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Aflibercept in pediatric solid tumors: moving beyond the trap

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Abstract

Angiogenesis plays a pivotal role in the growth and metastasis of adult and pediatric solid tumors. Clinical investigation of angiogenesis inhibitors is currently underway for childhood cancers. While the pediatric study of aflibercept provides proof of principle, challenges remain in developing clinical endpoints and biomarkers of angiogenesis for pediatric trials.
In this issue of *Clinical Cancer Research*, Glade Bender and colleagues report on the pediatric phase 1 trial of aflibercept, a novel soluble decoy receptor that neutralizes circulating vascular endothelial growth factor (VEGF) (1). A promising angiogenesis inhibitor, aflibercept (also called VEGF-Trap) is a recombinant protein comprising portions of the extracellular ligand-binding domains of human VEGF receptors 1 and 2 fused to the constant region (Fc) of human immunoglobulin G (IgG1).

Malignancies depend on increased vascularization and the formation of a new network of blood vessels called *angiogenesis* for tumor growth, invasion, and metastasis. Since Dr. Judah Folkman’s landmark report (2) that inhibition of angiogenesis by means of holding tumors in a nonvascularized dormant state would be an effective strategy to treat human cancer, the search for angiogenic factors, regulators of angiogenesis, and anti-angiogenic molecules over the next four decades have shed light on angiogenesis as an important therapeutic target for anticancer drug development. The most clinically relevant proangiogenic factor is VEGF, and the use of anti-VEGF agents has been validated in the clinic with the approval of the humanized anti-VEGF monoclonal antibody bevacizumab followed by several VEGF receptor tyrosine kinase inhibitors (TKIs - sorafenib, sunitinib, pazopanib, and axitinib) that targeted different parts of the angiogenic pathway (Figure 1). However, the clinical efficacy of angiogenesis inhibitors has recently been met with numerous phase III failures that showed modest survival benefits despite improvement in progression free survival.

Aflibercept potentially represents the next generation of angiogenesis inhibitors as a decoy receptor fusion protein rationally designed to sequester multiple VEGF ligands (all VEGF-A isoforms, VEGF-B and placental growth factor (PIGF)) with higher and...
broader affinity than their natural receptors (3), and thus can inhibit the binding and activation of the cognate VEGF receptors. Because previous studies have shown evasive resistance with treatment of anti-VEGF therapies by inducing compensatory proangiogenic pathways such as upregulating PlGF levels, the targeting of both VEGF and PlGF has the potential to reduce the development of resistance and increase efficacy without significantly increasing toxicity (4). Preclinical studies of aflibercept in various tumor xenograft models including pediatric cancers have demonstrated inhibition of tumor growth, angiogenesis and metastasis, reduction in microvessel density and perfusion, inhibition of ascites formation and improved survival (reviewed in (5)). Early phase clinical studies have provided proof of principle and demonstrated initial significant survival advantage with a manageable safety profile. In late phase studies, three phase III trials in lung, pancreatic, and prostate cancer failed to show an overall survival (OS) benefit, while the phase III VELOUR study in adults with metastatic colorectal cancer showed significant improvements in OS, progression-free survival and response rates (5).

The current Phase I study by Glade Bender et al. extends the clinical evaluation of aflibercept to the pediatric population with refractory solid tumors to determine the maximum tolerated dose (MTD), pharmacokinetic (PK), and dose-limiting toxicities (DLTs). The MTD was established as 2.5mg/kg/dose every 14 days in contrast to the adult recommended dose of 4mg/kg. At this MTD, the ability to achieve free aflibercept concentrations in excess of bound aflibercept levels was achieved but not sustained throughout the dosing interval. Three patients had stable disease for >13 weeks. The most common non-DLTs were hypertension and fatigue. Biomarker analyses demonstrated a
significant decrease in VEGF and increase in PlGF from baseline observed in response to
treatment by day 2.

The timeliness of this study underscores the importance of understanding the
biology of the angiogenic process in pediatric vs. that of adult solid tumors and
delineating the mechanism of angiogenesis inhibition of specific agents in each
respective target patient population. Past experience with the development of
antiangiogenic agents for the pediatric population raises concerns with the toxicities
specific to the growing child, the on- and off-target effects of angiogenesis inhibitors, and
their long-term impact on cardiovascular, endocrine, and bone health in children with
cancer (6). Clinical experience with VEGF inhibitors in early phase pediatric trials has
demonstrated comparable PK parameters and equivalent recommended doses, as well as
similar class toxicity between the adult and pediatric populations (Table 1A). In the
current study, children tolerated lower doses of aflibercept than adults despite similar PK
parameters due to the presence of dose-limiting tumor hemorrhage, pain, and necrosis
(Table 1B) (7). Hemorrhage is the most common fatal adverse event in adults receiving
bevacizumab regimens. While a meta-analysis of randomized clinical trials involving
bevacizumab showed a relative risk of 2.77 (95% CI, 1.07-7.16) for fatal hemorrhage
associated with bevacizumab treatment (8), no hemorrhage occurred in children with
solid tumors in the monotherapy phase I study of bevacizumab (9). It remains to be
determined whether the intratumoral bleed that occurred in this aflibercept pediatric trial
is associated with the study drug or can be attributed to the higher VEGF binding affinity
and broader target inhibition than with bevacizumab. Nonetheless, the tumor-related
toxicities observed may be attributed to the intrinsic nature of the tumor and/or its
vasculature, tumor histology, or the relative contribution of VEGF to pediatric tumor growth and the presence of these DLTs suggest a possible association with the mechanism of the drug or of its activity. Indeed, the biologic effect of aflibercept was shown in preclinical studies to correlate with free aflibercept concentrations in excess of bound (10). While the MTD of 2.5mg/kg was unable to sustain free in excess of complexed aflibercept for the duration of the dosing interval which may be due to an ongoing compensatory rise in VEGF production, this highlights the importance of understanding pediatric tumor VEGF production and the role that VEGF plays in the developing child with cancer. Anti-VEGF therapies should thus be sufficiently dosed in the pediatric population to avoid diversion by host-derived VEGF.

In spite of evidence of clinical activity, the exact mechanism of action of antiangiogenic drugs remains to be fully elucidated and defining the role of antiangiogenic agents in the treatment of childhood cancers is of equal importance. Data from the current study have tremendous clinical implications on the limitations and challenges involved in conducting pediatric antiangiogenic trials related to designing appropriate early phase studies with clinically relevant endpoints and surrogate markers predictive of treatment response. Combination studies are essential to evaluate the most effective treatment regimen of antiangiogenic agents combined with other targeted therapies and/or conventional therapies in order to improve clinical outcomes and to address what role drug combinations play in the efficacy of antiangiogenic agents for the pediatric population. As anti-VEGF agents move through the clinic, surrogate markers of tumor angiogenesis activity are important to guide clinical development of these agents and to select patients most likely to benefit from this approach. Recent research efforts
have focused on a number of candidate markers including tissue, imaging, and circulating biomarkers as well as identifying genetic and toxicity biomarkers to predict treatment response from anti-VEGF/VEGFR therapy and identify patients at risk of adverse events. If validated, these findings could help identify which subgroup of patients should receive antiangiogenic therapy and lead the way to possible future tailoring of individualized antiangiogenic therapy that will be of tremendous benefit to both the adult or pediatric populations.
**Figure 1. VEGF pathway inhibitors.** Monoclonal antibodies can target VEGF (bevacizumab) or the VEGF receptors. Small molecule VEGFR tyrosine kinase inhibitors (TKIs) can inhibit ligand-dependent receptor autophosphorylation of VEGFR-1 and/or VEGFR-2. Chimeric soluble receptors (aflibercept) can target all isoforms of VEGF-A, VEGF-B, and placental growth factor (not shown).
References


Table 1A. Comparison of adult vs. pediatric pharmacokinetics and toxicities on various angiogenesis inhibitors for refractory solid tumors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult population</th>
<th>Pediatric population</th>
</tr>
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<tbody>
<tr>
<td><strong>Bevacizumab</strong></td>
<td></td>
<td></td>
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<tr>
<td>Dose</td>
<td>10mg/kg IV every 2 wks; or 15mg/kg IV every 3 wks</td>
<td>10mg/kg IV every 2 wks; or 15mg/kg IV every 3 wks</td>
</tr>
<tr>
<td>Half-life (T1/2)</td>
<td>20 days</td>
<td>12 days</td>
</tr>
<tr>
<td>Common toxicities</td>
<td>Hypertension, proteinuria, bleeding, headache, infusion reactions</td>
<td>rash, mucositis, proteinuria, lymphopenia, hypertension, infusion reactions</td>
</tr>
<tr>
<td><strong>Sorafenib</strong></td>
<td></td>
<td></td>
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<tr>
<td>Dose</td>
<td>400mg PO twice daily continuous</td>
<td>200mg/m² PO daily x 28days</td>
</tr>
<tr>
<td>Half-life</td>
<td>25-48 hours</td>
<td>&gt;24 hours</td>
</tr>
<tr>
<td>Common toxicities</td>
<td>Rash, hand-foot syndrome, gastrointestinal symptoms, hypertension</td>
<td>Hypertension, rash, hand-foot syndrome, transaminase elevations</td>
</tr>
<tr>
<td><strong>Sunitinib</strong></td>
<td></td>
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<tr>
<td>Dose</td>
<td>50mg PO daily x4wks (q6wks)</td>
<td>15mg/m² PO daily x4wks (q6wks); 25-50 mg PO daily x4wks (q6wks) for GIST</td>
</tr>
<tr>
<td>Half-life</td>
<td>41-86 hours</td>
<td>39 hours</td>
</tr>
<tr>
<td>Common toxicities</td>
<td>Fatigue, gastrointestinal symptoms, hypertension</td>
<td>Myelosuppression, transaminase elevations, gastrointestinal symptoms, fatigue</td>
</tr>
</tbody>
</table>

Abbreviations: GIST, gastrointestinal stromal tumors; IV, intravenously; PO, orally

Table 1B. Comparison of adult vs. pediatric population on aflibercept dose, pharmacokinetics, and tolerability

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Adult population [Ref. (7)]</th>
<th>Pediatric population [Ref. (1)]</th>
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</thead>
<tbody>
<tr>
<td>Maximum tolerated dose</td>
<td>4 mg/kg IV every 2 weeks</td>
<td>2.5 mg/kg IV every 2 weeks</td>
</tr>
<tr>
<td>Half-life</td>
<td>5.5 days</td>
<td>4.5 days</td>
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<tr>
<td>Clearance</td>
<td>1.1 L/day</td>
<td>18.4 mL/kg/day</td>
</tr>
<tr>
<td>Volume of distribution at steady-state</td>
<td>7.88 L</td>
<td>101 mL/kg</td>
</tr>
<tr>
<td>Common adverse events</td>
<td>Dysphonia, hypertension, proteinuria</td>
<td>Hypertension, fatigue</td>
</tr>
<tr>
<td>Dose-limiting toxicities</td>
<td>Proteinuria, rectal ulceration</td>
<td>Tumor hemorrhage, tumor pain, tumor rupture</td>
</tr>
<tr>
<td>Best response</td>
<td>Partial response</td>
<td>Stable disease</td>
</tr>
</tbody>
</table>
Anti-VEGFR-1

Anti-VEGF (bevacizumab)

VEGF soluble receptors (aflibercept)

Anti-VEGFR-2

DC101, ramucirumab

VEGF-1

P

P

P

P

P

P

P

P

Endothelial cell

Small molecule
VEGFR TKIs
(sorafenib, sunitinib, pazopanib, axitinib)