Letter to the Editor

G-CSF Is a Cancer Stem Cell–Specific Growth Factor—Letter

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We read with interest the recent article by Agarwal and colleagues investigating the biologic significance of granulocyte colony-stimulating factor (G-CSF) in stem-like subpopulations of neuroblastoma cells (1). While we find their observations provocative, and do not debate their demonstration that CD114 (the G-CSF receptor) is expressed in a rare subpopulation of neuroblastoma cells and that this expression may be dynamic in relation to selective pressures such as chemotherapy, we think that their major conclusion to “suggest a comprehensive reevaluation of the clinical use of G-CSF in these patients to support white blood cell counts” is not supported by their data and, moreover, may be interpreted in such a way to jeopardize patient safety.

First, this interesting article comes on the backdrop of the routine use of this hematopoietic growth factor for children with high-risk neuroblastoma over the last quarter of a century, a time frame in which overall survival rates have increased by at least 20% (2), largely due to a near quadrupling of the dose intensification of cytotoxic chemotherapy used during this time frame. Moreover, a randomized clinical trial of G-CSF used to support a more intensive induction chemotherapy was shown to be safe, significantly reduce chemotherapy-related complications, and did not impair overall tumor response to therapy (3). Although the study was not designed to measure impacts on disease outcome, now with over 10 years of follow-up we detect no difference in outcomes for the 238 subjects randomized to receiving G-CSF or no hematopoietic growth factor to support an intensive induction chemotherapy regimen (log-rank P = 0.444; R. Ladenstein and U. Pötschger, unpublished data).

Second, the dose and schedule of G-CSF used by the authors for their murine studies is apparently excessive and likely not clinically relevant. The authors used 250 μg/kg for 21 days to determine an effect on tumor growth and metastasis, whereas the typical dose used in patients is 5 μg/kg daily for 8 to 10 days. The authors cite two articles investigating the use of G-CSF in ischemic heart disease and respiratory syncytial virus infection (their references 16 and 17) to justify their dosing, but these papers did not consider G-CSF pharmacokinetics and simply used high doses of G-CSF to study the impact of leukocytosis on recovery from insult in their model systems.

Food and Drug Administration guidance for defining human equivalent doses for drugs used in murine models suggests a conversion of animal dose in mg/kg to (animal weight in kg/human weight in kg)^1/3 (http://www.fda.gov/downloads/Drugs/Guidances/UCM078932.pdf; ref. 4), which for a typical 18-month-old child would be the equivalent of 35 μg/kg, seven times the dose used in the clinic. Thus, it is not at all clear that the increased tumor sizes and frequency of detecting bone marrow metastases shown in Fig. 2 are clinically relevant, especially in the G-CSF knockout mouse model (Fig. 2D), where it is known that systemic exposure will be even higher due to lack of receptor-mediated clearance (5).

Finally, the authors ignore the simple fact that G-CSF is typically used as a bridge between chemotherapy cycles, and that even if there is a recruitment of CD114^+ cells, they likely will be sensitive to subsequent cycles of currently used cytotoxic and/or immunotherapeutic agents. Taken together, we strongly recommend that there be no deviation from the current practice of using G-CSF to abrogate the infectious complications of the highly dose-intensive chemotherapy backbone used to treat high-risk neuroblastoma patients around the world. Unwarranted removal of G-CSF has the potential to directly increase patient morbidity and mortality.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References


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