Response:

The definition of resistance is in the eye of the beholder

We appreciate the observations made by Duyster et al that relate to sensitivity of clinical alleles of FIP1L1-PDGFRα associated with hypereosinophilic syndrome to inhibition with AMN107. Our cellular and biochemical experiments are generally in agreement in showing that the FIP1L1-PDGFRα T674I imatinib mesylate resistance allele is also highly resistant to inhibition with AMN107, with more than 100-fold higher IC50 than for FIP1L1-PDGFRα.1 There are several potential explanations for why we observed modest effects on cell growth and tyrosine phosphorylation content of FIP1L1-PDGFRα T674I transformed cells at 1 μM AMN107 compared with the results annotated here, but at most there may be a several fold difference in our estimates of cellular IC50.

Several other points merit consideration. First, we have previously reported that PKC412 is a potent inhibitor of the FIP1L1-PDGFRα T674I allele,2 with an IC50 of approximately 100 nM vs approximately 376 nM reported here for AMN107. From this perspective, PKC412 may be as appropriate an alternative for FIP1L1-PDGFRα patients who develop resistance due to acquired T674I as AMN107. In this context, it is also worth noting the importance of including controls for nonspecific or off-target toxicities for tyrosine kinase inhibitors such as AMN107 or PKC412, as they are selective rather than specific. Parental Ba/F3 cells would have been 1 such control in these experiments, but in our view the most compelling controls for nonspecific toxicity or off-target effects are kinase mutations that are selected for resistance to the kinase inhibitor in question. For example, we generated a PKC412 resistance allele in the context of FIP1L1-PDGFRα with an N659D substitution.3 We observed that cells stably transduced with FIP1L1-PDGFRα N659D were resistant to the effects of PKC412, establishing FIP1L1-PDGFRα as the critical target for cellular cytotoxicity mediated by PKC412 in this context, rather than off-target or nonspecific effects. Indeed, the finding of the FIP1L1-PDGFRα T674I imatinib mesylate resistance mutation in a patient with clinically resistant HES provides the most compelling evidence that FIP1L1-PDGFRα causes HES and is the target of imatinib mesylate. It would be useful to have comparable controls for AMN107 as well, although it seems most likely that the cytotoxic effects of AMN107 treatment are attributable to inhibition of the T674I allele.

Second, we completely agree that relative resistance of FIP1L1-PDGFRα T674I to AMN107 does not exclude potential clinical applicability and efficacy if adequate plasma concentrations can be achieved. It may be of value to consider either AMN107 or PKC412 as second-line agents. For the time being, the point is moot, as neither of these drugs is Food and Drug Administration (FDA) approved for any indication, but could potentially be accessed through compassionate use mechanisms.

It may be, as suggested by the authors, that FIP1L1-PDGFRα T674I will emerge as an important clinical problem in treatment of HES, but so far it has not. Over the last several years increasing numbers of patients with HES have been treated with imatinib mesylate, but there are only 2 reported cases of resistance to imatinib mesylate.3,4 Both of these developed in the context of acute eosinophilic leukemias rather than in HES. It is certainly possible that more cases will ultimately surface, and proactive development of inhibitors such as PKC412 and AMN107 that address this problem seems a prudent course of action. But it is possible that these will be no more effective in the setting of acute eosinophilic leukemia than imatinib mesylate is in the context of CML in blast crisis.

However, it is also possible that resistance will develop less frequently in FIP1L1-PDGFRα–positive HES due to the remarkable potency of imatinib mesylate in this context. Imatinib mesylate is several hundred-fold more potent as a FIP1L1-PDGFRα inhibitor than as a BCR-ABL inhibitor. Only time will tell, but one might hope that highly potent kinase inhibitors such as imatinib mesylate in the context of FIP1L1-PDGFRα, or AMN107 or dasatinib in the context of BCR-ABL–positive disease, will more effectively suppress emergence of resistant clones due to point mutations in the target kinases, than lower potency inhibitors.

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References


To the editor:

Bevacizumab therapy for POEMS syndrome

We read the case report from Badros and coworkers with great interest.1 A patient with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) was successfully treated with bevacizumab. Increased level of vascular-endothelial growth factor (VEGF) is thought to play a role in the pathophysiology of POEMS syndrome.2,3 Here we describe a POEMS syndrome patient with high VEGF levels, treated with bevacizumab, without clinical improvement.
A 41-year-old male presented with slowly progressing, distal and symmetric, sensory, and motor neuropathy. Bone marrow aspiration showed a normal plasma-cell count. Magnetic resonance imaging (MRI) of the pelvis showed a solitary mixed lytic and sclerotic pelvic lesion, and a biopsy showed infiltrating plasma cells. He also met the remaining diagnostic criteria for POEMS syndrome. After 2 months of therapy with 500 mg cyclophosphamide given every 14th day, the patient presented with a World Health Organization (WHO) performance status III and the progression of the polyneuropathy left him bedridden. His plasma VEGF (p-VEGF) was 765 pg/mL (normal, < 50 pg/mL). Based on the rapid response of bevacizumab in the patient reported by Badros et al,1 we decided to give 2 courses of 5 mg/kg bevacizumab q 14 days. This approach was chosen to try to improve on the neurologic symptoms by reducing the level of p-VEGF before starting radiation therapy toward the pelvic plasmacytoma. After the first bevacizumab infusion p-VEGF decreased from 765 to 62 pg/mL, and remained low (median, 52 pg/mL; range, 34–89 pg/mL). Still, the condition worsened with increased paresis. Bevacizumab was stopped and radiation therapy was started. Five weeks after the last bevacizumab infusion, the patient experienced multiorgan failure and severe capillary leak syndrome with edema, ascites, and pleural effusion. After 2 weeks of intensive care, he died of pneumonia.

VEGF may affect the blood-nerve barrier by increasing microvascular hyperpermeability, thereby increasing the endoneural pressure subsequent to edema and nerve damage.2 This makes VEGF a logical target in POEMS syndrome. Still, the pathogenesis of the polyneuropathy has not been fully clarified, and several other cytokines like interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) might contribute.3 Furthermore, the neuroprotective role of VEGF in neurodegenerative disorders4 might imply that a rapid removal of a chronic high level of VEGF might result in increased apoptotic activity in motor neurons under stress and hypoxia. Similarly, little is known about how endothelial cells that have been stimulated by a pathologically high level of VEGF over a long period of time react on the rapid removal of VEGF in plasma. It is known, though, that VEGF is an important survival factor for newly formed blood vessels, and that the removal of VEGF is followed by apoptosis of endothelial cells.5,6 The sudden collapse of a large volume of newly formed blood vessels following bevacizumab treatment might even lead to an increase of capillary leakiness and temporary impairment of the clinical condition, as seems to be the case in our patient. Following this, we suggest that, even if encouraging results have been reported, careful consideration should be taken before introducing bevacizumab in POEMS syndrome patients.

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References

Response:

Bevacizumab therapy for POEMS syndrome

In response to our letter describing clinical improvement in a POEMS patient after bevacizumab, Straume et al describe a patient treated with bevacizumab and radiation therapy who, 5 weeks later, developed capillary leak and died. Although capillary leak cannot be directly attributed to bevacizumab, the report emphasizes the need for caution when using bevacizumab in POEMS patients.

Here we report on another POEMS patient who has been treated successfully with bevacizumab in Limoges, France. A 60-year-old woman was diagnosed with POEMS after 2 years of progressive sensory/motor neuropathy that left her bedridden. She had monoclonal immunoglobulin A lambda (0.1 mg/dL), normal marrow examination, and no bone lesions. POEMS manifestations included hyperpigmentation, hemangiomas, edema, diabetes mellitus, and hypothyroidism. She was hospitalized with pulmonary hypertension (she lost 31 kg in 15 days). Most interestingly, progressive disappearance of hyperpigmentation and whitening of hemangiomas was seen. Currently, she has a good clinical status without edema or clinical sign of pulmonary hypertension, 2 months after a third infusion of bevacizumab. Such rapid clinical improvement in POEMS syndrome is unusual and is probably attributed to bevacizumab.

There is growing evidence that VEGF is critical in the pathogenesis of POEMS manifestations. VEGF levels correlate with POEMS clinical activity, thus providing a biochemical and therapeutic target to diagnose and monitor response. Several studies have shown that responses to therapy, including high-dose chemotherapy, were associated with inhibition of VEGF production and/or activity.1,2 Bevacizumab induces a rapid decrease in VEGF levels, making it an appropriate candidate in therapy of POEMS patients.

Straume et al raise a concern about the deleterious effects of rapid reduction of chronically high VEGF levels on the neuronal cells. Although this is an interesting hypothesis, there is currently...
no proof that low VEGF levels contribute to neurodegeneration. It is possible that low levels of VEGF are neuroprotective, while high levels cause neuronal sheath edema and ischemic polyneuropathy. VEGF’s effects on the endothelial cells are more complicated. VEGF increases vascular permeability and promotes angiogenesis by stimulating endothelial-cell growth. Extensive apoptosis of endothelial cells as suggested by Straume et al could have catastrophic consequences such as bleeding, a known side effect of bevacizumab. Although the data are limited, we hypothesize that endothelial damage stimulates platelet aggregation and release of VEGF that is stored at high levels in the platelets, thus maintaining adequate VEGF levels locally to preserve the newly formed blood vessels. It is worth noting that inhibition of platelet function has resulted in decreased VEGF levels and clinical improvement in POEMS syndrome. It is based on in vitro analysis, and current data suggest that this doesn’t necessarily represent the in vivo situation. In conclusion, measuring cytotoxicity using highly activated CL in vitro may over-exaggerate the effectiveness of these cells and thus underestimate the protective capacity of antiapoptotic molecules. Indeed, the experimental evidence pictures PI-9 as a crucial activation, and thus the diversity of granzymes expressed, determines the efficacy of inhibition by PI-9. In agreement, we have shown that expression of SPI-6 (mouse PI-9) in T lymphomas does not protect these cells against cytotoxicity induced by a CL in vitro, but does convey a level of protection in vivo. Also, the clinical data available support this notion. The group of Ouedjans and Kummer provided compelling evidence that PI-9 expression is associated with poor prognosis in anaplastic large B-cell lymphoma. More importantly, they showed that PI-9 expression is an important determinant in disease-free survival time of melanoma patients following immunotherapy.

In conclusion, measuring cytotoxicity using highly activated CL in vitro may over-exaggerate the effectiveness of these cells and thus underestimate the protective capacity of antiapoptotic molecules. Indeed, the experimental evidence pictures PI-9 as a crucial determinant in the outcome of immunotherapeutic approaches in cancer.

To the editor:

Does the serpin PI-9 protect tumor cells?

The report of Godal et al. raises an important issue on the effectiveness of apoptosis inhibitors in preventing death induced by cytotoxic lymphocytes (CLs) in clinically relevant settings. A large variety of tumors express apoptosis inhibitors such as Bcl-2 and PI-9, which protect cells from granzyme B (GrB)–induced apoptosis in vitro and were thus proposed to induce immune escape of tumors. Based on in vitro assays Godal et al. claim that expression of these apoptotic regulators is irrelevant for CL sensitivity of lymphomas and therefore unlikely to affect immunotherapy of lymphomas. However, a major limitation of this conclusion is that it is based on in vitro analysis, and current data suggest that this doesn’t necessarily represent the in vivo situation.

CL degranulation induces apoptosis mainly via GrB, while other granzymes bring about different modes of cell death. As PI-9 inhibits GrB, it effectively prevents apoptosis, but not these other deaths. In agreement, Godal et al. show that in vitro cytotoxicity of lymphomas does not depend on PI-9 or Bcl-2 expression, which then warrants the conclusion that these do not protect lymphomas. Although relevant, this conclusion is not supported by data from other groups. For instance, Classen et al. concluded that PI-9 expression in pediatric acute lymphoblastic leukemias is correlated with protection in vitro. Similarly, PI-9 expression in MCF-7 cells prevents death induced by long-term activated natural killer (NK) cells (expressing little GrB), while it is ineffective against shorty activated NK cells (expressing high levels of GrB). These findings suggest that PI-9 efficacy depend on the conditions used. Although this may appear trivial, Godal et al. assume that cytotoxicity measured in their in vitro assays is identical to the in vivo situation. This strongly contrasts with current knowledge, as it is clear that CLs isolated from blood contain less granzymes than most CL lines. For instance, granzyme M, which induces an alternative death pathway, is not detected in activated cytotoxic T lymphocytes (CTLs), while it is present in CTL lines. Similarly, NK cells have little GrB, while lymphokine-activated killer (LAK) cells contain enormous amounts. It is therefore likely that the level of CL

References

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Oddbjørn Straume, Jann Bergheim and Peter Ernst