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POSTER ABSTRACTS

604.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: MYELOID NEOPLASMS

Delivery of α-Particles By a Human-Rat Chimeric CD82 Monoclonal Antibody Potently Inhibits the Proliferation of CD82-Expressing Acute Myeloid Leukemia Cells in a Murine Xenograft Model

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[Background] We previously found that acute myeloid leukemia (AML) cells aberrantly express CD82, a member of the tetraspanin family, on their surface. Functional analyses of CD82 by either depletion or forced expression of *CD82* revealed that CD82 plays a role in the adhesion of AML cells to the bone marrow microenvironment in association with the inhibition of matrix metallopeptidase 9 (IJC 2013). In addition, CD82 transactivates several signaling pathways and upregulates anti-apoptotic Bcl-2L12 molecules in AML cells (Ikezoe T, et al. Int J Cancer. 2014;134:55, PLoS One. 2015;10: e0125017, Leukemia 2015;29:2296, Canc Sci. 2017;108:685). Alpha particle-emitting radionuclides are very attractive for cancer therapy, especially for micrometastases and isolated cancer cells commonly observed in leukemia, because of their high linear energy transfer and short effective path length in tissues. Astatine-211 (^{211}At), with an appropriate half-life (7.2 hours), emits α-particles with higher energy in a shorter distance than ß-particles. It is ideal for cancer therapy through targeting tumor cells with α-particles by breaking double-stranded DNA while minimizing damage to normal cells. We have recently generated ^{211}At-labeled human-rat chimeric CD82 monoclonal antibody (^{211}At-h/r CD82 mAb) to deliver α-particles to CD82-expressing AML cells.
[Aims] We conducted this study to evaluate the efficacy of a treatment strategy targeting CD82-expressing AML cells with ^{211}At-h/r CD82 mAb.
[Methods] Immunohistochemical staining was conducted to evaluate the binding of h/r CD82 mAb to U937 AML cells. ^{211}At was produced by ^{209}Bi(α, 2n) ^{211}At nuclear reactions using an cyclotron (MP-30, Sumitomo Heavy Industries Ltd., Tokyo, Japan) at our institution, and h/r CD82 mAb was radiolabeled as described in our previous report (Oriuchi N, et al. Sci Rep. 2020;10:6810). A high-level CD82-expressing human AML cells xenograft (U937) was established in nude mice. In the biodistribution study, the mice were intravenously injected with 0.25 MBq of ^{211}At-h/r CD82 mAb, and sacrificed at 1 min, 1, 3, 6, and 24 h after the injections (n=3 in each group). Blood, organs, and tumor tissues were collected, weighed, and measured for radioactivity using a gamma counter. The radioactivities of the blood, organs, and tumor tissues are presented as percent injected radioactivity dose per gram (%ID/g). In the treatment study, the mice were randomly divided into a nontreated (control, n=3) and two treated groups after the formation of palpable tumors. The mice in the treated groups were intravenously injected with either non-radiolabeled h/r CD82 mAb (h/r CD82 mAb, n=5) or 63.6 MBq of ^{211}At-h/r CD82 mAb (n=4) on day 0. The tumor size of each mouse was measured daily until day 40 treatment. When the surface of the tumor tissue ruptured or the tumor diameter exceeded 20 mm, the tumor size measurement was stopped, and the mice were euthanized.
[Results] Dense staining of CD82 by h/r CD82 mAb in a block of U937 cells was confirmed by immunohistochemical staining. The uptake levels of ^{211}At-h/r CD82 mAb in the tumor significantly increased over time, which were 1.3 ± 0.3%ID/g, 6.3 ± 0.4%ID/g, 8.4 ± 2.0%ID/g, and 8.7 ± 0.8%ID/g at 1 min, and 1, 3, and 6 h after the injection, respectively. The highest tumor uptake level was achieved 6 h after the injection. This study revealed that the tumor volume significantly increased over time in the control and h/r CD82 mAb groups (from 106.9±36.6 mm ^{3} on day 0 to 4195 ± 1359.7 mm ^{3} on day16 in the control group, $p<0.001$; from 115.5 ± 11.7 on day 0 to 4045.5 ± 1912.1 mm ^{3} on day16 in the h/r CD82 mAb group, $p<0.001$). There was no significant difference in tumor volume between the control and h/r CD82 mAb groups. In contrast, the tumor volume significantly decreased over time after treatment with ^{211}At-h/r CD82 mAb until day 10 (from 200.9±44.4 mm ^{3} on day 0 to

45.0 ± 60.5 mm ^{3} on day10, $p<0.001$ vs control and h/r CD82 mAb groups). Notably, two mice had no palpable tumor on day 45, indicating complete elimination of AML cells. [Conclusion] Delivery of α-particles by h/r CD82 mAb to CD82-expressing AML cells may be a promising strategy to overcome this lethal disease.

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