotherapy agent composed of a humanized anti-CD22 antibody conjugated to calicheamicin, a potent cytotoxic agent[42]. In this study, the R-INO regimen had the longest median OS with a median OS of 48.2 months, which seemed to be the most promising treatment for patients with r/r DLBCL, but, in another R-INO + ASCT regimen, the median OS was only 12.5 months[43]. Nonetheless, the R-INO regimen is a good option for patients not suited for intensive multiagent therapies[42].

Chimeric antigen receptor (CAR) T cells are a novel tumor immunotherapy that is rapidly emerging as a promising cellular immunotherapy for r/r DLBCL. In this study, we found the ORR of CAR-T cell therapy was the best of all treatments, with a value of 82%. Moreover, their median OS was longer (25.4 months). However, when two CAR-T cell therapies targeting CD19 and CD20 were used in combination, the median OS was only 8 months. This may be the result of immune escape, lack of patient-originated memory CAR-T cells, or failure of continued CAR-T cell expansion[44]. These results suggest that the efficacy of the two CAR-T cell combinations may not be superior to that of CAR-T alone. In addition, 89–95% of patients treated with CAR-T had grade 3 or worse adverse events, the most common of which was cytokine release syndrome (58–93%).

In the past few decades, the identification of valid or potential surrogates for clinical endpoints (e.g., OS and PFS) has been of great interest in the field of oncology to facilitate the expeditious development of new promising therapies. We analyzed the correlations between early available indicators (e.g., ORR and 6-month PFS) and clinical endpoints (e.g., 1-year PFS and 2-year OS). The results showed a moderate correlation between 6-month PFS and 2-year OS for r/r DLBCL ($R^2 = 0.746$), especially in combination therapy, with a high correlation between 6-month PFS and 2-year OS ($R^2 = 0.948$). It is suggested that 6-month PFS can be used as a potential surrogate endpoint for 2-year OS in r/r DLBCL treatment so that the clinical endpoint can be predicted in advance at the early stages of clinical trials. These findings are similar to those in the literature[32,45], which indicate that, in newly diagnosed DLBCL, the 6-month PFS is a potential surrogate endpoint for 2-year OS. Furthermore, a literature study on the correlation of efficacy indicators in patients with hepatocellular carcinoma treated with immune checkpoint inhibitors also found that the correlation between PFS and OS was more significant in combination therapy[46].

However, this study found that the correlation between ORR and PFS or OS was weak. For response assessment, computed tomography (CT), the traditional method of measuring tumor size, is unable to discriminate viable tumor masses from residual scar tissue and is therefore unreliable in the early treatment period when tumor volume reduction is actively ongoing. In contrast, functional nuclear imaging using positron emission tomography with 2-[18F] fluoro-2-deoxy-D-glucose (FDG-PET), which provides metabolic tissue characterization, is potentially more useful for response assessment.

Therefore, FDG-PET has been included in the post-treatment evaluation of malignant lymphoma[47–50]. Most clinical studies included in this review utilized CT scans without FDG-PET to assess tumor response, which may be one of the reasons why the ORR cannot predict OS and PFS.

This study has several limitations. The analysis data of this study are obtained from the literature, and some factors that may affect the efficacy, such as race, Ann Arbor stage, ECOG performance status, and genotype, have a high missing rate (> 30%), which cannot perform the covariate test. Furthermore, owing to data limitations, this study did not account for the heterogeneity of dose and treatment cycles among different treatment regimens. Finally, this study only included studies published in English in the past 10 years, and there was a certain publication bias.

Conclusions

In this study, the efficacy and safety of different treatment regimens for r/r DLBCL were comprehensively evaluated. Combination therapy had a significant benefit in terms of OS, PFS, and ORR compared with monotherapy. Although the ORR and PFS were significantly improved in patients receiving chemotherapy, there was no significant benefit in OS or significant increase in grade 3–5 adverse events. Yttrium-90 ibritumomab tiuxetan + BEAM + ASCT, R + BEAM + ASCT, and R-ESHAP-lenalidomide were the most effective regimens. In addition, this study found a high correlation between the 6-month PFS and 2-year OS, suggesting that it can be used as a surrogate endpoint for early evaluation of the efficacy of new treatments.

Declarations

Ethics approval and consent to participate This article does not contain any studies with animals performed by any of the authors.

Consent for publication All authors have read and approved the final manuscript.

Availability of data and materials All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests The authors declare that they have no conflict of interest.

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Authors' contributions LJ.L and QS.Z participated in conception and design of the work and revised the paper critically for important intellectual content. T.L & JS.Y selected studies and extracted the data, analyzed and interpreted the data, T.L & SJ.Z wrote the manuscript and revised the manuscript. QQ.C contributed to data extraction and cleaning. All authors read and approved the final manuscript. All authors have approved the final article.

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References

1. Armitage JO, Gascoyne RD, Lunning MA, Cavalli F. Non-Hodgkin lymphoma. Lancet. 2017;390(10091):298–310
2. Czuczman MS, Trneny M, Davies A et al. A Phase 2/3 Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Lenalidomide Versus Investigator's Choice in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Clin Cancer Res. 2017;23(15):4127–4137
3. Goy A, Ramchandren R, Ghosh N et al. Ibrutinib plus lenalidomide and rituximab has promising activity in relapsed/refractory non-germinal center B-cell-like DLBCL. Blood. 2019;134(13):1024–1036
4. Sehn LH, Donaldson J, Chhanabhai M et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J Clin Oncol. 2005;23(22):5027–33
5. Boue F, Gabarre J, Gisselbrecht C et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. J Clin Oncol. 2006;24(25):4123–8
6. Merli F, Luminari S, Rossi G et al. Cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab versus epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab for the initial treatment of elderly "fit" patients with diffuse large B-cell lymphoma: results from the ANZINTER3 trial of the Intergruppo Italiano Linfomi. Leuk Lymphoma. 2012;53(4):581–8
7. Pfreundschuh M, Kuhnt E, Trumper L et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol. 2011;12(11):1013–22
8. Sehn LH, Berry B, Chhanabhai M et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood. 2007;109(5):1857–61
9. Gisselbrecht C, Glass B, Mounier N et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(27):4184–90
10. Trneny M, Verhoef G, Dyer MJ et al. A phase II multicenter study of the anti-CD19 antibody drug conjugate coltuximab ravtansine (SAR3419) in patients with relapsed or refractory diffuse large B-cell lymphoma previously treated with rituximab-based immunotherapy. Haematologica. 2018;103(8):1351–1358
11. van Imhoff GW, McMillan A, Matasar MJ et al. Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The ORCHARRD Study. J Clin Oncol. 2017;35(5):544–551

12. Ayala E. Hematopoietic cell transplantation for B-cell lymphoma: an update. Cancer Control. 2012;19(3):175–86
13. Wildes TM, Augustin KM, Sempek D et al. Comorbidities, not age, impact outcomes in autologous stem cell transplant for relapsed non-Hodgkin lymphoma. Biol Blood Marrow Transplant. 2008;14(7):840–6
14. Briones J, Novelli S, Garcia-Marco JA et al. Autologous stem cell transplantation after conditioning with yttrium-90 ibritumomab tiuxetan plus BEAM in refractory non-Hodgkin diffuse large B-cell lymphoma: results of a prospective, multicenter, phase II clinical trial. Haematologica. 2014;99(3):505–10
15. Ardeshna KM, Kakouros N, Qian W et al. Conventional second-line salvage chemotherapy regimens are not warranted in patients with malignant lymphomas who have progressive disease after first-line salvage therapy regimens. Br J Haematol. 2005;130(3):363–72
16. Hitz F, Connors JM, Gascoyne RD et al. Outcome of patients with primary refractory diffuse large B cell lymphoma after R-CHOP treatment. Ann Hematol. 2015;94(11):1839–43
17. Nagle SJ, Woo K, Schuster SJ et al. Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. Am J Hematol. 2013;88(10):890–4
18. Crump M, Neelapu SS, Farooq U et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800–1808
19. Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. Hematology Am Soc Hematol Educ Program. 2011;2011:498–505
20. Chaganti S, Illidge T, Barrington S et al. Guidelines for the management of diffuse large B-cell lymphoma. Br J Haematol. 2016;174(1):43–56
21. Hutchings M, Mous R, Clausen MR et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. Lancet. 2021;398(10306):1157–1169
22. Wang L, Li LR, Young KH. New agents and regimens for diffuse large B cell lymphoma. J Hematol Oncol. 2020;13(1):175
23. Auger-Quittet S, Duny Y, Daures JP, Quittet P. Outcomes after (90) Yttrium-ibritumomab tiuxetan-BEAM in diffuse large B-cell lymphoma: a meta-analysis. *Cancer Med*. 2014;3(4):927 – 38
24. Zheng XH, Zhang XY, Dong QQ et al. Efficacy and safety of chimeric antigen receptor-T cells in the treatment of B cell lymphoma: a systematic review and meta-analysis. Chin Med J (Engl). 2020;133(1):74–85
25. Hou K, Yu Z, Jia Y et al. Efficacy and safety of ibrutinib in diffuse large B-cell lymphoma: A single-arm meta-analysis. Crit Rev Oncol Hematol. 2020;152:103010
26. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's lymphomas, version 4.2020. http://www.kimia-pharma.co/UserFile/Download/b-cell.pdf

27. Li L, Lv Y, Xu L, Zheng Q. Quantitative efficacy of soy isoflavones on menopausal hot flashes. Br J Clin Pharmacol. 2015;79(4):593–604
28. Mould DR. Model-based meta-analysis: an important tool for making quantitative decisions during drug development. Clin Pharmacol Ther. 2012;92(3):283–6
29. Wang F, Zhao C, Wen X, Zheng Q, Li L. Factors affecting the efficacy and safety of docetaxel combined with platinum in the treatment of advanced non-small cell lung cancer. Expert Rev Clin Pharmacol. 2021;14(10):1295–1303
30. Li T, Zhang Y, Cheng Q et al. Quantitative study on the efficacy of acupuncture in the treatment of menopausal hot flashes and its comparison with nonhormonal drugs. Menopause. 2021;28(5):564–572
31. Zha S, Li T, Zheng Q, Li L. Whether Patients With Stage / Colorectal Cancer Benefit From Adjuvant Chemotherapy: A Modeling Analysis of Literature Aggregate Data. Front Pharmacol. 2022;13:826785
32. Zhu R, Lu D, Chu YW et al. Assessment of Correlation Between Early and Late Efficacy Endpoints to Identify Potential Surrogacy Relationships in Non-Hodgkin Lymphoma: a Literature-Based Meta-analysis of 108 Phase II and Phase III Studies. Aaps J. 2017;19(3):669–681
33. Coiffier B, Thieblemont C, de Guibert S et al. A phase II, single-arm, multicentre study of coltuximab ravtansine (SAR3419) and rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. Br J Haematol. 2016;173(5):722–30
34. Timmerman J, Herbaux C, Ribrag V et al. Urelumab alone or in combination with rituximab in patients with relapsed or refractory B-cell lymphoma. Am J Hematol. 2020;95(5):510–520
35. Mounier N, El GT, Tilly H et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. Haematologica. 2013;98(11):1726–31
36. Gyan E, Damotte D, Courby S et al. High response rate and acceptable toxicity of a combination of rituximab, vinorelbine, ifosfamide, mitoxantrone and prednisone for the treatment of diffuse large B-cell lymphoma in first relapse: results of the R-NIMP GOELAMS study. Br J Haematol. 2013;162(2):240–9
37. Barnes JA, Jacobsen E, Feng Y et al. Everolimus in combination with rituximab induces complete responses in heavily pretreated diffuse large B-cell lymphoma. Haematologica. 2013;98(4):615–9
38. Niu M, Liu Y, Yi M, Jiao D, Wu K. Biological Characteristics and Clinical Significance of Soluble PD-1/PD-L1 and Exosomal PD-L1 in Cancer. Front Immunol. 2022;13:827921
39. Ferrucci PF, Vanazzi A, Grana CM et al. High activity 90Y-ibritumomab tiuxetan (Zevalin) with peripheral blood progenitor cells support in patients with refractory/resistant B-cell non-Hodgkin lymphomas. Br J Haematol. 2007;139(4):590–9
40. Wu L, Adams M, Carter T et al. lenalidomide enhances natural killer cell and monocyte-mediated antibody-dependent cellular cytotoxicity of rituximab-treated CD20 + tumor cells. Clin Cancer Res. 2008;14(14):4650–7

41. Lapalombella R, Yu B, Triantafillou G et al. Lenalidomide down-regulates the CD20 antigen and antagonizes direct and antibody-dependent cellular cytotoxicity of rituximab on primary chronic lymphocytic leukemia cells. Blood. 2008;112(13):5180–9
42. Fayad L, Offner F, Smith MR et al. Safety and clinical activity of a combination therapy comprising two antibody-based targeting agents for the treatment of non-Hodgkin lymphoma: results of a phase I/II study evaluating the immunoconjugate inotuzumab ozogamicin with rituximab. J Clin Oncol. 2013;31(5):573–83
43. Wagner-Johnston ND, Goy A, Rodriguez MA et al. A phase 2 study of inotuzumab ozogamicin and rituximab, followed by autologous stem cell transplant in patients with relapsed/refractory diffuse large B-cell lymphoma. Leuk Lymphoma. 2015;56(10):2863–9
44. Sang W, Shi M, Yang J et al. Phase II trial of co-administration of CD19- and CD20-targeted chimeric antigen receptor T cells for relapsed and refractory diffuse large B cell lymphoma. Cancer Med. 2020;9(16):5827–5838
45. Shi Q, Schmitz N, Ou FS et al. Progression-Free Survival as a Surrogate End Point for Overall Survival in First-Line Diffuse Large B-Cell Lymphoma: An Individual Patient-Level Analysis of Multiple Randomized Trials (SEAL). J Clin Oncol. 2018;36(25):2593–2602
46. Xu H, Cao D, Zheng Y et al. Potential predictors for survival in hepatocellular carcinoma patients treated with immune checkpoint inhibitors: A meta-analysis. Int Immunopharmacol. 2021;100:108135
47. Spaepen K, Stroobants S, Dupont P et al. Early restaging positron emission tomography with (18)F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma. Ann Oncol. 2002;13(9):1356–63
48. Haioun C, Itti E, Rahmouni A et al. [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. Blood. 2005;106(4):1376–81
49. Mikhaeel NG, Hutchings M, Fields PA, O'Doherty MJ, Timothy AR. FDG-PET after two to three cycles of chemotherapy predicts progression-free and overall survival in high-grade non-Hodgkin lymphoma. Ann Oncol. 2005;16(9):1514–23
50. Tychyj-Pinel C, Ricard F, Fulham M et al. PET/CT assessment in follicular lymphoma using standardized criteria: central review in the PRIMA study. Eur J Nucl Med Mol Imaging. 2014;41(3):408–15

Tables

Table 1a Parameter estimations of OS

	Final model		Bootstrap (997/1000)	
	Estimate（RSE%）	95% CI	Median	2.5^{th} – 97.5^{th} percentile
Parameter				
$SIGM_{-Monotherapy}$	1.26 (4.7)	1.14-1.38	1.26	1.14-1.37
$SIGM_{-Combine}$	1.51 (5.0)	1.36-1.66	1.51	1.36-1.66
$MU_{-Monotherapy}$	2.18 (5.7)	1.94-2.42	2.17	1.94-2.45
$MU_{-Combine}$	2.78 (5.8)	2.46-3.10	2.78	2.46-3.1
Inter-study variability				
SIGM,%	26 (14.2)	19-34	25	18.4-33
MU,%	60 (10.9)	47-73	58	44.2-70
Residual error				
Added error	0.63 (11.3)	0.49-0.77	0.62	0.495-0.77

Table 1b Parameter estimations of PFS

	Final model		Bootstrap (962/1000)	
	Estimate (RSE%)	95% CI	Median	2.5th-97.5th percentile
Parameter				
$SIGM_{\text{-Monotherapy without Chemotherapy}}$	1.01 (6.1)	0.89-1.13	1.01	0.90-1.16
$SIGM_{\text{-Combine without Chemotherapy}}$	1.37 (6.3)	1.20-1.54	1.37	1.18-1.50
$SIGM_{\text{-Combine with Chemotherapy}}$	1.59 (9.4)	1.30-1.88	1.61	1.27-2.00
$MU_{\text{-Monotherapy without Chemotherapy}}$	0.884 (11.2)	0.69-1.08	0.89	0.70-1.08
$MU_{\text{-Combine without Chemotherapy}}$	1.67 (13.1)	1.24-2.10	1.66	1.20-2.00
$MU_{\text{-Combine with Chemotherapy}}$	2.18 (11.8)	1.68-2.68	2.20	1.67-2.99
Inter-study variability				
SIGM,%	29.6 (14.7)	21-38	28	18-37
MU,%	62 (12.3)	47-77	56	42-73
Residual error				
Added error	1.049 (8.3)	0.88-1.22	1.02	0.87-1.20

Figures

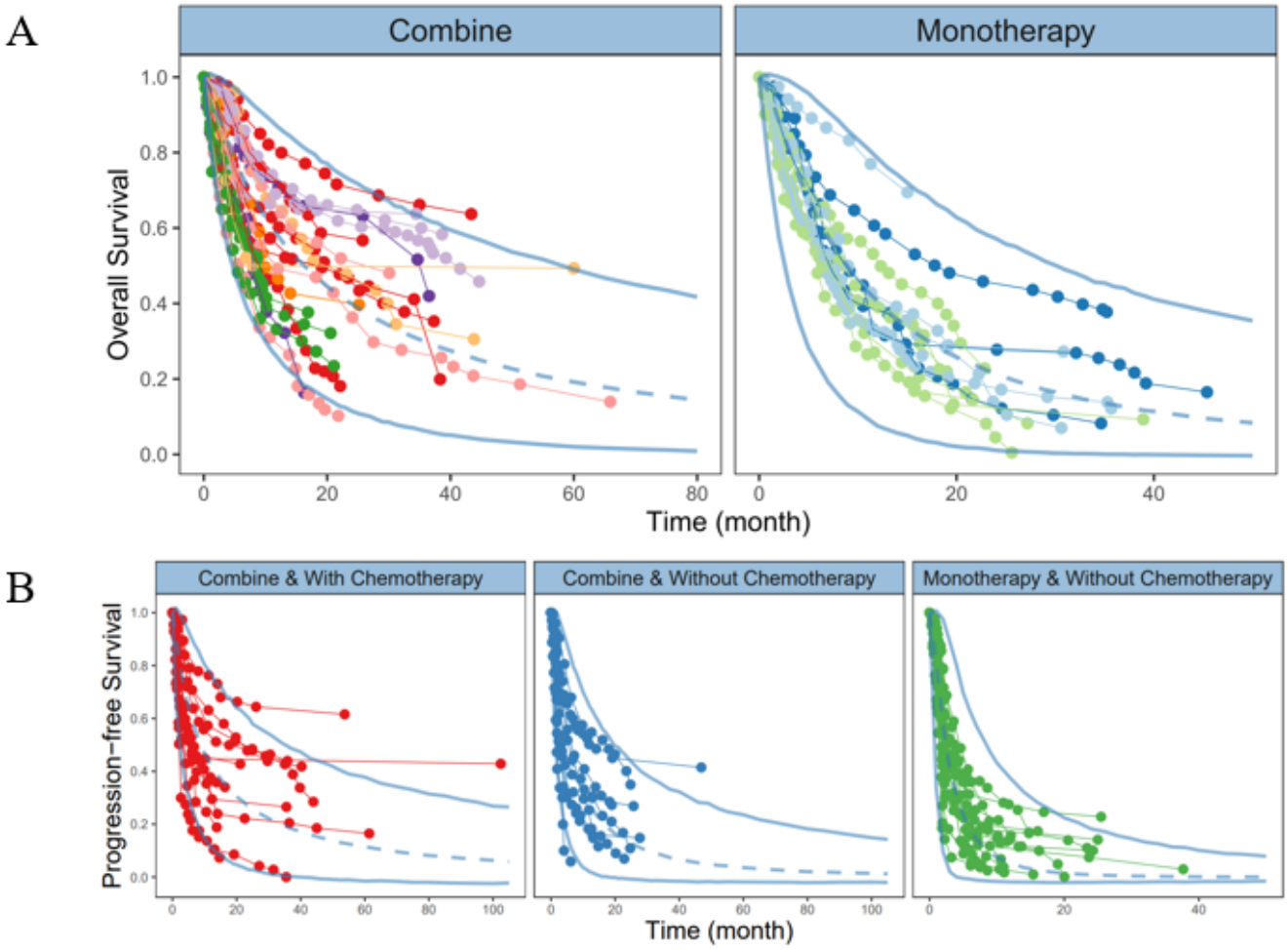

Figure 1

Visual predictive check of the final model of OS(A) and PFS(B). Solid points represent observed efficacy data. Points linked by a line are from the same arm. Blue lines are the model-predicted 5th, 50th, and 95th percentiles of efficacy. With Chemotherapy: patients received chemotherapy. Without Chemotherapy: patients did not receive chemotherapy.

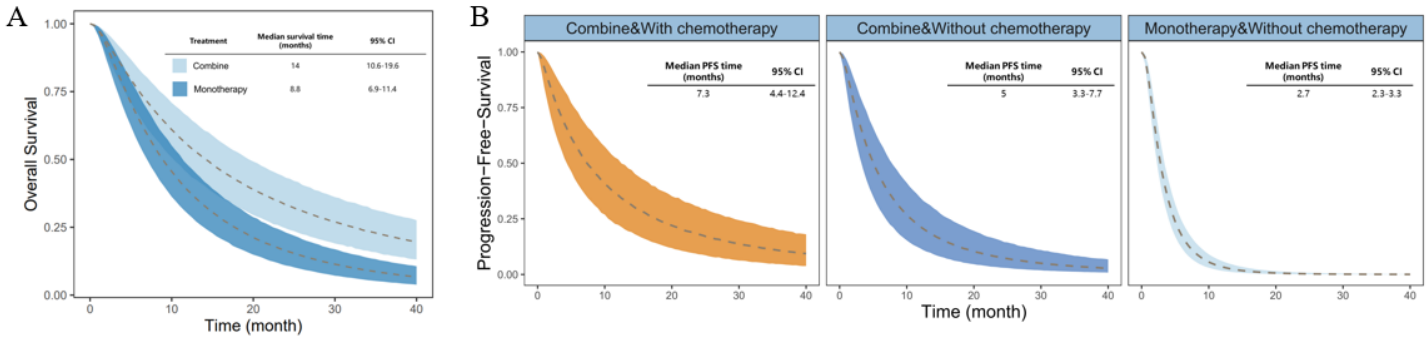

Figure 2

The predicted distribution of typical response of OS (A) and PFS (B). The dotted lines represent the typical efficacy, and the shaded areas are their 95% CIs. With chemotherapy: patients received chemotherapy. Without chemotherapy: patients did not receive chemotherapy.

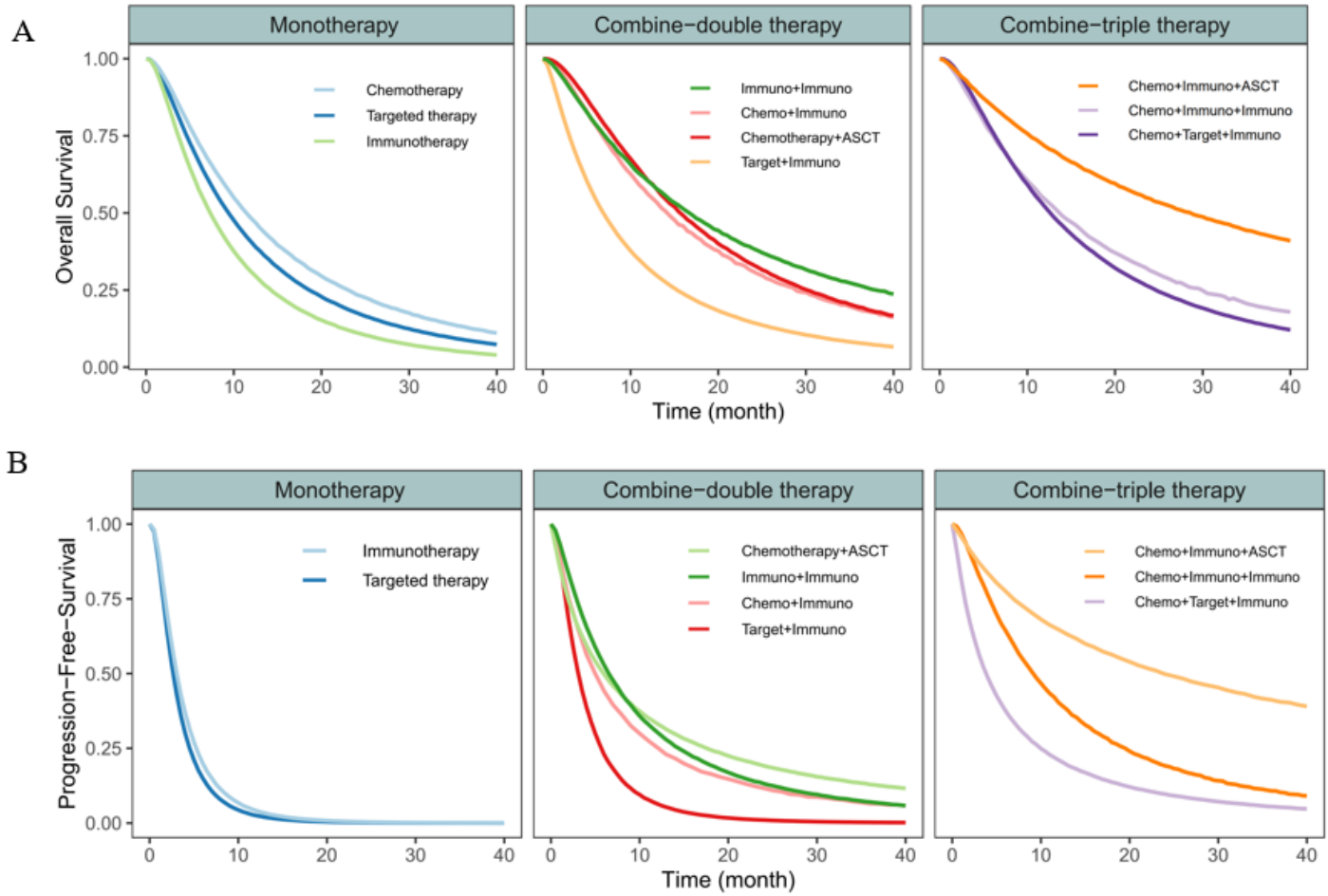

Figure 3

Predicted typical time course of OS (A) and PFS (B) of different treatment strategies. Immuno: Immunotherapy; Chemo: chemotherapy; Target: Targeted therapy; ASCT: Autologous Stem Cell Transplant.

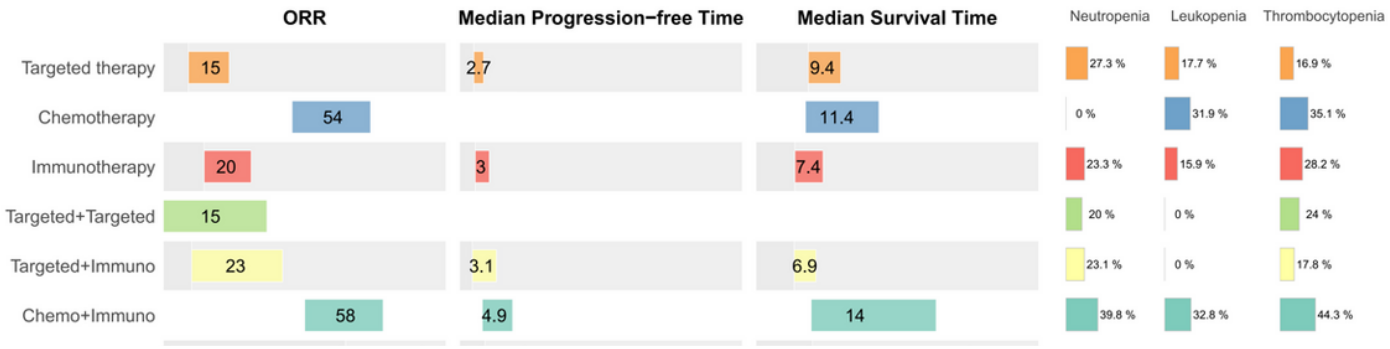

Figure 4

The ORR, median PFS, median OS and grade 3-5 adverse events of different treatment strategies. The length of the box represents the 95% confidence interval of the model prediction. Immuno: Immunotherapy; Chemo: chemotherapy; Targeted: Targeted therapy; ASCT: Autologous Stem Cell Transplant; NR: not reported.

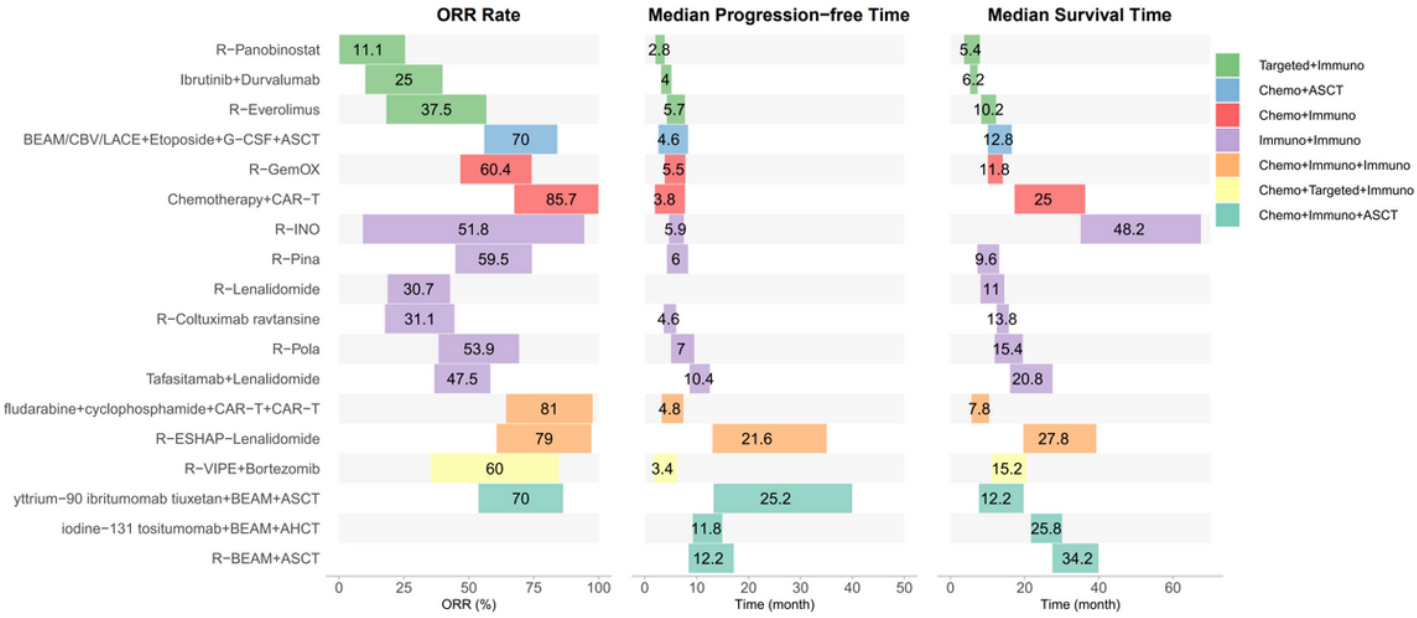

Figure 5

The ORR, median PFS and median OS of different treatment regimens. The length of the box represents the 95% confidence interval of the model prediction. R: Rituximab; GemOX: Gemcitabine and oxaliplatin; INO: Inotuzumab ozogamicin; Pina: pinatuzumab vedotin; Pola: polatuzumab vedotin.

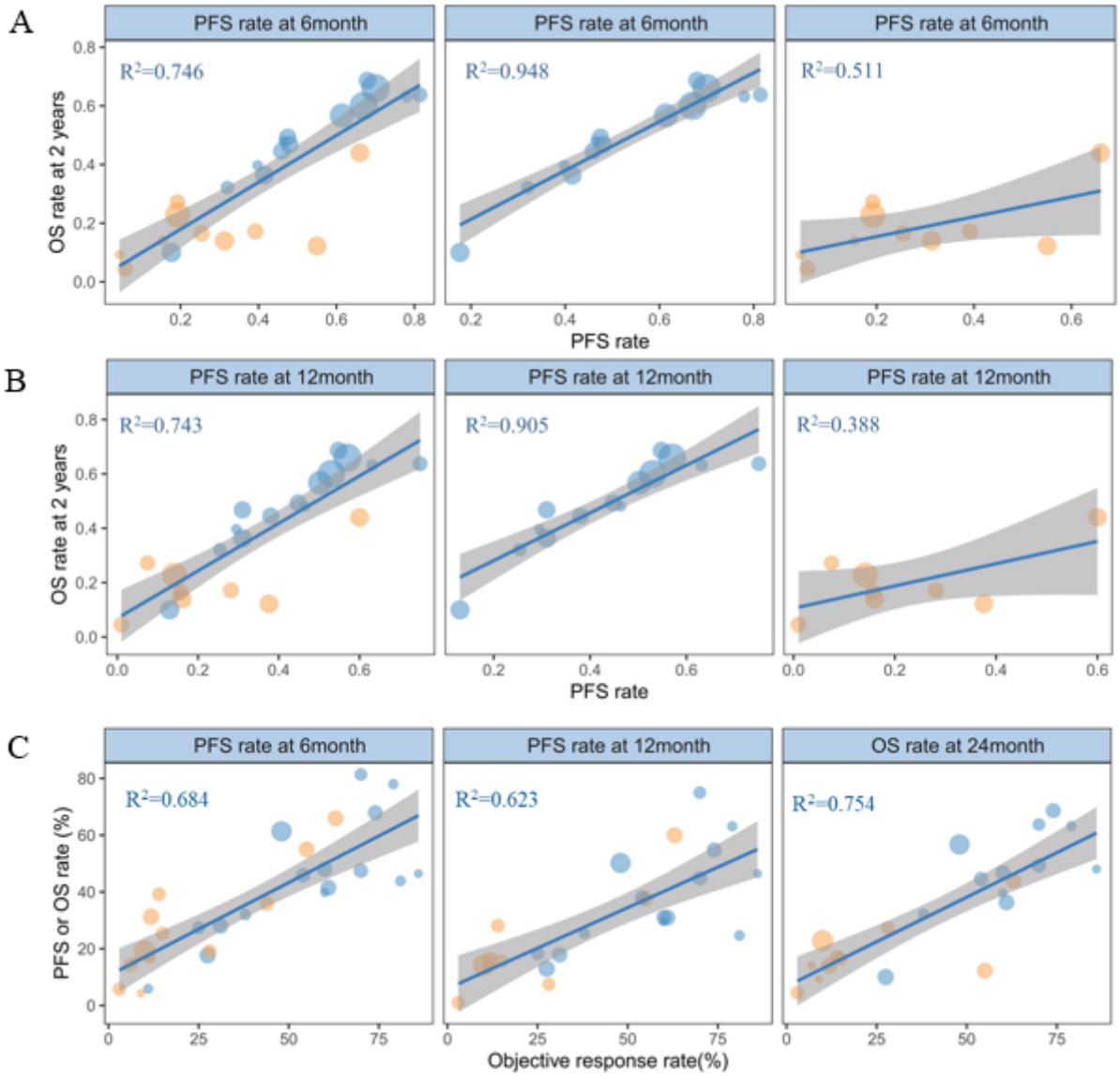

Figure 6

Correlations between (A) 6-month PFS and 2-year OS and (B) 12-month PFS and 2-year OS and (C) ORR and 6-month PFS,12-month PFS and 2-year OS. Yellow solid points represent monotherapy, blue solid points represent combination therapy. Symbol size is proportional to the number of patients included in the trial. The solid line represents the linear fit and the shaded area represents the 95% confidence interval. OS: overall survival rate, PFS progression-free survival, ORR: overall response rate.

Supplementary Files

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- SupplementaryMaterial.docx