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GENETIC LANDSCAPES AND CURATIVE EFFECT OF CAR T CELLS IMMUNOTHERAPY IN RELAPSE AND REFRACTORY DLBCLS

Topic: 19. Aggressive Non-Hodgkin lymphoma - Clinical

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma. Although potentially curable with targeted drug, monoclonal antibody, immunochemotherapy, refractory or relapsed lymphoma occurs in 40% of patients.

Aims: We investigated whether molecular subtypes can be robustly identified using methods potentially applicable in routine clinical practice, providing evidence that curative effect of CAR T cells immunotherapy differs in diverse subtype.

Methods: We have studied 105 relapse and refractory DLBCL (R&R DLBCL) patients using target region sequencing. clustering technique was applied to targeted region sequencing data derived from 105 R&R DLBCL patients cohort with full clinical follow-up(n=94).

Results: A total of 745 potential driver mutations were identified in 199 out of the 339 genes with a similar number in GCB and non-GCB. The most frequently mutated genes were TP53, KMT2D, PIM1, MYD88, CREBBP, CD79B and B2M found in more than 15% of cases. The frequency of TP53 in our R&R DLBCL cohort were higher than initial patients as reported. MYD88 CD79B, TNFAIP3, PRDM1 and SPEN were significantly more frequently mutated in more than 10% of non-GCB-DLBCL patients whereas KMT2D, CREBBP, DDX3X, B2M, TNFRSF14, BCL2, EZH2, CARD11, SOCS1, MYC and KRAS mutations were more common in more than 10% of GCB-DLBCL. PIM1, PCLO, TET2, STK11, TBL1XR1, NUDT15, CCND3 and TP53 in the gene were equally distributed in both DLBCL subtypes. Using clustering techniques applied to targeted region sequencing data derived from 105 R&R DLBCL patients cohort with full clinical follow-up (n=94), we investigated whether molecular subtypes can be robustly identified using methods potentially applicable in routine clinical practice. Six molecular subtypes were resolved, termed A53, MCD, BN2, KCB, N1, and JAK/STAT, along with an unclassified group. The subtypes of BN2 and N1 showed good prognosis, whereas MCD, KCB and JAK/STAT had intermediate outcomes. The subtypes characterized by genetic alterations of TP53 acquired the worst survival, as well demonstrated that TP53 mutations were independent predictors of survival in R&R DLBCL patients. The KCB subtype contained the majority of cases of transformed follicular lymphoma and strongly enriched for cases of double-hit GCB-type DLBCL, with inferior outcomes. Most patients (n=80, 76.2%) in our cohort received chimeric antigen receptor (CAR) T cells immunotherapy. These subtypes differed phenotypically, as judged by differences in gene-expression signatures and responses to immunochemotherapy, with favorable frequency of complete reponse (CR) in the BN2 and N1 subtypes, intermediate in MCD, KCB, and JAK/STAT subtypes, inferior outcomes in the A53 subtypes. We suggested that N1 subtype showed good prognosis due to their sensitive curative effect with CAR T cells immunotherapy.

Summary/Conclusion: Our findings confirm the existence of molecular subtypes of R&R DLBCL, providing evidence that curative effect of CAR T cells immunotherapy differs in diverse subtype. CAR T cells immunotherapy can prolong survival times of in some subtyes thought previously associated with worse outcomes. We provide a potential precision-medicine strategies for R&R DLBCL patients with poor prognosis.

Key words: relapse and refractory DLBCL, gene mutation, molecular subtypes, CAR T cells immunotherapy

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