

In conclusion, the present study suggests that the simultaneous administration of GO with most agents studied would be advantageous for antileukemic activity. The simultaneous administration of GO with methotrexate or vincristine would have little cytotoxic effect, and these combinations may be inappropriate. Our findings may be useful in clinical trials of combination chemotherapy including GO or other monoclonal antibodies linked to calicheamicin.

Disclosure

No disclosures.

Conflict of Interest

The authors declare that they have no potential conflicts of interest.

Acknowledgements

The study was partially supported by a Grant in Aid (No.13204075) from the Japanese Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

- 1 Zein N, Sinha AM, McGahren WJ and Ellestad GA: Calicheamicin gamma II: an antitumor antibiotic that cleaves double-stranded DNA site specifically. *Science* 240(4856): 1198-1201, 1988.
- 2 Sievers EL, Appelbaum FR, Spielberger RT, Forman SJ, Flowers D, Smith FO, Shannon-Dorcy K, Berger MS and Bernstein ID: Selective ablation of acute myeloid leukemia using antibody-targeted chemotherapy: a phase I study of an anti-CD33 calicheamicin immunoconjugate. *Blood* 93: 3678-3684, 1999.
- 3 Hinman LM, Hamann PR, Wallace R, Menendez AT, Durr FE and Upeslacis J: Preparation and characterization of monoclonal antibody conjugates of the calicheamicins: a novel and potent family of antitumor antibiotics. *Cancer Res* 53: 3336-3342, 1993.
- 4 Jedema I, Barge RM, van der Velden VH, Nijmeijer BA, van Dongen JJ, Willemze R and Falkenburg JH: Internalization and cell cycle-dependent killing of leukemic cells by gemtuzumab ozogamicin: rationale for efficacy in CD33-negative malignancies with endocytic capacity. *Leukemia* 18: 316-325, 2004.
- 5 Griffin JD, Linch D, Sabbath K, Larcom P and Schlossman SF: A monoclonal antibody reactive with normal and leukemic human myeloid progenitor cells. *Leuk Res* 8: 521-534, 1984.
- 6 Dinndorf PA, Andrews RG, Benjamin D, Ridgway D, Wolff L and Bernstein ID: Expression of normal myeloid-associated antigens by acute leukemia cells. *Blood* 67: 1048-1053, 1986.
- 7 Scheinberg DA, Tanimoto M, McKenzie S, Strife A, Old LJ and Clarkson BD: Monoclonal antibody M195: a diagnostic marker for acute myelogenous leukemia. *Leukemia* 3: 440-445, 1989.
- 8 Terstappen LW, Sastford M, Konemann S, Loken MR, Zurlutter K, Buchner T, Hidemann W and Wormann B: Flow cytometric characterization of acute myeloid leukemia. Part II. Phenotypic heterogeneity at diagnosis. *Leukemia* 6: 70-80, 1992.
- 9 Sievers EL, Larson RA, Stadtmauer EA, Estey E, Lowenberg B, Dombret H, Karanes C, Theobald M, Bennett JM, Sherman ML, Berger MS, Eten CB, Loken MR, van Dongen JJ, Bernstein ID and Appelbaum FR; Mylotarg Study Group: Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. *J Clin Oncol* 19: 3244-3254, 2001.
- 10 Larson RA, Boogaerts M, Estey E, Karanes C, Stadtmauer EA, Sievers EL, Mineur P, Bennett JM, Berger MS, Eten CB, Munteanu M, Loken MR, Van Dongen JJ, Bernstein ID and Appelbaum FR; Mylotarg Study Group: Antibody-targeted chemotherapy of older patients with acute myeloid leukemia in first relapse using Mylotarg (gemtuzumab ozogamicin). *Leukemia* 16: 1627-1636, 2002.
- 11 Piccaluga PP, Martinelli G, Rondoni M, Malagola M, Gaitani S, Isidori A, Bonini A, Gugliotta L, Luppi M, Morselli M, Sparaventi G, Visani G and Baccarani M: Gemtuzumab ozogamicin for relapsed and refractory acute myeloid leukemia and myeloid sarcomas. *Leuk Lymphoma* 45: 1791-1795, 2004.
- 12 Larson RA, Sievers EL, Stadtmauer EA, Lowenberg B, Estey EH, Dombret H, Theobald M, Voliotis D, Bennett JM, Richie M, Leopold LH, Berger MS, Sherman ML, Loken MR, van Dongen JJ, Bernstein ID and Appelbaum FR: Final report of the efficacy and safety of gemtuzumab ozogamicin (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence. *Cancer* 104: 1442-1452, 2005.
- 13 Amadori S, Suciu S, Stasi R, Willemze R, Mandelli F, Selleslag D, Denzlinger C, Muus P, Stauder R, Berneman Z, Pruijt J, Nobile F, Cassibba V, Marie JP, Beeldens F, Baila L, Vignetti M and de Witte T: Gemtuzumab ozogamicin (Mylotarg) as single-agent treatment for frail patients 61 years of age and older with acute myeloid leukemia: final results of AML-15B, a phase 2 study of the European Organisation for Research and Treatment of Cancer and Gruppo Italiano Malattie Ematologiche dell'Adulso Leukemia Groups. *Leukemia* 19: 1768-1773, 2005.
- 14 Nabhan C, Rundhaugen LM, Riley MB, Rademaker A, Boehlke L, Jatoi M and Tallman MS: Phase II pilot trial of gemtuzumab ozogamicin (GO) as first-line therapy in acute myeloid leukemia patients age 65 or older. *Leuk Res* 29: 53-57, 2005.
- 15 Tsimberidou AM, Giles FJ, Estey E, O'Brien S, Keating MJ and Kantarjian HM: The role of gemtuzumab ozogamicin in acute leukaemia therapy. *Br J Haematol* 132: 398-409, 2006.
- 16 Stasi R, Evangelista ML, Buccisano F, Venditti A and Amadori S: Gemtuzumab ozogamicin in the treatment of acute myeloid leukemia. *Cancer Treat Rev* 34: 49-60, 2008.
- 17 Lo-Coco F, Cimino G, Breccia M, Noguera NI, Diverio D, Finolezzi E, Pogliani EM, Di Bona E, Micalizzi C, Kropp M, Venditti A, Tafuri A and Mandelli F: Gemtuzumab ozogamicin (Mylotarg) as a single agent for molecularly relapsed acute promyelocytic leukemia. *Blood* 104: 1995-1999, 2004.
- 18 Lucio P, Gaipa G, van Lochem EG, van Wering ER, Porwit-MacDonald A, Faria T, Bjorklund E, Biondi A, van den Beemd MW, Baars E, Vidriales B, Parreira A, van Dongen JJ, San Miguel JF and Orfao A; BIOMED-I concerted action report: flow cytometric immunophenotyping of precursor B-ALL with standardized triple-stainings. BIOMED-I Concerted Action Investigation of Minimal Residual Disease in Acute Leukemia: International Standardization and Clinical Evaluation. *Leukemia* 15: 1185-1192, 2001.

- 19 Cotter M, Rooney S, O'Mearaigh A and Smith OP: Successful use of gemtuzumab ozogamicin in a child with relapsed CD33-positive acute lymphoblastic leukaemia. *Br J Haematol* 122: 687-688, 2003.
- 20 Zwaan CM, Reinhardt D, Jurgens H, Huismans DR, Hahlen K, Smith OP, Biondi A, van Wering ER, Feingold J and Kaspers GJ: Gemtuzumab ozogamicin in pediatric CD33-positive acute lymphoblastic leukemia: first clinical experiences and relation with cellular sensitivity to single-agent calicheamicin. *Leukemia* 17: 468-470, 2003.
- 21 Amadori S, Suciu S, Willemze R, Mandelli F, Selleslag D, Stauder R, Ho A, Denzlinger C, Leone G, Fabris P, Muus P, Vignetti M, Hagemeyer A, Beeldens F, Anak O and De Witte T; EORTC leukemia group; GIMEMA leukemia group: Sequential administration of gemtuzumab ozogamicin and conventional chemotherapy as first-line therapy in elderly patients with acute myeloid leukemia: a phase II study (AML-15) of the EORTC and GIMEMA leukemia groups. *Haematologica* 89: 950-956, 2004.
- 22 Aplenc R, Alonso TA, Gerbing RB, Lange BJ, Hurwitz CA, Wells RJ, Bernstein I, Buckley P, Krimmel K, Smith FO, Sievers EL and Areeci RJ; Children's Oncology Group: Safety and efficacy of gemtuzumab ozogamicin in combination with chemotherapy for pediatric acute myeloid leukemia: a report from the Children's Oncology Group. *J Clin Oncol* 26: 2390-2395, 2008.
- 23 Brethon B, Yakouben K, Oudot C, Bourtard P, Bruno B, Jérôme C, Nelken B, de Lumley L, Bertrand Y, Dalle JH, Chevret S, Leblanc T and Baruchel A: Efficacy of fractionated gemtuzumab ozogamicin combined with cytarabine in advanced childhood myeloid leukaemia. *Br J Haematol* 143: 541-547, 2008.
- 24 Chevallier P, Delaunay J, Turlure P, Pigneux A, Hunault M, Garand R, Guillaume T, Avet-Loiseau H, Dmytruk N, Girault S, Milpied N, Ifrah N, Mohty M and Harousseau JL: Long-term disease-free survival after gemtuzumab, intermediate-dose cytarabine, and mitoxantrone in patients with CD33(+) primary resistant or relapsed acute myeloid leukemia. *J Clin Oncol* 26: 5192-5197, 2008.
- 25 Chevallier P, Mahe B, Garand R, Talmant P, Harousseau JL and Delaunay J: Combination of chemotherapy and gemtuzumab ozogamicin in adult Philadelphia-positive acute lymphoblastic leukemia patient harboring CD33 expression. *Int J Hematol* 88: 209-211, 2008.
- 26 Clavio M, Vignolo L, Albarello A, Talmant P, Harousseau JL and Delaunay J: Adding low-dose gemtuzumab ozogamicin to fludarabine, Ara-C and idarubicin (MY-PLAI) may improve disease-free and overall survival in elderly patients with non-M3 acute myeloid leukaemia: results of a prospective, pilot, multi-centre trial and comparison with a historical cohort of patients. *Br J Haematol* 138: 186-195, 2007.
- 27 Van PN, Xinh PT, Kano Y, Tokunaga K and Sato Y: Establishment and characterization of a novel Philadelphia-chromosome positive chronic myeloid leukemia cell line, TCC-S, expressing *P210* and *P190 BCR/ABL* transcripts but missing normal *ABL* gene. *Hum Cell* 218: 25-33, 2005.
- 28 Kano Y, Sakamoto S, Kakahara T, Akutsu M, Inoue Y and Miura Y: *In vitro* effects of amsacrine in combination with other anti-cancer agents. *Leuk Res* 15: 1059-1066, 1991.
- 29 Steel GG and Peckham MJ: Exploitable mechanisms in combined radiotherapy-chemotherapy: the concept of additivity. *Int J Radiat Oncol Biol Phys* 5: 85-93, 1979.
- 30 Kano Y, Ohnuma T, Okano T and Holland JF: Effects of vincristine in combination with methotrexate and other antitumor agents in human acute lymphoblastic leukemia cells in culture. *Cancer Res* 48: 351-356, 1988.
- 31 Kano Y, Suzuki K, Akutsu M, Inoue Y, Yoshida M, Sakamoto S and Miura Y: Effects of CPT-11 in combination with other anticancer agents in culture. *Int J Cancer* 50: 604-610, 1992.
- 32 Kano Y, Akutsu M, Tsunoda S, Suzuki K and Adachi K: *In vitro* schedule-dependent interaction between paclitaxel and SN-38 (the active metabolite of irinotecan) in human carcinoma cell lines. *Cancer Chemother Pharmacol* 42: 91-98, 1998.
- 33 Dowell JA, Korth-Bradley J, Liu H, King SP and Berger MS: Pharmacokinetics of gemtuzumab ozogamicin, an antibody-targeted chemotherapy agent for the treatment of patients with acute myeloid leukemia in first relapse. *J Clin Pharmacol* 41: 1206-1214, 2001.
- 34 DiJoseph JF, Armellino DC, Boghaert ER, Khandke K, Dougher MM, Sridharan L, Kunz A, Hamann PR, Gorovits B, Udata C, Moran JK, Popplewell AG, Stephens S, Frost P and Damle NK: Antibody-targeted chemotherapy with CMC-544: a CD22-targeted immunoconjugate of calicheamicin for the treatment of B-lymphoid malignancies. *Blood* 103: 1807-1814, 2004.
- 35 DiJoseph JF, Dougher MM, Kalyanrug LB, Armellino DC, Boghaert ER, Hamann PR, Moran JK and Damle NK: Antitumor efficacy of a combination of CMC-544 (inotuzumab ozogamicin), a CD22-targeted cytotoxic immunoconjugate of calicheamicin, and rituximab against non-Hodgkin's B-cell lymphoma. *Clin Cancer Res* 12: 242-249, 2006.
- 36 DiJoseph JF, Dougher MM, Armellino DC, Evans DY and Damle NK: Therapeutic potential of CD22-specific antibody-targeted chemotherapy using inotuzumab ozogamicin (CMC-544) for the treatment of acute lymphoblastic leukemia. *Leukemia* 21: 2240-2245, 2007.

*Received June 4, 2009**Revised September 9, 2009**Accepted September 25, 2009*

