Humoral influence on cytotoxicity in myeloid leukemia therapies

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TITLE	Enhancement of drug cytotoxicity by recruitment of leukemic myeloblasts with humoral stimulation.
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Understanding the complex biology of the host's response to leukemia and leukemia treatments is critical for optimization of antileukemia therapy. Classical cytotoxic therapies such as nucleoside analogs and anthracyclines mechanistically require cell cycle progression to achieve their greatest therapeutic effects. Most current standard leukemia induction regimens consist of a week or less of cytotoxic chemotherapy followed by a period of hematologic aplasia and subsequent recovery. During this period of aplasia, humoral growth factors are stimulated which enhance normal hematopoietic recovery but also influence residual leukemia cells. In their seminal paper describing the humoral recruitment of enhanced drug cytotoxicity in leukemic myeloblasts,[1] Karp and Burke elegantly demonstrated that a humoral factor stimulated after chemotherapy exposure could influence leukemic sensitivity to subsequent therapy (Figure 1). Karp and Burke also postulated that understanding the kinetics and biological consequences of this humoral response could lead to optimization of antileukemia therapies. This humoral factor likely consists of multiple cytokines, and subsequent cloning and *in vitro* experimentation with the growth factor ligands granulocyte-macrophage colony-stimulating factor,[2] granulocyte colony-stimulating factor (G-CSF) and interleukin-3[3] recapitulated the humoral enhancement of cytotoxicity with cytarabine (ara-c). This cytotoxic effect can be further modulated by the administration of G-CSF and fludarabine prior to cytarabine.[4] Later efforts safely incorporated G-CSF into frontline induction therapy for acute myeloid leukemia in the form of FLAG (fludarabine, ara-c, G-CSF).[5] FLAG-based therapies have produced favorable antileukemic outcomes when compared to conventional non-humoral-stimulated cytarabine/daunorubicin

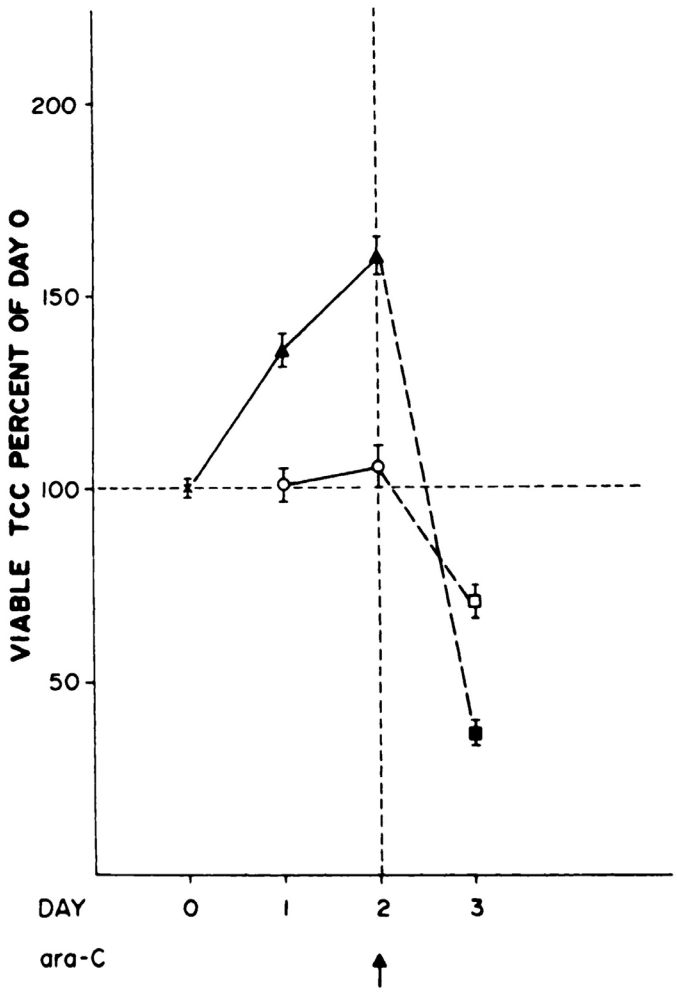

Chart 5. Viable TCC for the 14 AML bone marrow cell cultures. Data are expressed as percentage of Day 0 viable TCC. ▲, Stim; ○, Leuk; ▲- - -■, Stim → ara-C; ○- - -□, Leuk → ara-C. *Bars*, S.E.

Figure 1. Leukemia cells treated with humoral stimulants and later exposed to cytarabine have lower subsequent viability than cells never exposed to humoral stimulation. TCC: tumor cell count; AML: acute myeloid leukemia; Stim: pooled stimulatory serum; Leuk: patients' leukemic pretreatment serum; ara-C: cytarabine; S.E.: standard error. Figure reproduced, with permission, from Karp & Burke.[1]

(7+3)-based chemotherapy.[6] In the era of novel therapies, enhancement of antitumor cytotoxic effects with humoral factors such as G-CSF appears to be relevant, as the addition of G-CSF to azacitidine/venetoclax-based therapy is associated with higher minimal residual disease-negative remission rates (55% *vs*. 33%) and prolonged overall survival (25.5 months *vs*. 12.8 months).[7] In the future novel therapy era, careful observations of the humoral influence on antileukemia therapies will be required in the hope of improving the progress we have made with new landmark agents. In summary, understanding the host's response to chemotherapy for leukemia – described in the landmark paper by Karp and Burke – led to the optimization of multiple therapeutic regimens through enhanced antitumor effects associated with improved overall survival.

Disclosures

No conflicts of interest to disclose.

References

1. Karp JE, Burke PJ. Enhancement of drug cytotoxicity by recruitment of leukemic myeloblasts with humoral stimulation. Cancer Res. 1976;36(10):3600-3603.
2. Karp JE, Burke PJ, Donehower RC. Effects of rhGM-CSF on intracellular ara-C pharmacology in vitro in acute myelocytic leukemia: comparability with drug-induced humoral stimulatory activity. Leukemia. 1990;4(8):553-556.
3. Andreeff M, Tafuri A, Hegewisch-Becker S. Colony-stimulating factors (rhG-CSF, rhGM-CSF, rhIL-3, and BCGF) recruit myeloblastic and lymphoblastic leukemic cells and enhance the cytotoxic effects of cytosine-arabinoside. Haematol Blood Transfus. 1990;33:747-762.
4. Gandhi V, Estey E, Du M, Nowak B, Keating MJ, Plunkett W. Modulation of the cellular metabolism of cytarabine and fludarabine by granulocyte-colony-stimulating factor during therapy of acute myelogenous leukemia. Clin Cancer Res. 1995;1(2):169-178.
5. Estey E, Thall P, Andreeff M, et al. Use of granulocyte colony-stimulating factor before, during, and after fludarabine plus cytarabine induction therapy of newly diagnosed acute myelogenous leukemia or myelodysplastic syndromes: comparison with fludarabine plus cytarabine without granulocyte colony-stimulating factor. J Clin Oncol. 1994;12(4):671-678.
6. Russell NH, Wilhelm-Benartzi C, Othman J, et al. Fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin with gemtuzumab ozogamicin improves event-free survival in younger patients with newly diagnosed AML and overall survival in patients with NPM1 and FLT3 mutations. J Clin Oncol. 2024;42(10):1158-1168.
7. DiNardo CD, Pratz KW, Panayiotidis P, et al. The impact of post-remission granulocyte colony-stimulating factor use in the phase 3 studies of venetoclax combination treatments in patients with newly diagnosed acute myeloid leukemia. Am J Hematol. 2025;100(1):185-188.