

LETTER TO THE EDITOR

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The addition of rituximab to CHOP therapy alters the prognostic significance of CD44 expression

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Abstract

Expression of CD44 splice isoforms has been previously reported to correlate with inferior outcomes in DLBCL patients treated with CHOP therapy. However, it is unclear whether this observation remains valid in the R-CHOP era. In this study, we correlated CD44H and CD44v6 status with survival outcomes among DLBCL patients with an emphasis on the comparison between CHOP- and R-CHOP-treated subgroups. Our results suggest that rituximab has significantly decreased the prognostic value of CD44H. We also observed that the therapeutic benefit of rituximab is largely restricted to CD44H-positive cases in this cohort.

Keywords: DLBCL, Prognosis, CHOP, Rituximab, CD44 variant isoforms, Bone marrow involvement

To the Editor

Although incorporation of rituximab into CHOP (R-CHOP) has dramatically improved the outcome of DLBCL [1-5], approximately 40% of patients still succumb to the disease [6]. One of the prognostic markers studied in the CHOP era is CD44, a transmembrane glycoprotein with many alternative splicing isoforms [7]. Variations in its extracellular domain lead to isoform-specific activities of CD44 in cell adhesion, lymphocyte homing, and cell signaling [7]. In general, CD44 plays a positive role in cell survival and invasiveness, and it is implicated in cancer stem cell maintenance in certain solid tumors [8]. The objective of the current study is to compare the prognostic significance of CD44 isoforms in the CHOP and R-CHOP treatment groups.

This study enrolled 117 de novo DLBCL patients among whom 53 were treated with CHOP and 64 were treated with R-CHOP (Additional file 1; Additional file 2: Table S1). As expected, the incorporation of rituximab markedly improved the overall survival (OS) and event-free survival (EFS) rates (not shown). We used immunohistochemistry (IHC) to examine the expression of CD44H (the standard isoform) and CD44v6 (isoforms containing the

variant exon 6) in diagnostic specimens (Additional file 3: Figure S1). Expression of CD44H and CD44v6 was detected in 65.0% and 34.2% of patients, respectively, with strong correlation to each other (Spearman's correlation, $r = 0.423$, $p < 0.001$). The baseline clinical features were not significantly different between the CD44H+ and CD44H- patients. The CD44v6+ and CD44v6- cases were also very comparable (Additional file 2: Table S2).

In the entire cohort of 117 patients, CD44H positivity strongly correlated with poor OS ($p = 0.002$, Figure 1A) and EFS ($p = 0.011$, Figure 1B) outcomes. Specifically, the 5-year OS rates in the CD44H+ and CD44H- subgroups were 82% and 41%, respectively. CD44v6 positivity also correlated with poor prognosis, although the trend was only marginally significant (OS: $p = 0.050$; EFS: $P = 0.058$, Figure 1C and D). Nevertheless, because CD44v6 showed an IPI-independent survival impact in multi-variable analysis (Additional file 2: Table S3), the relatively weak survival association based on the Kaplan-Meier estimates likely reflects the low frequency of CD44v6 expression and hence a greater sample size requirement. CD44v6 did not show any prognostic value when the cohort was divided into treatment subgroups (not shown). The negative prognostic value for CD44H detected among all patients could also be observed in the CHOP subgroup (OS: $p = 0.021$; EFS: $P = 0.044$, Figure 1E and F), but not the R-CHOP subgroup (OS: $p = 0.095$; EFS: $P = 0.211$, Figure 1G and H). Because the OS response was very similar among all R-CHOP-treated cases and CHOP-treated CD44H- patients,

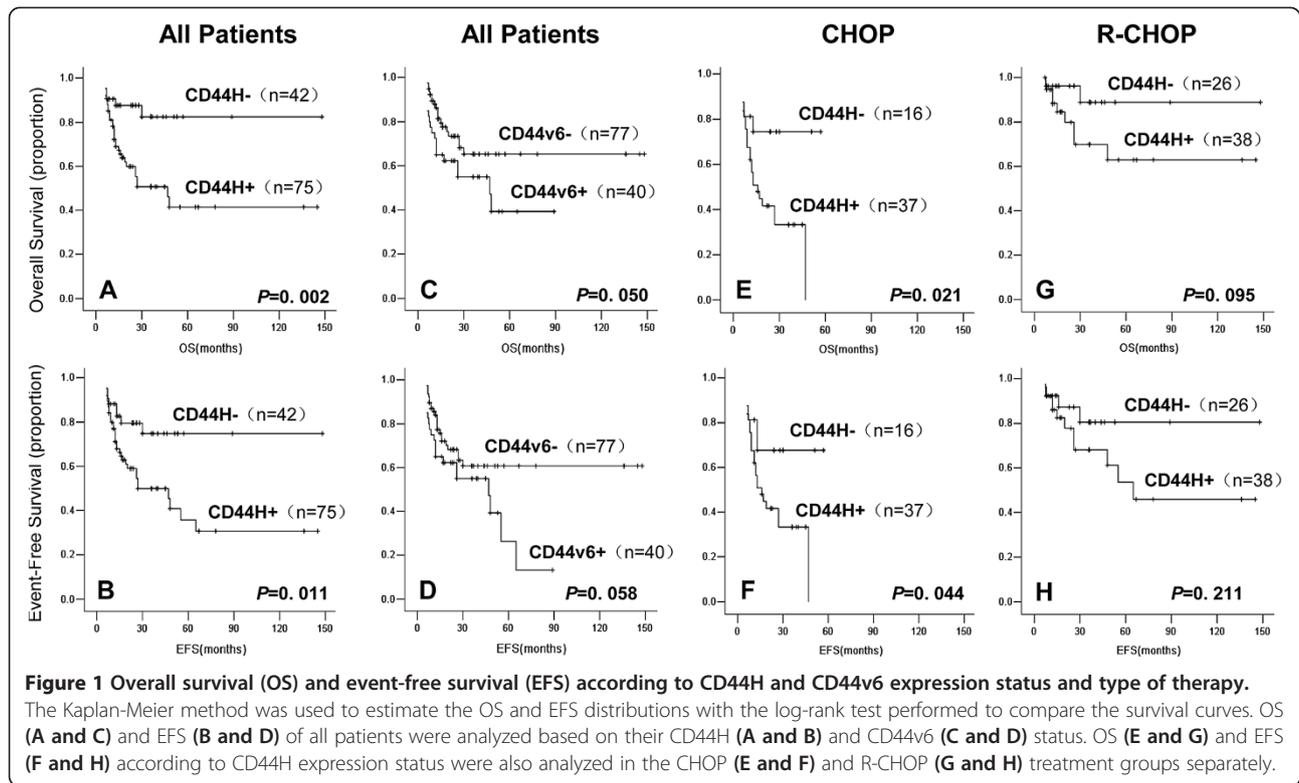
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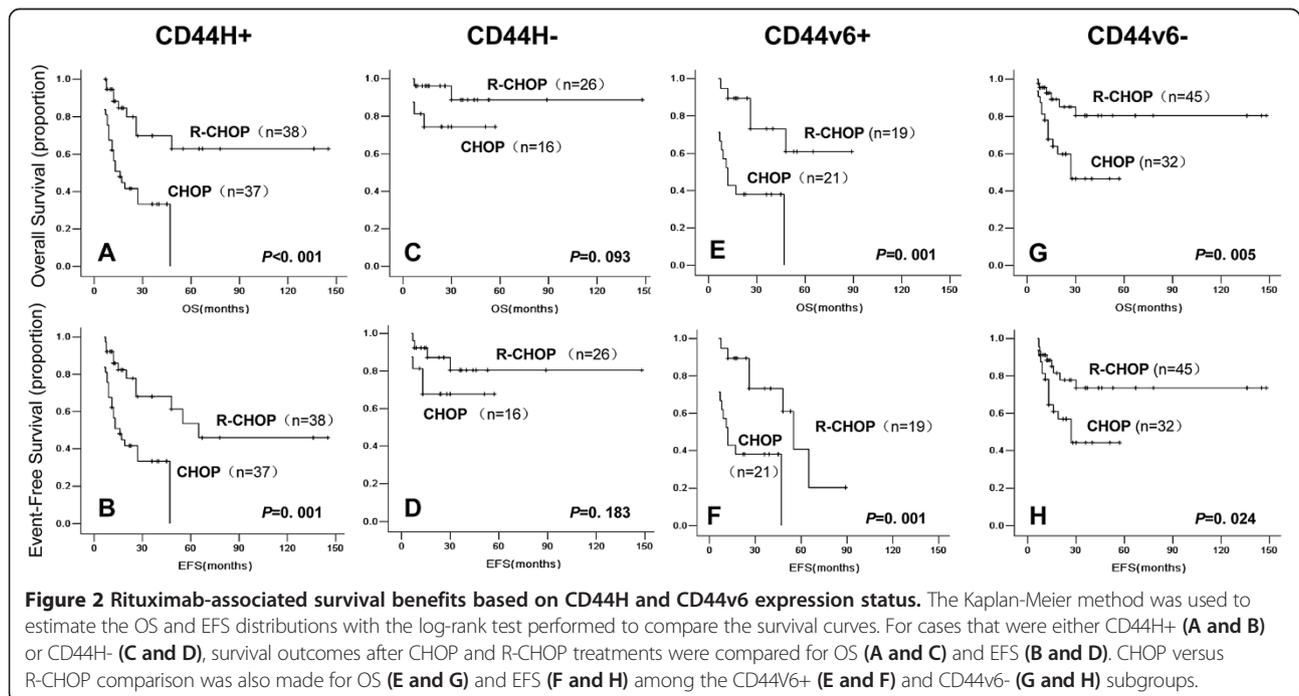
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we reasoned that the extremely unfavorable response to CHOP among CD44H-positive patients may have been specifically ameliorated by rituximab. To test this notion, the rituximab-associated survival benefit was examined in patient subgroups of different CD44 expression status. For

CD44H, although rituximab substantially improved the outcome for CD44H+ patients (OS: $p < 0.001$; EFS: $P = 0.001$, Figure 2A and B), the impact of this agent was insignificant for the CD44H- cases (OS: $p = 0.093$; EFS: $P = 0.183$, Figure 2C and D). Interestingly, this phenomenon



appeared to be specific to CD44H because the rituximab-associated survival benefit was significant irrespective of the CD44v6 status (Figure 2E to H).

Possibly due to the use of different antibodies and different IHC staining/scoring methods, there have been some controversial observations on the prognostic importance of CD44 in CHOP-treated DLBCL patients. In agreement with the majority of published studies [9–11], we have observed a negative survival impact of CD44H and CD44v6 expression in our entire study cohort (Figure 1 and Additional file 2: Table S3) as well as the CHOP treatment group (Figure 1E and F), although there were differences between these two markers. As the first study aimed to examine CD44 isoform expression in the R-CHOP era, our data suggest that rituximab has decreased the prognostic significance of CD44H, while the impact of rituximab on CD44v6 awaits future studies of larger cohorts. We also observed that the rituximab-associated survival benefit was profound among CD44H-positive cases but fairly limited among the CD44H-negative subgroup.

Additional files

Additional file 1: Information on Patients and Methods.

Additional file 2: Table S1. Clinical features and CD44 variant expression in the CHOP and RCHOP groups. **Table S2.** Patient characteristics according to CD44H and CD44v6 expression status.

Table S3. Prognostic factors and multivariable survival analysis.

Additional file 3: Figure S1. Representative immunohistochemical staining of DLBCL samples for CD44H and CD44v6 expression. (A, C), negative control stain using isotype-matched Abs. (B) CD44H staining in a positive case. (D) CD44v6 staining in a positive case.

Competing interests

The authors declare no conflicts of interest.

Authors' contributions

FR and BHY designed the study and analyzed and interpreted the data. WXL and XM collected and analyzed data. WYQ and HF collected data. ZT and LXZ provided study material and helped with the IHC staining. BHY, WXL and FR wrote the manuscript. All authors read and approved the final manuscript.

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