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Outcomes of MYC-associated lymphomas after R-CHOP with and without consolidative autologous stem cell transplant: Subset analysis of randomized trial intergroup SWOG S9704

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Summary

Double hit lymphoma (DHL) and double protein-expressing (MYC and BCL2) lymphomas (DPL) fare poorly with R-CHOP; consolidative autologous stem cell transplant (ASCT) may improve outcomes. S9704, a phase III randomized study of CHOP +/−R with or without ASCT allows

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evaluation of intensive consolidation. Immunohistochemical analysis identified 27 of 198 patients (13.6%) with MYC IHC overexpression and 20 (74%) harboring concurrent BCL2 overexpression. Four had DHL and 16 had DPL only. With median follow-up 127 months, there is a trend favoring outcomes after consolidative ASCT in DPL and MYC protein overexpressing patients, whereas all DHL patients have died irrespective of ASCT.

Keywords

Double Hit Lymphoma; Double Protein Lymphoma; MYC; BCL2; Autologous Stem Cell transplant

Background

Diffuse large B-cell lymphoma (DLBCL), the prototype of aggressive Non-Hodgkin lymphoma (NHL), has clinical and biologic variants with diverse clinical outcomes[1]. Historically, dual translocations of *MYC* and *BCL2* (or *BCL6*) "double hit lymphoma" (DHL) are associated with a rapid clinical course and poor survival[2]. DHL is fortunately uncommon, with reported frequencies of 2–8% among DLBCL patients[3]. The commercial availability of a reliable stain for MYC protein overexpression[4] has furthered evaluation of MYC's role in lymphomas, although the definition of overexpression varies[5]. In general, dual MYC and BCL protein overexpression (DPL) is also associated with a poor prognosis and is more common than DHL[5].

SWOG S9704 was a phase III randomized study of aggressive NHL treated with CHOP +/−R for 5 cycles followed by either 3 additional cycles of CHOP +/−R or one additional cycle of induction chemotherapy followed by autologous stem cell transplant (ASCT) consolidation. ASCT improved progression free survival (PFS) for high-risk patients, but biologic subsets were not separately evaluated in the initial analysis[6]. While we have previously evaluated the impact of histopathology and MYC protein expression[7] the current report includes an updated dataset with an emphasis on the impact of transplant.

Methods

This randomized intergroup trial included eligible patients 15 to 65 years with biopsy-confirmed aggressive non- Hodgkin's lymphoma, high-intermediate or high-risk age adjusted IPI (aaIPI)[8]. Stratification factors and detailed treatment information have been published[6].

All cases had central pathology review. 198 available patient samples were tested for MYC protein overexpression. BCL2 IHC (≥30% positive cells), COO classification (germinal center: GC versus non-germinal center: non-GC per Hans algorithm[9]), and FISH for *MYC* were performed in all MYC IHC positive cases with sufficient tissue. FISH for *BCL2* rearrangements was performed in cases with a *MYC* rearrangement (Figure 1). A descriptive analysis of outcomes was performed using clinical annotations through SWOG statistical center, and review of S9704 database. Tissue microarrays, immunohistochemistry, FISH

studies, statistical analysis were performed as previously described[7] with additional details available (Supplemental Material).

Results

As previously published, there were no significant differences between randomized groups, and early ASCT improved PFS for high-intermediate-risk or high-risk disease with 2-year PFS of 69% and 55%, respectively. Among 370 eligible patients from S9704, 260 had DLBCL or B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (BCLU) and 198 cases had available tissue for the current analysis. Twenty-seven MYC IHC positive patients were identified. Among 27 MYC IHC positive patients, 8 received CHOP. 16/27 had concurrent BCL2 overexpression by IHC and were classified as DPL. Four patients had DHL with associated dual protein expression. Seven of 27 were MYC positive only by IHC without DPL or DHL (Figure 1).

Patient Characteristics and Outcomes

Median age, aaIPI, bulky disease and elevated LDH were similar between MYC IHC positive and DPL patients. COO was performed in 17/27 MYC IHC positive patients and 11 had GC and 6 had non-GC DLBCL. In the DPL group, COO was evaluable in 10/16 patients and 4 had GC and 6 had non-GC DLBCL (Supplemental Table 1).

The median follow-up is 127 months (range, 93.8–158.2 months). In an analysis of actual treatment received, two year PFS for the transplant and non-transplant group was 63% and 16%, respectively (p*=0.02; Figure 2a). Median PFS was 6 months (95% CI: 4.5–9.0) for no transplant, and 31 months for transplant (95% CI; 6.3, not reached). Two-year OS for transplant and non-transplant group was 63% and 16%, respectively (p*=0.04; Figure 2b). Similarly, in the DPL group, 9 patients in the no transplant group and 3 patients in the transplant group have progressed or died; the median PFS was 7 months (95% CI: 2.8, 13.9) versus 31 months (95% CI: 16.3, not reached) for non-transplanted versus transplanted patients, respectively. The Kaplan Meier estimate of 2 year PFS, OS for transplant and non-transplant groups were 60% and 18%, respectively (p*=0.19 for PFS and p*=0.25 for OS; Figures 2c and 2d).

In MYC positive patients, 19/27 patients could be randomized, with disease progression precluding randomization in others. 11/19 patients did not receive transplant, and their 2 year PFS was 27% compared to 8/19 patients who received transplant with a 2 year PFS of 63% (p*=0.11; Figure S1a); similarly, the 2-year OS for the non-transplant group was 27% and the transplant group was 63%, respectively (p*=0.17; Figure S1b). Among patients with DPL, 12/16 patients were randomized; the 2-year PFS and OS was 29% for the non-transplant group and 60% for the transplant group, respectively (p*=0.43 for PFS and p*=0.53 for OS); (Figure S1c and S1d). p* (two-sided Logrank).

Three of four DHL patients survived to randomization, and one was randomized to transplant. All progressed and died with a median overall survival of 5.9 months (95% CI: 5.3, 6.7 months).

Discussion

DHL and DPL are associated with inferior outcomes following standard chemoimmunotherapy[10]. When correlating DHL with COO, DHL appears associated with the GC type of DLBCL whereas several groups have observed that non-GC DLBCL is enriched for DPL, and provocatively suggest that the major underlying reason for poor outcomes in non-GC DLBCL is due to MYC and BCL2 protein overexpression[11]. Our analysis sought to determine the frequency of DHL and DPL among a MYC IHC positive transplant-eligible population, and to evaluate the impact of consolidative ASCT in a prospective dataset. The key observations are the rarity of both DHL and DPL in younger patients, the universally dismal outcome of DHL, and the suggestion that consolidative ASCT may be useful in DPL patients.

The overall incidence of MYC IHC positivity was low in our population, identifying only 27/198 (13.6%) cases with available tissue. This is in contrast to other retrospective series in which the incidence of MYC IHC positivity occurs in 30–50% of cases[5]. Similarly, we had 4 cases of DHL and 16 cases (8% of the available samples) of DPL. This discrepancy may be due to differences in the median age across series and additional cases that were MYC IHC negative may not have been captured. The median age of S9704 patients was 51 years (range, 18–66 years), reflecting a transplant-eligible population. In contrast, most retrospective DHL and DPL series demonstrate that over half of the patients with DPL are older than 60 years, and some report a median age of 71 years[12]. Thus, despite enrolling high IPI and advanced stage patients in S9704, the low frequency of DPL in our series suggests a strong correlation with advanced age that may impact future trials in this population.

Despite general consensus that dual MYC and BCL2 protein expression confer a negative prognosis in DLBCL, the optimal IHC cut-point defining overexpression is not uniform[5, 13]. The definition of BCL2 expression was 30% in the Hans Classifier[9]; however, the largest series to study DPL used a cut-point of 70%[12]. We used a cutoff of 30%; despite this conservative cut-point, we still identified a relatively small sample size.

A critical, as yet unanswered, question in DHL and DPL is the optimal initial therapy and whether or not consolidative ASCT improves outcomes. Most data are retrospective series or registry databases, and focused primarily on DHL rather than DPL. These series collectively show that R-CHOP is insufficient therapy with median overall survival of 10 months or less; Compared to augmented or intensified regimens, the use of R-CHOP appears inferior[14]. All four patients with DHL in our series have died of disease with a median survival of six months despite consolidative ASCT in one, emphasizing the role of an effective induction.

The role of high dose therapy in DPL and DHL is undefined. Some have proposed that achievement of CR determines outcome rather than consolidative ASCT[15]. However, these studies evaluated DHL and not DPL; our small analysis thus offers one of the first reports to address consolidative transplant in DPL. Of note, the median age of the 16 DPL patients was 56.3 years, placing these patients among the oldest of the entire initial series that had a median age of 51 years. Furthermore, only 12 could be randomized, mainly due to

progressive disease during induction. While numbers are small and confidence intervals wide, DPL patients randomized to ASCT had superior outcomes (median PFS 29 months versus 3 months).

In summary, this is a subset analysis of the S9704 trial, one of the largest available data sets to prospectively address the question of upfront ASCT in patients with MYC positive lymphomas in the rituximab era. While our data are limited by small numbers, we observed a trend that MYC IHC positive and DPL patients consolidated with ASCT may have improved outcomes; however, nearly one-third of MYC IHC positive patients were unable to be randomized due to early progression or death. True FISH-defined DHL were infrequent even in this high-risk cohort and had a dismal prognosis. Clearly, MYC positive aggressive B-cell lymphomas, DHL and DPL represent unmet needs and constitute the basis of an intergroup study under development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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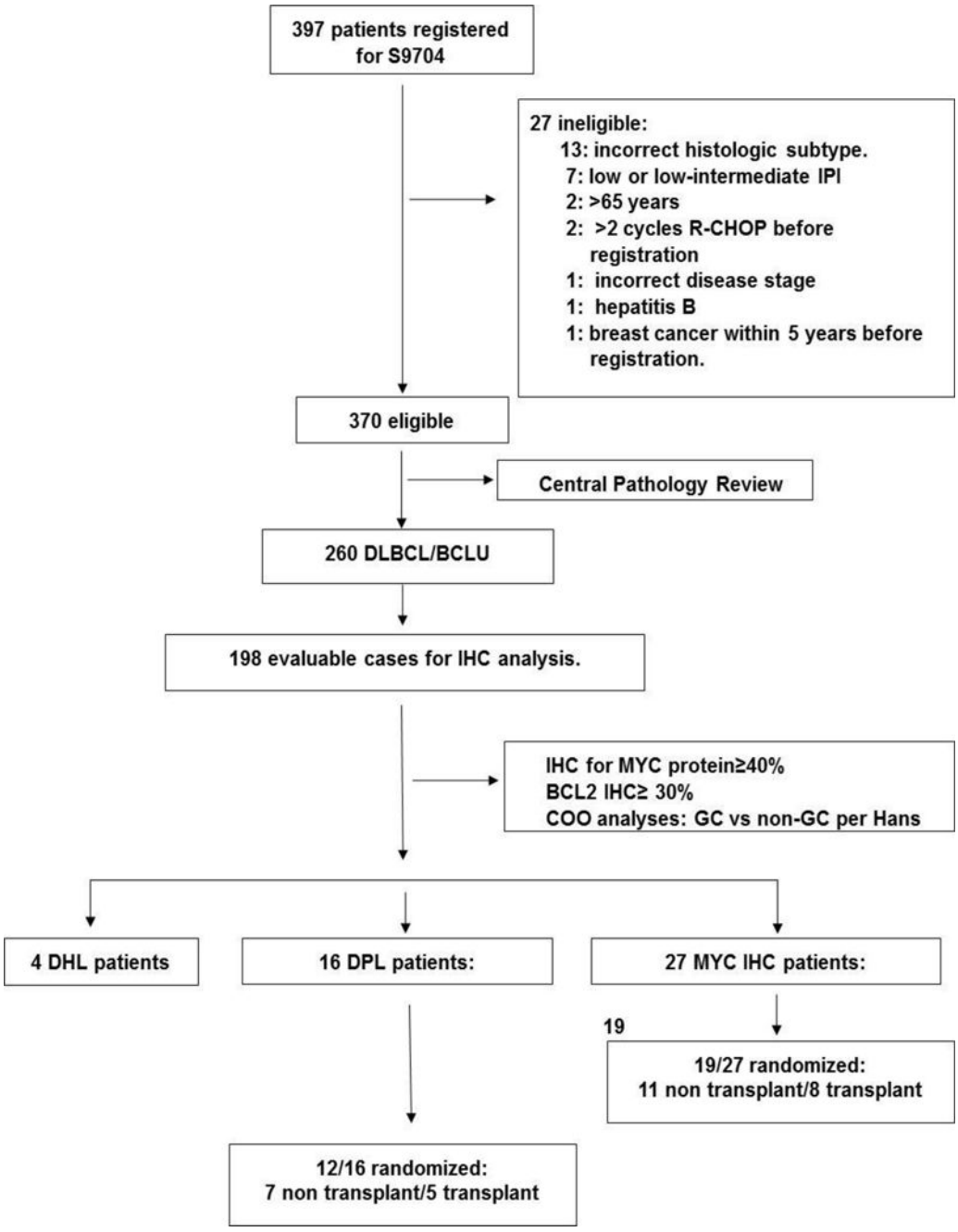

Figure 1.

Consort Diagram showing disposition of patients. Of the 397 patients registered for S9704, 370 were eligible, 198 cases were evaluable for IHC analysis and 27 MYC IHC positive patients were identified.

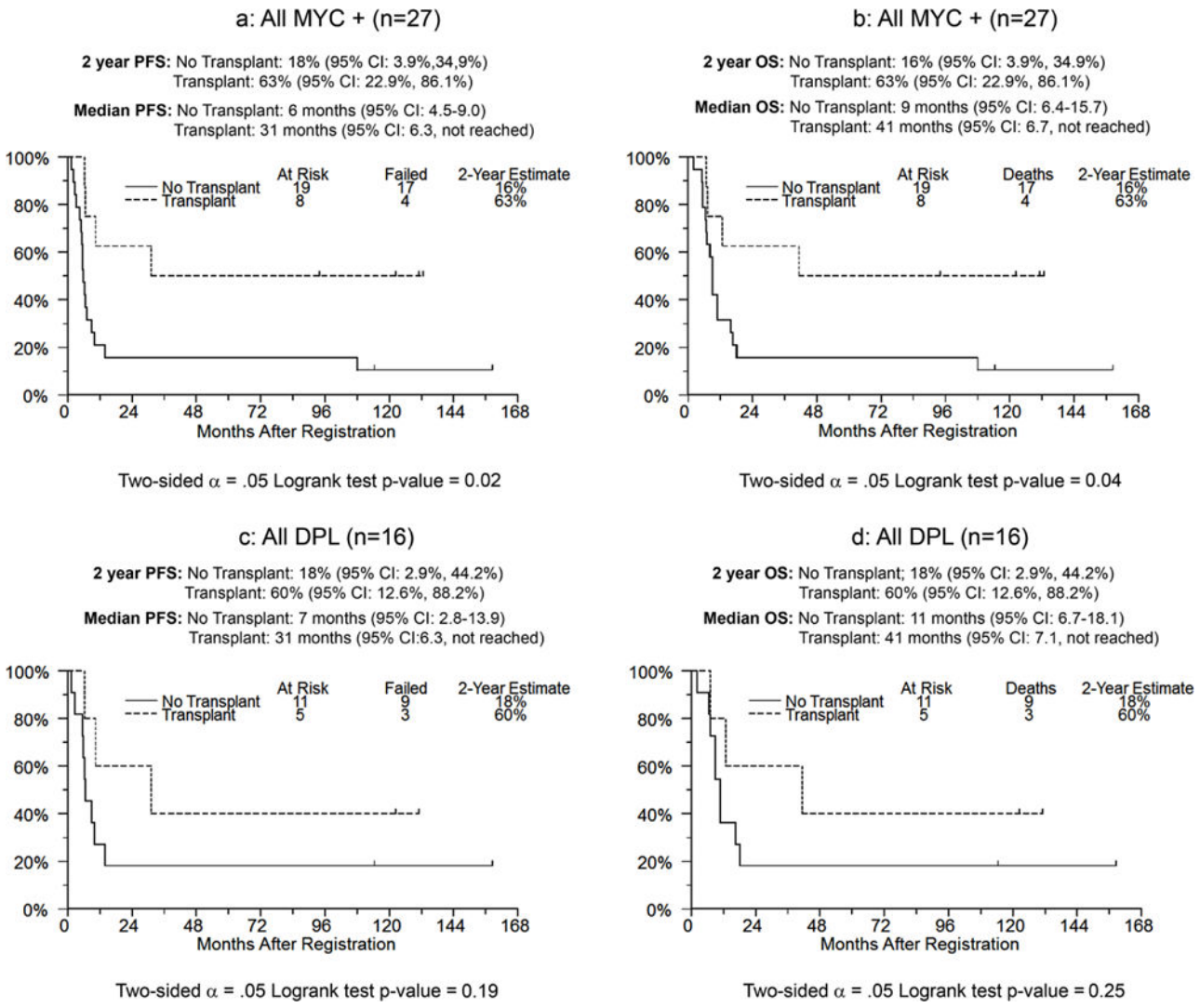

Figure 2.

Progression free survival and overall survival of all patients with and without transplant for MYC IHC positive patients (Figures 2a and 2b), and DPL patients (Figures 2c and 2d) respectively.