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Opinion Article

Treatment of Atypical Cancer Cells with Lipopolymer-Mediated siRNA Transport for Myeloid Lymphoma Treatment

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DESCRIPTION

Broad-spectrum cytotoxic chemotherapeutic agents and small molecule inhibitors targeted at particular aberrant proteins are used as the first-line treatment for myeloid leukemia. These aberrant proteins are caused by mutations in a single gene or the fusion of multiple genes as a result of chromosomal rearrangements. Abelson murine leukemia viral oncogene homolog 1 tyrosine kinase gene fusion with the Breakpoint Cluster Region (*BCR*) gene results in the Philadelphia chromosome, which is present in approximately 95% of patients with Chronic Myeloid Leukemia (CML).

The resulting *BCR-ABL* oncogene is constitutively active and, as a result of the enhanced tyrosine kinase activity, causes unchecked myeloid cell accumulation and growth. The Tyrosine Kinase Inhibitor (TKI) imatinib, which targets *BCR-ABL*, has revolutionized the treatment of CML. The 5-year relative survival rate is now 4 times greater than it was in the mid-1970s (22%). In contrast to CML, Acute Myeloid Leukemia (AML) has a multifactorial etiology that includes a genetic landscape that is very heterogeneous and a number of cooperative molecular abnormalities.

Nearly one-third of newly diagnosed cases of AML exhibit Internal Tandem Duplications (ITD) or point mutations in the Fms-Like Tyrosine Kinase 3 (*FLT3*) gene, the most prevalent genetic abnormality in AML. Despite the paradigm shift brought about by the development of TKIs in the clinical treatment of myeloid leukemia, compelling evidence of TKI efficacy loss due to resistance has emerged.

Imatinib resistance and failure to achieve a full cytogenetic response were observed in 24% of patients within 18 months of starting treatment in the crucial IRIS study, which showed imatinib to be more effective and safe for treating newly diagnosed CML patients. Additionally, 63%-72% of patients receiving second-line therapy with second-generation *BCR-ABL* TKIs failed to produce a substantial molecular response after 2 years of follow-up, and 30%-50% of patients experienced imatinib therapeutic failure after 5 years. In the phase 3 RATIFY trial for AML, which served as the foundation for the drug's approval, 40% of patients were unable to establish remission, and 40% of those who did so relapsed. Similar to this, in the phase 3 ADMIRAL trial, 30.5% of the patients experienced relapses during the study, with the bulk of these (96%), happening within 4 weeks of the last gilteritinib dosage.

Although methods like clinical rotation and sequential exposure to the variety of TKIs that are now in use, being developed, and undergoing clinical evaluation help to increase therapeutic efficacy, these inhibitors are ultimately vulnerable to oncoming resistance. Allogeneic hematopoietic stem cell transplantation is advantageous for patients with chronic phase CML after failure with two or more TKIs and for *FLT3*-mutated AML patients at first complete remission, but it is also linked to complications like graft-versus-host disease, with results being greatly influenced by the stage of the illness and age. Furthermore, even after an allogeneic hematopoietic stem cell transplant, *FLT3-ITD* mutations are linked to greater risks of early recurrence.

Alternative treatment modalities that can compete with TKIs in terms of efficacy and safety and/or work in concert with them to create a more robust and long-lasting response than monotherapy are needed to get beyond these limits of existing medicines. By using small interfering RNAs complementary to the target oncogene, RNA interference provides an excellent platform to downregulate or "switch-off" genes post transcription through a straightforward sequence-specific process.

The huge size and highly anionic nature of naked siRNAs prevent them from passing through cell membranes, making them vulnerable to destruction by endogenous enzymes. To get past these physiological barriers, siRNAs need a strong carrier that can encapsulate or complex the payload, safeguard it from degradation as it travels through the physiological milieu, enter cells, release the functionally active payload inside the cells, and elicit little to no immune response or negative reactions.

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