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Alpha-Particle Therapy for Acute Myeloid Leukemia

Early studies using the humanized anti-CD33 monoclonal antibody lintuzumab labeled with β-emitters showed significant activity against acute myeloid leukemia (AML) but produced prolonged myelosuppression necessitating hematopoietic cell transplantation (HCT). Targeted α-particle therapy may produce more efficient tumor killing while sparing normal cells. An initial phase I trial of bismuth-213 (213Bi)-lintuzumab in relapsed and refractory (R/R) AML provided proof-of-principle for systemically administered α-particle therapy (Jurcic, Blood 2002). 213Bi-lintuzumab demonstrated rapid targeting of disease sites without significant extramedullary toxicity. Target-to-whole body dose ratios were greatly enhanced compared to β-emitting immunoconjugates. Anti-leukemic effects were seen across all dose levels with a decrease in marrow blasts in 78% of patients. In a subsequent phase I/II trial, 213Bi-lintuzumab was administered following partial cytoreduction with cytarabine (Rosenblat, Clin Cancer Res 2010). Among patients receiving the maximum tolerated dose of 37 MBq/kg or higher, responses were seen in 24% of patients. The 46-minute half-life of 213Bi, however, remained an obstacle to its widespread use. Therefore, a more potent second-generation construct containing actinium-225 (225Ac) ($t_{½}$ = 10 days), which generates four α-particle emissions, was developed. A phase I study demonstrated that a single dose of 225Ac-lintuzuamb was safe at doses of 111 kBq/kg or less and produced marrow blast reductions in 67% of evaluable patients with R/R AML (Jurcic, ASH 2011). Dose-limiting toxicity was prolonged myelosuppression, and no evidence of radiation-induced nephrotoxicity was seen. Based on these findings, 225Ac-lintuzumab was investigated in a multicenter phase I/II trial in combination with low-dose cytarabine for older patients with untreated AML (Jurcic, SNMMI 2017). During the first cycle of therapy, two fractions of 225Ac-lintuzumab (18.5-74 kBq/kg/fraction) were administered one week apart after completion of chemotherapy. Five of 18 patients (28%) had objective responses. All responses occurred after the first cycle. The baseline peripheral blood blast count was a strong predictor of outcome, as responses were seen only in patients with peripheral blast counts < 200/μL. This is most likely explained by preferential antibody binding to peripheral sites in patients with higher circulating blast counts, leading to decreased marrow targeting. Because of this observation, a multicenter phase II trial of 225Ac-lintuzumab monotherapy using hydroxyurea to lower peripheral blast counts if needed was undertaken in older AML patients (Finn, ASH 2017). Objective responses were seen in nine of 13 patients (69%) after two doses of 225Ac-lintuzumab (74 kBq/kg) administered one week apart. Myelosuppression, however, was considered to be longer than acceptable in this population, and additional patients were treated with two fractions of 55.5 kBq/kg each. 225Ac-lintuzumab has shown significant activity in AML both alone and in combination with chemotherapy. Future development of 225Ac-lintuzumab includes combinations with standard chemotherapy and novel targeted agents for R/R AML, treatment for measurable residual disease in AML, and conditioning before HCT in patients with high-risk myelodysplastic syndromes.

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