HHS Public Access

Author manuscript

Cancer Res. Author manuscript; available in PMC 2016 September 15.

Published in final edited form as:

Cancer Res. 2015 September 15; 75(18): 3992. doi:10.1158/0008-5472.CAN-15-1599.

G-CSF Is a Cancer Stem Cell–Specific Growth Factor—Response to Maris et al.

Eugene S. Kim[1,2], **Saurabh Agarwal**[3], and **Jason M. Shohet**[3,*]

[1]Division of Pediatric Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, Texas- 77030, USA

[2]Division of Pediatric Surgery, Department of Surgery, Keck School of Medicine, University of Southern California, Los Angeles, CA- 90027, USA

[3]Department of Pediatrics, Section of Hematology-Oncology, Texas Children's Cancer Center, and Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, Texas-77030, USA

Dear Editor

We appreciate the thoughtful commentary of Maris and colleagues (1) regarding our recent publication demonstrating that G-CSF acts as a growth factor for neuroblastoma cancer stem cells (CSC) in vivo (2). In the study, both gain-of-function and loss-of function studies confirm a significant role for G-CSF stimulating CSC-dependent xenograft growth and metastasis in experimental neuroblastoma. However, we agree that our data are not a mandate to avoid G-CSF in our patients and certainly do not recommend any actions that would "jeopardize patient safety" or recommend the "unwarranted removal" of G-CSF from protocols.

As noted by Maris and colleagues, the empiric use of G-CSF for granulocyte support is an integral component of modern dose intensive chemotherapy for neuroblastoma. This is supported in part by an earlier randomized study by Ladenstein and colleagues (3), which demonstrated that G-CSF partially ameliorates acute toxicities of intensive chemotherapy. This study, however, was not designed to evaluate the impact of G-CSF on long-term outcomes. The majority of patients completing their induction chemotherapy went on to receive high-dose chemotherapy and autologous stem cell rescue, which required G-CSF administration for both peripheral stem cell harvesting and engraftment. Because both their randomized cohorts eventually received significant exposures to G-CSF, we respectfully maintain that this study does not support any conclusions linking G-CSF administration and long term survival.

Regarding the dose of G-CSF used in our study, we utilized a dose that increased granulopoiesis, avoided extreme leukocytosis, and is consistent with other murine studies (4). We are aware of FDA guidelines defining initial human equivalents for murine drug

[*]**Corresponding author:** Jason M Shohet, MD, PhD, Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine Houston, TX - 77030, Tel: 832-824-4735, Fax: 832-825-1206, jmshohet@txch.org.

Conflict of Interest: The authors disclose no potential conflicts of interest.

studies. However, it is unclear that this methodology applies to recombinant human proteins circulating in mice. Further study on the dose responsiveness of neuroblastoma CSCs in our models would address this issue. Regardless of the dose of G-CSF used for exogenous administration, our experiments also showed that using an anti–G-CSF antibody, to sequester free endogenous cytokine and block G-CSF/GCSF–receptor signaling, resulted in potent inhibition of metastasis and tumor growth as in other tumor models.

Maris and colleagues state 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." We do not yet know if this is the case. Yet, chemoprotective anti-p53 functions are well described for cytokine-activated STAT3 signaling in multiple stem cell and tumor models, including neuroblastoma (5). Thus, G-CSF/STAT3 signaling may protect rather than sensitize neuroblastoma CSCs from genotoxic damage. Supporting this hypothesis, we clearly demonstrate that G-CSF treatment activates antiapoptotic STAT3 target genes in the CSC subpopulation (Fig. 5; ref. 2). Furthermore, we previously demonstrated that multiple cycles of genotoxic chemotherapy enrich for the CD114+ CSC subpopulation *in vivo* (6). These data suggest that G-CSF may protect CSCs from chemotherapy, although experiments to formally test this are in progress.

In summary, we greatly appreciate the interest our study has generated and hope to stimulate additional research focused on targeting neuroblastoma CSCs. Based on our observations demonstrating critical biologic effects of G-CSF/STAT3 signaling on this tumor subpopulation, we agree that additional clinical and preclinical research is required. However, we respectfully maintain that our findings should prompt a discussion and reevaluation of the risks and benefits of G-CSF in high-risk neuroblastoma. This is especially true as advances in supportive care (e.g., antibiotic/antifungal therapies, and patient monitoring) have altered the risks of neutropenia in our pediatric patient population over the past decade. As always, new biologic findings need to be validated and incorporated into revised risk/benefit calculations and communicated to our patients based on objective data, keeping patient safety as our highest priority.

References

1. Maris JM, Healy J, Park J, Ladenstein R, Potschger U. G-CSF Is a Cancer Stem Cell-Specific Growth Factor-Letter. Cancer research. 2015; 75:3391.
2. Agarwal S, Lakoma A, Chen Z, Hicks J, Metelitsa LS, Kim ES, et al. G-CSF Promotes Neuroblastoma Tumorigenicity and Metastasis via STAT3-Dependent Cancer Stem Cell Activation. Cancer research. 2015; 75:2566–2579. [PubMed: 25908586]
3. Ladenstein R, Valteau-Couanet D, Brock P, Yaniv I, Castel V, Laureys G, et al. Randomized Trial of prophylactic granulocyte colony-stimulating factor during rapid COJEC induction in pediatric patients with high-risk neuroblastoma: the European HR-NBL1/SIOPEN study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010; 28:3516–3524. [PubMed: 20567002]
4. Kowanetz M, Wu X, Lee J, Tan M, Hagenbeek T, Qu X, et al. Granulocyte-colony stimulating factor promotes lung metastasis through mobilization of Ly6G+Ly6C+ granulocytes. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107:21248–21255. [PubMed: 21081700]

5. Ara T, Nakata R, Sheard MA, Shimada H, Buettner R, Groshen SG, et al. Critical role of STAT3 in IL-6-mediated drug resistance in human neuroblastoma. Cancer research. 2013; 73:3852–3864. [PubMed: 23633489]
6. Hsu DM, Agarwal S, Benham A, Coarfa C, Trahan DN, Chen Z, et al. G-CSF receptor positive neuroblastoma subpopulations are enriched in chemotherapy-resistant or relapsed tumors and are highly tumorigenic. Cancer research. 2013; 73:4134–4146. [PubMed: 23687340]