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ORIGINAL ARTICLE

Upfront autologous stem cell transplantation for untreated diffuse large B cell lymphoma patients in rituximab era: a systematic review and meta-analysis

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Abstract

To assess the survival outcomes and adverse events (AEs) of high-intermediate- or high-risk patients with diffuse large B cell lymphoma (DLBCL) who underwent conventional chemotherapy plus rituximab with or without first-line autologous stem cell transplantation (ASCT). Related studies published on Medline, Embase, Cochrane Library, and Web of science were searched, comprising both retrospective and randomized clinical trials (RCTs). The primary endpoints were overall survival (OS) and progression-free survival (PFS). The meta-analysis was performed using the software RevMan v5.3. Four RCTs and six retrospective trials with a total of 1811 patients were identified. Pooled data indicated that conventional chemotherapy plus rituximab followed by ASCT as the first-line therapy contributed to better PFS (HR = 0.73, 95% CI 0.62–0.86, $p = 0.0002$) but did not significantly improve OS (HR = 0.74, 95% CI 0.55–1.01, $p = 0.06$) of high-intermediate/high-risk patients. Subgroup analyses of patients with complete remission after induction chemotherapy may benefit from the upfront ASCT (OS, HR = 0.48, 95% CI 0.28–0.82, $p = 0.008$). The incidences of grade ≥ 3 hematological and non-hematological AEs occurred more frequently in the transplantation group. High-intermediate or high-risk untreated patients with DLBCL only achieved short-term survival benefit with the upfront ASCT.

Keywords Diffuse large B cell lymphoma · ASCT · Rituximab · Conventional chemotherapy

Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma with obvious aggressiveness and heterogeneity [1, 2]. It is potentially curable using rituximab-containing conventional chemotherapy, but the outcomes still remain unsatisfactory due to the high relapse rate in high-intermediate-risk or high-risk patients, classified using the International Prognostic Index (IPI) or age-adjusted IPI (aaIPI). Although the use of novel drugs such as monoclonal antibodies, targeted drugs, and immunotherapy has significantly improved the survival of diffuse large B cell lymphoma patients in recent years [3, 4], autologous stem cell transplantation (ASCT) still plays an important role in the overall treatment process. High-dose chemotherapy (HDC) followed by ASCT used as salvage therapy has been proposed as the standard treatment in relapsed or refractory DLBCL [5, 6]; however, international consensus regarding the role of first-line ASCT in untreated DLBCL patients is yet to be proposed.

Thereby, the efficacy of first-line ASCT is still inconclusive. Before the rituximab era, several studies [7, 8]

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indicated that upfront ASCT conveyed no survival benefit over conventional chemotherapy. A randomized clinical trial (LNH93-3) [9] even demonstrated that the efficacy of early HDT with ASCT in high-risk patients was inferior to ACVBP chemotherapy regimen. A meta-analysis comprising of 15 randomized controlled trials (RCTs) further identified no evidence of ASCT in improving OS (HR 1.05, 95% CI 0.92–1.19) or event-free survival (EFS) (HR 0.92, 95% CI 0.80–1.05) when compared with conventional chemotherapy [10]. Subsequently, in the rituximab era, the addition of anti-CD20 antibody rituximab significantly improves survival outcomes [11].

The possibility of synergistic effects between rituximab and ASCT that could reverse the outcomes has aroused wide interests. However, conflicting results have been reported on the efficacy of upfront HDC/ASCT in the rituximab era [12–16]. Various arguments on the long- and short-term survivals from different studies made it a dilemma to implement ASCT as a first-line treatment in clinical practice. On this basis, we performed this meta-analysis to rationally evaluate and summarize existing evidences on the role of HDC-ASCT as a first-line treatment in high-intermediate- and high-risk patients with DLBCL.

Methods

Data sources and search

Literature searches of Medline, the Cochrane Library, Embase, and Web of Science were done until August 1, 2019. Search terms and their combinations used in the search strategy included diffuse large B cell lymphoma, DLBCL, High-dose therapy, HDT, High-dose chemotherapy, HDC, autologous stem cell transplantation, ASCT, rituximab, and R-CHOP.

Inclusion and exclusion criteria

All eligible studies were trials that compared conventional chemotherapy plus rituximab with or without ASCT as the first-line therapy for high-intermediate- or high-risk patients with DLBCL. All included patients underwent primary treatment with no contraindications. When multiple reports describing the same population in original and updated studies that were derived from one trial were identified, only the most recent or complete report was included for the present study analysis.

We excluded studies involving patients with central nervous system involvement and severe immunodeficiency disease. Due to insufficient information, case reports, comments, and conference articles were also excluded.

Data extraction

Two authors (SYM and XPT) independently extracted information using predefined extraction forms. The following details were extracted: first author, year of publication, study design, institution and country of study, patient number, median age, details of IPI or aaIPI, follow-up time, responses to induction chemotherapy, induction chemotherapy regimens, survival outcomes, grade ≥ 3 adverse events. Any disagreement was resolved by the adjudicating senior author (QQC).

Progression-free survival (PFS) and overall survival (OS) were the primary outcomes of interest. Hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted from complete survival curves and sufficient survival data. We also assessed treatment-related adverse events, reported as risk ratios (RRs) and 95% confidence intervals (95% CIs).

Quality assessment and statistical analysis

The Cochrane risk of bias tool was used to assess the quality of RCTs [17] from 7 items, namely, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The quality of retrospective studies was assessed and scored using the modified Newcastle-Ottawa scale [18, 19], which comprises three factors, namely, patient selection, comparability of the study groups, and evaluation of outcome. A score of 7–9 represented high-quality study.

This meta-analysis was performed using the Review Manager software, version 5.3. The chi-square test was used to evaluate the heterogeneity of the included studies, with $p > 0.10$ or $I^2 \leq 50\%$ indicating no significant heterogeneity. Fixed- or random-effect models were used based on the heterogeneity test. HR was used as the pooled statistic indicator for time-event data, and an HR < 1 represented a survival benefit favoring upfront ASCT. HR values were obtained from the retrieved study text or were estimated from survival curves using the Engauge Digitizer software version 4.1 as previously described by Jayne F Tierney; if the HR of an event of the control versus research arm was reported rather than vice versa, then the HR of the research arm versus control was obtained by taking the reciprocal of the HR, i.e., 1/HR and associated CI [20]. A related risk ratio (RR) > 1 represented the treatment-related advent events occurring more frequently in the upfront ASCT group.

Results

Literature search

A total of 1920 publications were identified using the predefined search strategy, of which 605 studies were identified as replicated. By screening the studies' titles and abstracts, 1273 were considered not eligible. Subsequently, 32 of the remaining 42 studies were excluded after full review for the following reasons: 25 studies were repeated reporters of certain same populations; 2 studies did not use conventional chemotherapy regimens as control, and another 2 studies included patients with low-risk IPI or aaIPI scores. The last 3 studies were excluded because of insufficient information, poor use of rituximab, and central nervous system involvement, respectively. Finally, 10 trials [13–16, 21–26] with a total of 1811 patients were included. Figure 1 shows the details of the selection process.

Characteristics of the included studies

The characteristics of the included studies are shown in Table 1. There were 4 open-label, multicenter, phase III randomized studies and 6 retrospective studies.

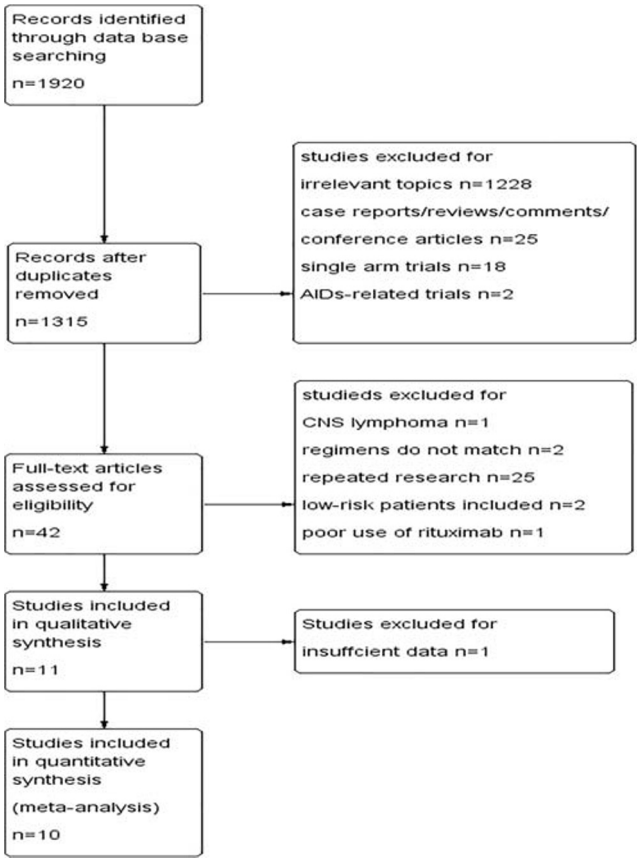

Fig. 1 Flowchart showing publication selection. CNS, central nervous system

Quality assessment

The quality of the 4 included RCTs was assessed using the Cochrane risk of bias tool, all of them were open-label trials with a high risk of allocation concealment, and none of them clarified explanation for blinding. The quality of retrospective studies was assessed using the modified Newcastle-Ottawa scale. The included retrospective studies were not representative enough of the local populations, the evaluation of the outcomes was not sufficient, and methods for handling missing data and intention-to-treat analyses were not adequately described in majority of the retrospective studies. The quality assessment for the included RCTs studies is shown in Supplementary Fig. 1.

Survival outcomes

Pooled data from 9 studies that assessed the PFS showed no obvious heterogeneity between the upfront ASCT and non-ASCT groups ($p = 0.36$, $I^2 = 9\%$). The meta-analysis revealed that conventional chemotherapy plus rituximab followed by autologous stem cell transplantation as the first-line therapy showed superior PFS (HR = 0.73, 95% CI 0.62–0.86, $p = 0.0002$; Fig. 2a) as compared with conventional chemotherapy alone. All of the included 10 studies reported OS, but certain heterogeneity was observed among these studies ($p = 0.03$, $I^2 = 52\%$), and we can infer from the result that the upfront ASCT did not significantly improve the OS (HR = 0.74, 95% CI 0.55–1.01, $p = 0.06$; Fig. 2b).

Overall survival after complete remission

The analysis of survival outcomes for patients attaining complete remission (CR) after induction chemotherapy was found in three retrospective studies, and no obvious heterogeneity was observed ($p = 0.84$, $I^2 = 0\%$); the result showed that the upfront ASCT groups had better overall survival than the non-ASCT groups (HR = 0.48, 95% CI 0.28–0.82, $p = 0.008$) when the upfront ASCT was performed as consolidation treatment in patients with complete remission following rituximab-containing chemotherapy induction (Fig. 2c).

Subgroup outcome analysis based on aaIPI

The 4 included multiple, open-label, phase III randomized clinical trials (RCTs) classified patients into high- and high-intermediate-risk groups according to IPI or aaIPI scores; then, stratification analysis was performed. No significant differences were observed in high-risk patients (HR = 0.78, 95% CI 0.54–1.14, $p = 0.20$) (Fig. 3b); however, patients with high-intermediate-risk tended to have inferior overall survival if treated with conventional chemotherapy plus rituximab followed by

Table 1 Characteristics of included studies

Author	Year	Type	Patients (exp/ctr)	Median age (exp/ctr)	CT regimens (ASCT)	CT regimens (non-ASCT)	Quality
Cortelazzo	2016	RCT	113/122	53 (19–65)/49 (19–66)	R-HDS + ASCT	8R-CHOP	RCT
Schmitz	2012	RCT	132/130	47 (19–60)/50 (16–60)	R-MegaCHOEP + ASCT	R-CHOEP-14	RCT
Chiappella	2017	RCT	199/200	48 (36–56)/49 (38–56)	R-CHOP/MegaCHOP-14 + R-Mad + BEAM + ASCT	R-CHOP/MegaCHOP-14	RCT
Stiff	2013	RCT	125/128	51 (18.3–65.9)	R-CHOP + ASCT	R-CHOP	RCT
Zhao	2017	R	41/53	45 (15–68)/51 (17–65)	R-CHOP + R-BEAM + ASCT	R-CHOP	7
Yoon	2015	R	23/35	42.1 (21–60)/46.8 (17–59)	R-CHOP + BumelTT + ASCT	R-CHOP	8
Wang	2019	R	33/32	43 (18–60)	R-HDC + ASCT	R-CHOP/R-CHOP-like	7
Nakaya	2017	R	27/77	62 (36–72)/67 (20–75)	R-CHOP + MEAM + ASCT	R -CHOP	7
Kim	2016	R	81/138	52/54.5	R-CHOP + BuEAM/BuCyE + ASCT	R-CHOP	8
Shin	2016	R	75/47	49 (15–65)	R-CHOP + BCNU/BEAM/BEAC + ASCT	R-CHOP + salvage ASCT	7

RCT, randomized control trial; *R*, retrospective trials; *CT*, chemotherapy; *exp.*, experiment group; *ctr*, control group; *ASCT*, autologous stem cell transplantation; *R-HDS*, rituximab + high-dose chemotherapy; *R-CHOP*, rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone; *R-MAD*, rituximab plus high-dose cytarabine plus mitoxantrone plus dexamethasone; *BEAM*, carmustine, etoposide, cytarabine, and melphalan

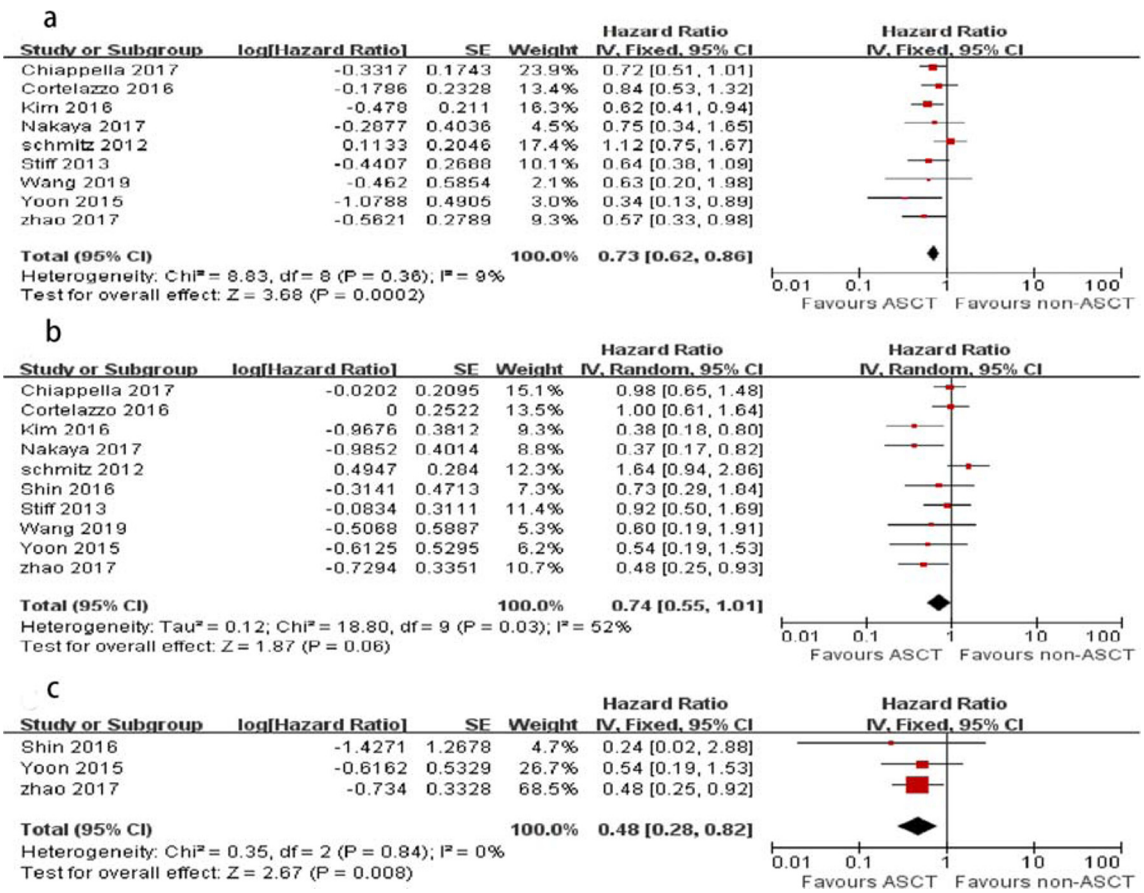

Fig. 2 Forest plot and meta-analysis of survival outcomes. Forest plot and meta-analysis of **a** progression-free survival, **b** overall survival in the entire group, and **c** overall survival for patients attained complete remission after induction chemotherapy. SE, standard error; CI, confidence interval; ASCT, autologous stem cell transplantation

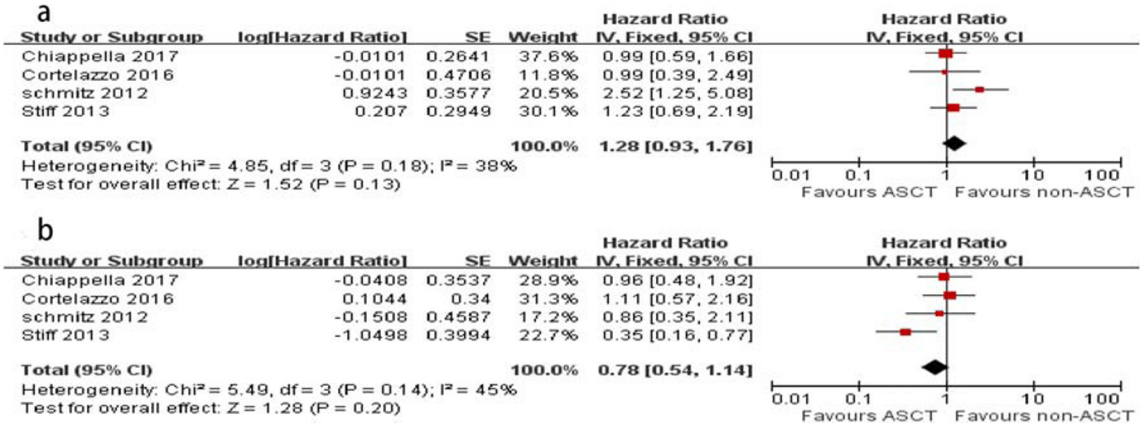

Fig. 3 Forest plot and meta-analysis of overall survival based on aaIPI. Forest plot and meta-analysis of overall survival in patients with **a** high-intermediate-risk and **b** high-risk patients according to aaIPI scores. SE, standard error; CI, confidence interval; ASCT, autologous stem cell transplantation

autologous stem cell transplantation as the first-line therapy (HR = 1.28, 95% CI 0.93–1.76, $p = 0.13$) (Fig. 3a).

Treatment-related toxicity

The incidences of grade 3 or worse hematological adverse events were proved to be higher in the transplantation arm (anemia, RR = 3.75, 95% CI 2.45–5.74, $p < 0.00001$; neutropenia, RR = 1.88, 95% CI 1.12–3.14, $p = 0.02$; thrombocytopenia, RR = 11.47, 95% CI 5.94–22.12, $p < 0.00001$, respectively) (Fig. 4). Grade 3 or worse non-hematological adverse events including infection (RR = 4.37, 95% CI 2.30–8.32, $p < 0.0001$), cardiac disease (RR = 3.76, 95% CI 2.16–6.56, $p < 0.0001$) gastrointestinal events (RR = 4.27, 95% CI 2.37–7.70, $p < 0.00001$) occurred more frequently in transplantation group (Fig. 5 and Supplementary Figure 2, 3, and 4).

Discussion

This meta-analysis comprised 4 RCTs and 6 retrospective studies with a total of 1811 patients compared the efficiency and safety of immunochemotherapy with or without autologous stem cell transplantation in the rituximab era. Our findings showed that the upfront ASCT only improved short-term survival, but no significant difference for long-term survival was observed in high-intermediate or high-risk group. However, of the patients who achieved CR after induction

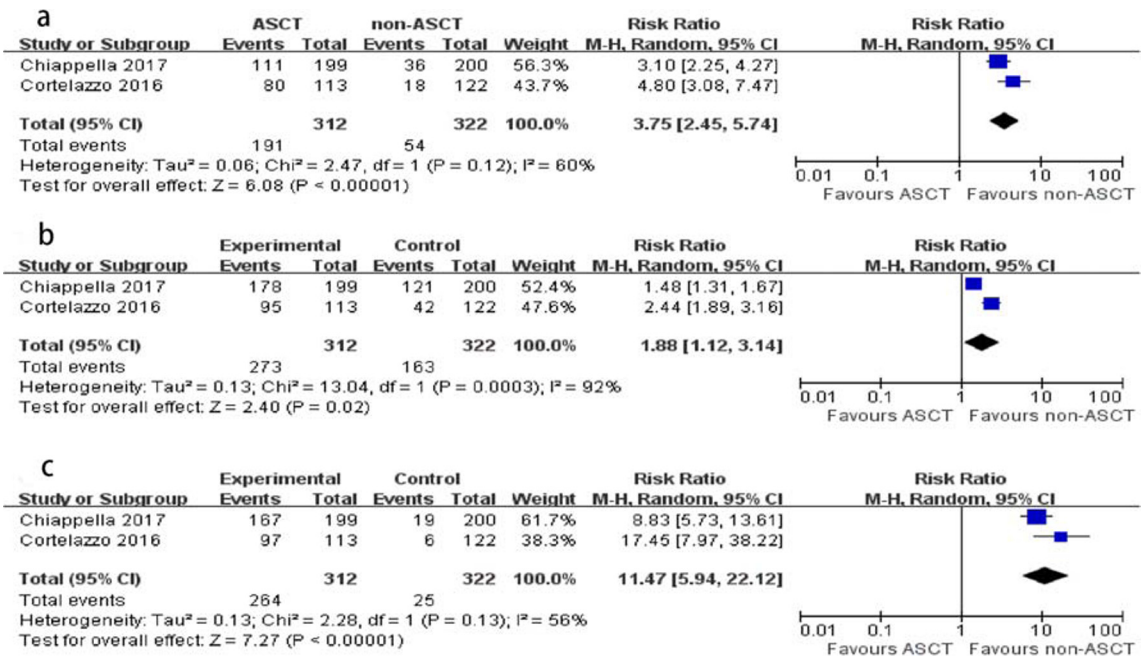

Fig. 4 Forest plot and meta-analysis of grade 3 or worse hematological adverse events occurrence. **a** Anemia. **b** Neutropenia. **c** Thrombocytopenia. SE, standard error; CI, confidence interval; ASCT, autologous stem cell transplantation

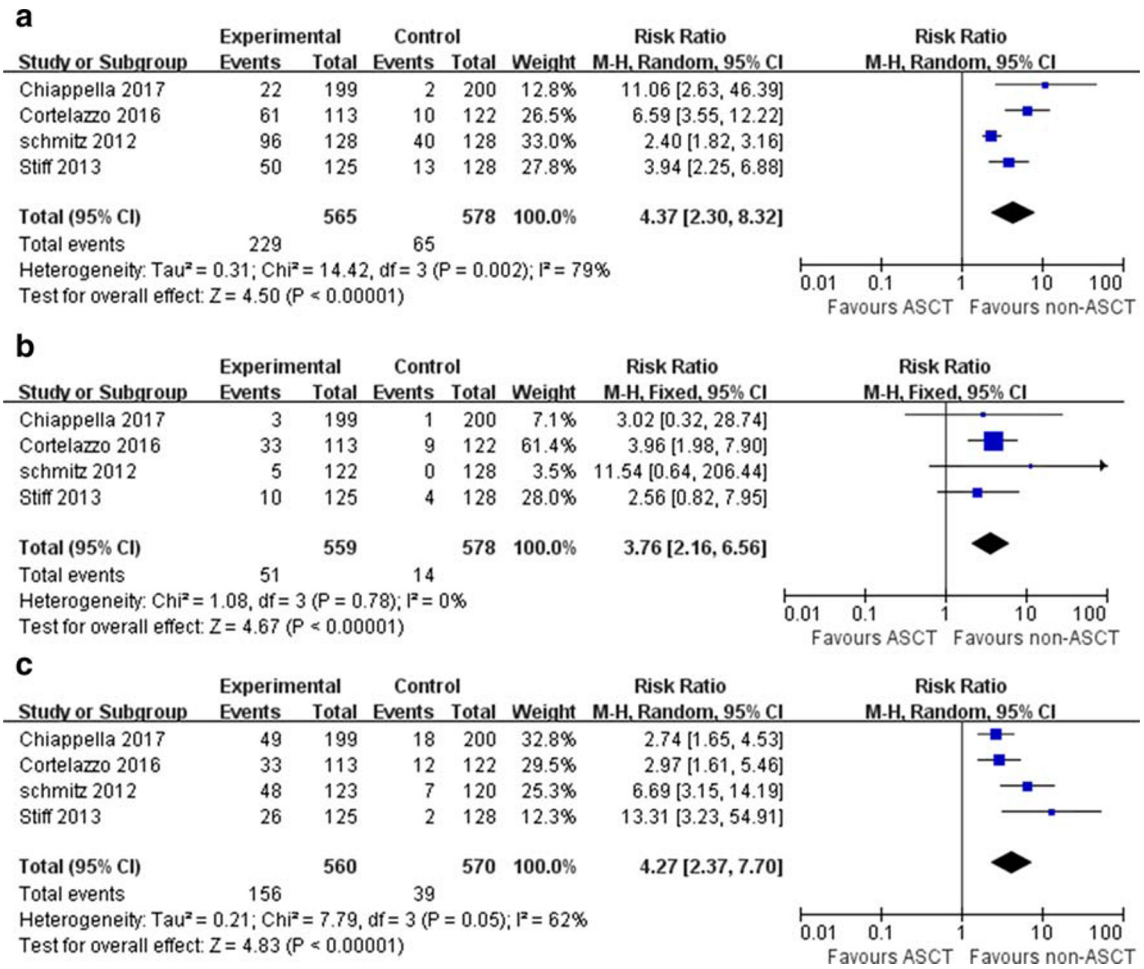

Fig. 5 Forest plot and meta-analysis of Grade 3 or worse non-hematological adverse events occurrence. **a** Infection. **b** Cardiac disease. **c** Gastrointestinal events. SE, standard error; CI, confidence interval; ASCT, autologous stem cell transplantation

chemotherapy, three retrospective studies indicated that these patients achieved long-term survival benefits. In addition, the incidences of grade 3 or worse hematological adverse events and non-hematological toxicities (infection, gastrointestinal events, and cardiac disease) tended to be higher in the transplantation group.

The main result of our research showed that DLBCL patients in high-intermediate- or high-risk group only achieved short-term but without long-term survival benefit from the upfront ASCT consolidation, which is consistent with the well-known previous reporters [13, 21, 22, 27]. The essential cause of this result is associated with the considerable relapse rate and poor efficacy of salvage treatment. After attack by high-dose chemotherapy, there may be mobilization failure and poor recovery of hematopoiesis after transplantation, which result in a considerable risk of relapse after transplantation. Besides, the subsequent treatment efficacy for relapse patients is not satisfactory. Patients with disease progression after ASCT always have an extremely poor survival [28]. Ultimately, there is only a temporary improvement of PFS but without benefit of overall survival.

In order to identify patients who will gain maximal benefit with the upfront HDT/ASCT and reduce the risk of mistreatment, we conducted subgroup analyses to explore whether patients with complete remission (CR) after induction chemotherapy could benefit from the upfront ASCT. Our results showed that the ASCT should not be performed too early during the course of treatment; the CR under PET-CT monitoring [29] with full courses of induction therapy should be confirmed before the use of upfront auto-HSCT, which may be related to the reduction of tumor burden. However, this conclusion is derived from the finding of the included three retrospective studies. Until present, there have been no randomized controlled trials in which all subjects had received CRs after induction chemotherapy, and we expect upcoming relevant RCTs to validate the results.

Screening for patients who may benefit from the upfront ASCT using the IPI score has certain limitations as the high-risk patients selected in our study did not show any improvements in OS. DLBCL is a group of diseases that are highly heterogeneous in phenotype and genetics. The non-germinal center B cell (non-GCB) subtype is more related to poor

prognosis than the germinal center B cell (GCB) subtype. We tried to investigate the association between molecular classifications (GCB versus non-GCB) and ASCT. However, only two included trials [16, 25] displayed related results; insufficient data prevents us from doing a subgroup analysis, but both of them showed that neither PFS nor OS was improved in the upfront-HSCT group in GCB/non-GCB patients, which suggests the possibility that upfront ASCT may adverse the poor prognosis of non-GCB subtype in high-risk DLBCL. A recent study conducted by Schmitz et al. has made a breakthrough in the gene stratification and pathological mechanism; they identified 4 genetic subtypes (MCD, BN2, N1, and EZB) of DLBCL with significant different genetics, epigenetics, and clinical features, which provides a theoretical basis for precision-medicine strategies in DLBCL [30]. Then, Bjoern et al. demonstrated that DLBCL can be defined into 5 robust subsets based on their genetic, mutation characteristics, and temporal ordering of identified alterations; providing new insights into the pathogenesis of DLBCL whose genetic characteristics are independent of the IPI system could suggest new combination therapy strategies [31]. As a result, genetic tools are considered the currently potentially effective prognostic prediction method. Besides, Zhong et al. constructed a prognostic nomogram to predict the OS of DLBCL patients and validated it in four cohorts, but the C-index in the ASCT cohort was low (0.61) and did not show the effect of selecting patients who may benefit from ASCT [32].

Inevitably, our research has certain limitations. On the one hand, considering the limited number of studies related to this topic, as well as the quality of trials, only 4 RCTs and 6 retrospective trials were included. To ensure the credibility of the conclusion obtained from this meta-analysis, we rigorously assessed the quality of the included studies. The four RCTs are all multicenter, large-scale phase III clinical trials conducted by international authoritative medical institutions. Although the included 6 retrospective studies were not representative enough of the local populations, and the evaluation of the outcomes was not sufficient, their quality assessment scores were all above 7 and were considered high-quality studies. In addition, retrospective analyses accounted for a large proportion of our study. Although retrospective studies have inevitable defects, the important information they provide cannot be easily ignored. On the other hand, differences in induction or preparative regimens for the ASCT, response after induction treatment, length of follow-up among studies, and intensity and duration of treatment before transplantation were inevitable. However, different regimens and intensities of chemotherapy always lead to different treatment-related adverse events. Therefore, when we performed meta-analysis about treatment-related adverse events, the included four RCTs showed certain obvious heterogeneity. Considering that the number of involved studies was limited and subgroup analysis was difficult to implement, we choose to use the random-effect model for statistics of some adverse event (AE)–related analysis.

The upfront ASCT improved PFS but not OS among untreated patients in high-intermediate or high-risk group who had a first remission to induction chemotherapy. The standard treatment was still chemoimmunotherapy based on R-CHOP regimen. The upfront ASCT remains a treatment option for young patients with high- intermediate/high IPI score, especially for those who received CR after induction chemotherapy.

Conclusion

High-intermediate or high-risk untreated patients with DLBCL only achieved short-term survival benefit with the upfront ASCT.

Author contributions Study concept and design: Qing-Qing Cai, Shu-Yun Ma

Acquisition of data: Shu-Yu Ma, Xiao-Peng Tian, Jun-Cai, Guang-Zheng Zhong, Xu Chen

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Statistical analysis: Shu-Yun Ma, Xiao-Peng Tian, Jun-Cai

Supervision: Qing-Qing Cai

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Compliance with ethical standards

Ethical approval and consent to participate As a systematic review and meta-analysis, no ethical approval or consent to participate was required.

Conflict of interest The authors declare that they have no conflicts of interest.

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