


Not all hematopoietic growth factors are created equal: should we gain information for their use with immunotherapy?

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ABSTRACT

Myeloid growth factors, either granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage CSF, are widely used to reduce the incidence and severity of chemotherapy-induced neutropenia by prophylactic or therapeutic administration. However, their activity in the novel therapeutic regimens, which often rely on the association between immunotherapy and chemotherapy, has not been thoroughly characterized yet. This paper presents some of the preclinical and clinical research regarding the putative interplay between myeloid growth factors and the immune system, advocating further studies to elucidate their potential positive or negative consequences on the outcomes when administered with immunotherapeutic agents.

INTRODUCTION

The use of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage CSF (GM-CSF) for prevention and treatment of neutropenia induced by chemotherapy is stated by several international guidelines. Nevertheless, limited data exist regarding their activity and their positive or negative influence on the outcomes when administered with immunotherapy plus chemotherapy.

Combination of immunotherapy using immune-checkpoint inhibitors (ICIs) and chemotherapy is widely employed to improve response rate and overcome primary resistance to immunotherapy alone: this strategy has shown increased effectiveness, at the price of higher toxicity. In particular, grade ≥ 3 neutropenia rate varies from 10% to 22% in clinical trials, while febrile neutropenia (FN) rate varies from 1.9% to 6.2%, depending on the type of chemoimmunotherapy association (table 1). However, when ICIs are administered without chemotherapy, FN is very uncommon, affecting only about 0.45% of patients.¹ While the administration of myeloid growth factors is essential to avoid severe consequences of FN and to maintain dose intensity, it is still not clear whether

their use could potentially augment or impair immunotherapy efficacy.

G-CSF AND CANCER

Several solid tumors may express G-CSF or its receptor: it is hypothesized that the activation of this pathway may accelerate tumor proliferation and progression, thus making G-CSF-positive cancers more clinically aggressive and often diagnosed in advanced stages. The mechanisms mostly related to G-CSF-mediated tumor progression are thought to be induction of immune tolerance and angiogenesis.²

From a preclinical point of view, there is evidence that G-CSF induces circulating endothelial progenitor cells (EPCs) and myeloid-derived suppressor cells (MDSCs) recruitment in murine models of melanoma and lung cancer.² While EPCs are likely important in enhancing tumor angiogenesis, MDSCs have a crucial role in inducing immune tolerance and promoting angiogenesis through the production of specific factors. A previous study suggested that G-CSF, but not GM-CSF, expression increased the number of MDSCs and induced refractoriness to antivascular endothelial growth factor therapy.³ A G-CSF-dependent tumor regrowth following therapy with vascular disrupting agents in mice has also been demonstrated.² Moreover, it has been proposed that the signal transduction pathway activated by G-CSF may contribute to epithelial to mesenchymal transition, a critical event for the acquisition of metastatic spread, and to maintenance of a pool of cancer stem cells.²

Clinical data suggest that secretion of G-CSF could occur in different malignancies, especially in non-small cell lung cancer: at time of diagnosis, elevated G-CSF levels are associated with paraneoplastic leucocytosis, advanced disease, and have been proposed



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Table 1 FN rates in the main trials of association between chemotherapy and immunotherapy

Trial	Cancer type	Drugs	FN: chemotherapy +immunotherapy arm	FN: chemotherapy arm	G-CSF or GM-CSF use
KEYNOTE-407	NSCLC squamous	Pembrolizumab+carboplatin+(nab)-paclitaxel	5.4%	3.6%	Permitted as for guidelines
KEYNOTE-189	NSCLC non-squamous	Pembrolizumab+cis- or carboplatin+pemetrexed	5.7%	2.0%	Permitted as for guidelines
IMpower133	SCLC	Atezolizumab+carboplatin+etoposide	2.5%	4.4%	NA
KEYNOTE-048	HNSCC	Pembrolizumab+cis- or carboplatin+5-fluorouracil	6.2%	5.2%	Permitted as for guidelines
IMpassion130	Breast cancer	Atezolizumab+nab-paclitaxel	1.9%	2.2%	NA

FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HNSCC, head and neck squamous cell carcinoma; NA, not available; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

as a negative prognostic biomarker.⁴ Autocrine and/or paracrine growth stimulation via G-CSF has also been described in other neoplasms, such as melanoma and bladder cancer, and cases of rapid progressive tumors have been reported in the literature.^{2,5}

DUAL ROLE OF GM-CSF IN CANCER

GM-CSF is a glycoprotein whose activity is primarily inflammatory, due to its role as a growth and differentiation factor for granulocytes, macrophage populations, and dendritic cells (DCs), which are antigen-presenting cells involved in primary and secondary T-cell immune responses, particularly against tumors.⁶

The effects of GM-CSF seem to be dose-dependent and context-dependent: at lower doses GM-CSF could modulate the DCs into a 'tolerogenic phenotype' involved in regulatory T cells (Treg) homeostasis, leading to hyporesponsivity or anergy of effector T cells; in contrast, higher doses of GM-CSF could promote myeloid proliferation, macrophages activation and angiogenesis inhibition, leading to an increased immune response.⁷ However, the window of activity in terms of immunostimulation should be balanced, as suprathreshold dose of GM-CSF might favor immune evasion strategies by differentiating precursors cells into myeloid suppressor ones.⁶⁻⁸

Preclinical studies showed that modified melanoma cells, engineered to express GM-CSF, lead to a greater tumor immune response when treated with radiotherapy.⁸

Moreover, it has been shown that the combination of PD-1 blockade with GM-CSF secretion could improve antitumor response by the upregulation of several Th1 cytokines, including interferon- γ , tumor necrosis factor- α , interleukin (IL)-2 and IL-12, which are chemoattractant for neutrophils, monocytes, and lymphocytes, releasing the state of immunosuppressive microenvironment and augmenting the tumor-reactive T-cell response.⁹

Clinical response greater than 50% for hormone-refractory prostate cancer combining systemic GM-CSF with ipilimumab, an ICI that blocks Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), was initially demonstrated; subsequently, in a phase III clinical trial intratumoral administration of talimogene laherparepvec, containing

the gene coding for human GM-CSF, enhanced antitumor immune response, thus leading to increased efficacy in comparison to administration of subcutaneous GM-CSF.¹⁰

Other initial clinical experiences raised the possibility of important therapeutic interactions between immunotherapy and GM-CSF. A clinical benefit has been observed in melanoma using the combination of an ICI and sargramostim, a recombinant GM-CSF, possibly due to improved antigen presentation via recruitment of DCs and macrophages.⁷ Moreover, patients treated with sargramostim and ICI reported less severe adverse events compared with ICI alone.

Finally, GM-CSF showed to induce an increased immune response when administered concomitantly with radiation therapy, presumably by boosting the DCs differentiation.

Therefore, GM-CSF activity seems to be depending on dose, presence or absence of other relevant cytokines, and on additional factors in the tumor microenvironment, such as CTLA-4 expression and degree of inflammation; it would be interesting to determine whether GM-CSF promotes antitumor immune responses or tumor spread, but it also seems quite clear that it plays a key role in modulating immune response.

CONCLUSION

Preclinical studies have showed a theoretical negative interaction between G-CSF and the immune system. Even if reliable and convincing clinical data to support this hypothesis lack, more caution should be put in administering myeloid growth factors in the context of immunotherapy.

On the other hand, GM-CSF could have a favorable impact when added to immunotherapy with ICIs, both in terms of modulating immune response and reducing severe adverse events, thus potentially increasing effectiveness. Its role, however, could be dose-dependent: as the clinical experiences are still limited, the optimal timing and dose of GM-CSF administration are not clearly defined.

Therefore, we advocate further research into this topic and suggest collecting real-world clinical data about the concurrent use of G-CSF or GM-CSF and immunotherapy with ICIs, eventually uncovering their potential positive or negative influence on the outcomes of patients.

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