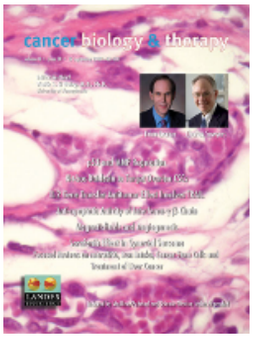

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Commentary

The role of G-CSF in the treatment of advanced tumors

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The granulocyte colony-stimulating factor (G-CSF) induces proliferation and differentiation of myeloid precursor cells to granulocytes. Therefore, it was initially adopted in oncology for the treatment of neutropenia resulting from cancer chemotherapy.[1] However, over the last few years several reports have proposed a more direct antitumoral activity for G-CSF.

In 2005, Bottoni et al. published a paper reporting the results of a study obtained in patients with brain melanoma metastases after treatment with BOLD, a polychemotherapy of bleomicin, vincristin, lomustine and dacrabazine, along with a prolonged administration of G-CSF.[2] In one patient, G-CSF was administered to treat his severe neutropenia; this patient had a complete response to this treatment, as both brain and liver melanoma metastases disappeared. This experience was further extended to other patients bearing melanoma metastases; interestingly, a complete response was observed in three out of eight patients (37.5%), stable disease in three patients and disease progression in two patients. The complete response was long lasting and two patients are currently alive and disease free.

In the same year, Vuoristo et al. published a randomized trial with BOLD versus dacarbazine (DTIC) +/- recombinant interferon α (rIFNα) in patients with melanoma metastases.[3] The response rates were 8% (2/25) in patients treated with DTIC, 13% (4/31) in patients treated with BOLD, 12% (3/25) in patients treated with DTIC plus rIFNα, and 24% in those treated with BOLD plus rIFNα (6/25). All responses were low and the differences were not statistically significant. All eight of the complete responses occurred in patients with soft tissue and/or lung metastases and the BOLD regimens produced six of them. However, no complete response was described in patients with brain metastases. Finally, there were no significant differences in survival.

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More recently Gonzalez Astorga et al. reported eleven patients with metastatic melanoma treated with cisplatin 20 mg/m(2) i.v. days 1.4, dacarbazine 800 mg/m(2) i.v. day 1, vinblastine 1.5 mg/m(2) i.v. days 1.4, interleukin (IL)-2 9 MIU/m(2) s.c. 5.8 d and interferon (IFN)α-2b 5 MIU/m^2 s.c. days 5.9, 11, 13 and 15, with the support of G-CSF and antibiotics.[4] The authors reported the following results: 18% complete response (CR), 27% partial response (PR), 9% stable disease (SD) and 46% disease progression. Again, a polychemotherapy followed by G-CSF produced CR and PR in more than 40% of the patients.[4]

As mentioned before, G-CSF is frequently administered to patients with advanced metastatic disease after chemotherapy to treat or prevent neutropenia. In a similar way, it is also used in bone marrow transplantation to recover from the bone marrow depression induced by chemotherapy.[5]

While GM-CSF (granulocyte macrophage colony-stimulating factor) is able to increase the blood concentration of both granulocytes and monocytes, G-CSF stimulates only granulocytes. Both drugs have been used to treat leukopenia in metastatic patients following aggressive chemotherapy. GM-CSF has been extensively studied in melanoma both in vitro and in vivo. Several trials have also used GM-CSF as an adjuvant treatment for melanoma at high risk to progress. Some of these trials are still in progress. In 2009, Spitler et al. reported their experience with GM-CSF given for 3 y as an adjuvant treatment to a group of ninety-eight patients with melanoma at high risk of recurrence: stage II (T4), stage III and stage IV after surgical operation.[6] Prolonged administration of GM-CSF was well tolerated; grade 1 or 2 side effects occurred in 82% of the patients. There were no grade 3 or 4 treatment-related side effects. The 5 y melanoma-specific survival rate was 60%. GM-CSF has also been given to high-risk melanoma patients in association with thalidomide or IL-2.[7,8] Other authors recently proposed a similar association with GM-CSF and IL-2 after chemotherapy for the treatment of patients with other advanced cancers such as colon carcinoma and non small cell lung carcinoma.[9,10]

Recently, several reports insisted on the importance of the association of G-CSF (also in its pegylated form) with chemotherapy to treat patients with advanced breast carcinoma. For instance, in 2007, Steger reported on the complete response observed after neoadjuvant epirubicin plus docetaxel and granulocyte colony-stimulating factor.[11] A total of 292 patients with biopsy-proven

breast cancer were accrued and randomly assigned to either three or six cycles of epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2 on day 1 and granulocyte colony-stimulating factor on days 3–10 (ED + G), every 21 d. Compared with three cycles, six cycles of ED + G resulted in a significantly higher pCR rate (18.6 vs. 7.7%, respectively; p = 0.0045), a higher percentage of patients with negative axillary status (56.6 vs. 42.8%, respectively; p = 0.02) and a trend towards more breast-conserving surgery (75.9 vs. 66.9%, respectively; p = 0.10). Rates of adverse events were similar. The authors concluded that six cycles of ED + G should be the standard neoadjuvant treatment for operable breast cancer.[11] In 2009, Wesolowski et al. reported the effectiveness of weekly docetaxel, weekly doxorubicin, daily oral cyclophosphamide and G-CSF (ConTAC Regimen) in advanced malignancies, not only in breast cancer but also in other carcinomas.[12]

Tolerability and adverse events that G-CSF may induce in treated patients are generally limited to grade I or II. In some cases, after prolonged treatment with G-CSF, some leukemic reactions have been registered. However, G-CSF and GM-CSF have been extensively used to treat acute leukemias.[13] Whether administered before, during or after chemotherapy for acute myeloid leukemia and acute lymphoblastic leukemia, these agents reduce the duration of neutropenia and seem to be safe and well tolerated. Growth factors have also been used to recruit quiescent leukemia cells into S-phase of the cell cycle to increase their susceptibility to chemotherapy with the goal to reduce relapse and resistance. Randomized trials evaluating this priming strategy have consistently shown improvement in disease- or event-free survival in the intermediate-risk group of patients with acute myeloid leukemia.

In conclusion, G-CSF has been extensively used in the therapy of several advanced neoplasms often with success and rarely with adverse events. Lately, parallel to all of these clinical reports, many basic experimental studies have appeared in the literature that have tried to investigate, both in vitro and in vivo, the molecular mechanisms by which G-CSF can inhibit tumor progression. In this issue of *Cancer Biology & Therapy*, Marino et al. investigate the potential relationships between G-CSF and tumor progression.[14] This study was carried out in vivo using a syngeneic BALB/c mouse mammary tumor model. The authors demonstrated that the in vivo peritumoral administration of G-CSF effectively inhibited LM3 murine mammary adenocarcinoma growth by activating the migration of neutrophils and mononuclear cells, which would induce an apoptotic effect responsible for tumor cell death. Because G-CSF had no effect on LM3 cell proliferation in vitro, the antitumor response would not be the result of a cytokine direct action on tumor cells. In fact, an inflammatory infiltrate of neutrophils and mononuclear cells was evident in the border and inside the mass of G-CSF-treated tumors. Protein expression analysis showed that G-CSF treatment increased the amount of Fas-L, TRAIL and Bax proteins, whereas it decreased the expression of pro-caspase 3 and Bcl-2 protein levels. In addition, cytokine arrays showed an increase in the amount of IL-12, IL-13 and TNFalpha. Based on these results, the authors hypothesized that G-CSF, within the tumor microenvironment, would induce an immune response, which in turn eliminates tumor cells by apoptosis.

In their study, the authors also performed a careful investigation about the possible role of tumor angiogenesis towards cancer cells. In fact, even though most studies indicate an anticancer activity for G-CSF, some authors published observations showing a possible role of G-CSF in promoting tumor progression by increasing circulating endothelial progenitor cells and inducing angiogenesis.[15,17] Conversely, in their study Marino et al. found that the histological examination of tumor slices from treated and non-treated mice did not reveal any difference in tumor vascularization.[14] In addition, they did not find a change in the expression levels of an angiogenic factor, such as VEGF, either by cytokine array or when tumor lysates were examined by western blot with an specific anti-VEGF antibody. The relationship between G-CSF and tumor cells is very complex, however; since, for example, some tumors themselves can produce G-CSF and/or GM-CSF. This phenomenon is well known and it has been reported for at least 30 y.[18,20] Furthermore, several different neoplasms have been shown to secrete G-CSF and/or GM-CSF and this secretion could account for the leukocytosis present in these patients. However, it is not clear if the secreted G-CSF can promote or inhibit tumor progression.[21]

There are some studies in the literature reporting some activity of G-CSF, particularly on brain tumor cells. For instance, in 1999, Papadopoulos et al. published a paper reporting a complete response in two out of eighteen patients after chemotherapy and G-CSF given for primary and recurrent brain tumors.[22] In 2000, Fujita et al. used G-CSF along with chemotherapy to treat cerebral secondary lesions from non-small cell lung cancer obtaining 50% of PR.[23] In this context, we mention that the presence of a specific receptor for G-CSF on neurons and microglia cells has been well demonstrated and the expression of G-CSF in the brain is inversely correlated to tumor progression of gliomas.[24] Furthermore, G-CSF increases blood-brain permeability in mice,[25] whereas it has been demonstrated that G-CSF plays an important role for recovery after ischemic or traumatic brain injury.[26,27] All these observations led to the hypothesis that G-CSF may be helpful for brain metastases not only by treating and preventing leukopenia but also by promoting both permeability of blood-brain barrier and recovery of normal neurons.

In conclusion, although the mechanisms are not still completely understood, the treatment with G-CSF represents a very promising support to conventional anticancer therapies of patients bearing metastases derived from various types of tumors.

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