Future prospects for DLBCL treatment: Combination of WEE1 inhibitors with CHOP and radiation therapy.

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About the Study

Diffuse large B-cell lymphoma (DLBCL) is the most aggressive and common form of non-Hodgkin lymphoma. DLBCL arises during B-cell development in the germinal center reaction as a result of high levels of genomic rearrangements to create high affinity B-cell receptors. Therefore, an important hallmark of DLBCL is the high levels of genomic instability; DNA damage and DNA damage response proteins [1]. Current treatment for DLBCL consisting of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) combined with the anti-CD20 antibody rituximab cures roughly 60% of patients, leaving 40% of patients with relapse or refractory disease, highlighting the need for therapy improvement [2].

We recently performed a guilt-by-association analysis in 1800 DLBCL patients to find targets associated with the MS4A1 gene, which codes for CD20, in order to explore additional treatment options for DLBCL [3]. We found that the WEE1 kinase, a cell cycle regulator, was highly associated with MS4A1. During normal cell cycle progression, WEE1 regulates cell cycle transition from the G2 phase into the M phase by blocking CDC2/CDK1 trough phosphorylation of tyrosine 15. In addition, WEE1 is activated in response to DNA damage to allow repair [4]. Inhibition of WEE1 with a chemical blocker therefore allows continuous cell cycling resulting in high levels of DNA damage [5]. WEE1 inhibition is currently being studied in clinical trials for both solid cancers and hematological malignancies [6]. We initially showed high protein expression of WEE1 in DLBCL patients and DLBCL cell lines, and demonstrated mono-therapy with WEE1 inhibitor ADZ1775 was highly lethal in DLBCL cell lines or combined with rituximab [3].

Based on these findings, we explored the effect of additional treatment with AZD1775 combined with radiation therapy (RT) and CHOP chemotherapy in DLBCL cell lines [7]. Cell viability experiments showed additive and synergistic effects for AZD1775 combined with both RT and CHOP in multiple DLBCL cell lines. In addition, analysis of DNA damage marker yH2AX showed that combination of AZD1775 with RT or CHOP significantly increased the levels of DNA damage (5-7 fold increase) compared to mono-therapy with RT or CHOP. We also observed that treatment of DLBCL cells with AZD1775 caused abrogation of the mitotic arrest, which results in premature mitotic entry. These results were in line with previous publication, which showed that WEE1 inhibition caused micronuclei formation and apoptosis [5].

Since CHOP is composed of different chemotherapeutic components (cyclophosphamide, doxorubicin, and vincristine) which each have different biological mode of action, we further analyzed the effect of the individual compounds in combination with AZD1775. Protein analysis of phosphorylated CDC2 (Tyr15), the downstream target of WEE1, showed that WEE1 activity was enhanced as a result of treatment with cyclophosphamide and doxorubicin mono-therapy, whereas vincristine treatment abolished both WEE1 activity and WEE1 protein expression. In addition, cell viability was significantly reduced when AZD1775 was combined with doxorubicin, suggesting that WEE1 up regulation by doxorubicin could enhance sensitivity for AZD1775.

Taken together, our data demonstrate great potential for WEE1 inhibition as an additional treatment to RT and CHOP in DLBCL, which has the ability to strengthen the current regimen.

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