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Commentary

Nanoparticle Formulation to Improve the Efficacy of Radiation Therapy Against Radiation-resistant Leukemia

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Patients with B-precursor acute lymphoblastic leukemia (BPL) are often treated with TBI-based conditioning, followed by hematopoietic stem-cell transplantation (HSCT). However, the leukemic relapse in high-risk BPL patients remained the major cause of patient mortality (Gaynon et al., 2006; Balduzzi et al., 2014). The incidence of post-HSTC relapse correlated with the level of residual leukemia burden prior to total body irradiation (TBI), indicating the radiation-resistant population of BPL cells may have contributed to the relapse. STAT-3 signaling pathway, along with PI3-K and NFkB pathways, regulates the cell survival after exposure to radiation-induced oxidative stress (Uckun et al., 2010), therefore contributes to the radiation resistance of BPL cells. Spleen tyrosine kinase (SYK), a key regulator of STAT-3, was chosen as the main target of reducing the radiation resistance (Mocsai et al., 2010). The authors identified C61, a small-molecule chemical compound inhibitor for SYK phosphorylation, which sensitized the resistant BPL cells toward radiation.

Despite the high selectivity and potent inhibition of C61 against SYK phosphorylation, the in vivo performance of C61 is still limited by pharmacokinetic problems. The low molecular weight of C61 is expected to have short blood circulation and quickly be cleared through the kidney (Levchenko et al., 2002). The in vivo stability of C61 against various proteases needs to be addressed. In the current issue of *EBioMedicine*, Uckun et al. used liposome nanoparticles to encapsulate C61, increased its blood retention and preserved its integrity for proper function (Uckun et al., 2015). The liposome formulation could also alleviate the potential toxic side effects of free C61 (Elbayoumi and Torchilin, 2010).

In their recent work published in *EBioMedicine*, Uckun et al. first studied the correlation between SYK-STAT3 pathway and incidence of relapse in primary ALL samples. The results confirmed that SYK was a key regulator for STAT3 regulation, while patients with early relapse had significantly higher expression levels of SYK-STAT3 genes. The authors then confirmed with in vitro that C61-liposome in combination with low-dose TBI, could deplete leukemia-initiating BPL cells. The xenograft model study showed promising results that the C61-liposome + TBI regimen resulted in a median EFS time of >150 days and a remarkable 150-day leukemia-free survival of 80 ± 10%. The authors then evaluated the treatment efficacy in CD22ΔE12xBCR-ABL double transgenic (Tg) model of advanced murine BPL. The combination regiment had the longest duration of remission (54 ± 27 days) compared to TBI (7 ± 4 days, $p = 0.021$) or C61-liposome (0 ± 0 days, $p = 0.0016$). The median OS times were 112 days for C61-LNP + TBI but only 4 days for CON (Log-rank test, $P < 0.0001$), 3 days for C61-LNP alone ($P < 0.0001$), and 14 days for TBI alone ($P = 0.0002$).

In general, the authors presented an interesting nanoparticle formulation for the radiosensitization of BPL. The animal studies proved that C61-liposome + TBI is a promising treatment strategy to overcome BPL relapse.

Disclosure

The authors disclosed no conflicts of interest.

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