Aflibercept in Pediatric Solid Tumors: Moving Beyond the Trap
Cindy H. Chau and William D. Figg

Angiogenesis plays a pivotal role in the growth and metastasis of adult and pediatric solid tumors. Clinical investigation of angiogenesis inhibitors is currently under way for childhood cancers. While the pediatric study of aflibercept provides a proof-of-principle, challenges remain in developing clinical endpoints and biomarkers of angiogenesis for pediatric trials. Clin Cancer Res; 18(18); 4868–71. ©2012 AACR.

In this issue of Clinical Cancer Research, Glade Bender and colleagues report on the pediatric phase I trial of aflibercept, a novel soluble decoy receptor that neutralizes circulating 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 (VEGFR) 1 and 2 fused to the constant region (Fc) of human immunoglobulin G (IgG1).

Malignancies depend on increased vasculization and the formation of a new network of blood vessels called angiogenesis for tumor growth, invasion, and metastasis. Because Folkman and colleagues’ 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 antiangiogenic molecules over the next 4 decades has 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 (TKI—sorafenib, sunitinib, pazopanib, and axitinib) that target different parts of the angiogenic pathway (Fig. 1). However, the clinical efficacy of angiogenesis inhibitors has recently been met with numerous phase III failures in trials 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 PIGF levels, the targeting of both VEGF and PIGF 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 shown inhibition of tumor growth, angiogenesis, and metastasis; reduction in microvessel density and perfusion; inhibition of ascites formation; and improved survival (reviewed in ref. 5).

The timeliness of this study underscores the importance of understanding the biology of the angiogenic process in pediatric versus 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 about 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 shown comparable pharmacokinetic parameters and equivalent recommended doses, as well as similar class toxicity between the adult and pediatric populations (Table 1). In the current study, children tolerated lower doses of aflibercept than adults did despite similar pharmacokinetic parameters due to the presence of dose-limiting tumor hemorrhage, pain, and necrosis.

Table 1. Comparison of adult versus pediatric pharmacokinetics and toxicities in various angiogenesis inhibitors for refractory solid tumors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult population</th>
<th>Pediatric population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>Dose 10 mg/kg i.v. every 2 wks; or 15 mg/kg i.v. every 3 wks</td>
<td>Dose 10 mg/kg i.v. every 2 wks; or 15 mg/kg i.v. every 3 wks</td>
</tr>
<tr>
<td></td>
<td>Half-life (T_{1/2}) 20 d</td>
<td>Half-life 12 d</td>
</tr>
<tr>
<td></td>
<td>Common toxicities Hypertension, proteinuria, bleeding, headache, infusion reactions</td>
<td>Rash, mucositis, proteinuria, lymphopenia, hypertension, infusion reactions</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Dose 400 mg p.o. twice daily by continuous infusion</td>
<td>Dose 200 mg/m² p.o. daily for 28 d</td>
</tr>
<tr>
<td></td>
<td>Half-life 25–48 h</td>
<td>&gt;24 h</td>
</tr>
<tr>
<td></td>
<td>Common toxicities Rash, hand–foot syndrome, gastrointestinal symptoms, hypertension</td>
<td>Hypertension, rash, hand–foot syndrome, aminotransferase elevations</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Dose 50 mg p.o. daily for 4 wk (every 6 wks)</td>
<td>Dose 15 mg/m² p.o. daily for 4 wks (every 6 wks); 25–50 mg p.o. daily × 4 wks (every 6 wks) for GIST</td>
</tr>
<tr>
<td></td>
<td>Half-life 41–86 h</td>
<td>Half-life 39 h</td>
</tr>
<tr>
<td></td>
<td>Common toxicities Fatigue, gastrointestinal symptoms, rash, hand–foot syndrome, hypertension</td>
<td>Myelosuppression, aminotransferase elevations, gastrointestinal symptoms, fatigue</td>
</tr>
</tbody>
</table>

Abbreviations: GIST, gastrointestinal stromal tumors; p.o., orally.
Table 2. Comparison of adult versus pediatric population for aflibercept dose, pharmacokinetics, and tolerability

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Adult population [ref. 7]</th>
<th>Pediatric population [ref. 1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTD</td>
<td>4 mg/kg i.v. every 2 wks</td>
<td>2.5 mg/kg i.v. every 2 wks</td>
</tr>
<tr>
<td>Half-life</td>
<td>5.5 d</td>
<td>4.5 d</td>
</tr>
<tr>
<td>Clearance</td>
<td>1.1 L/d</td>
<td>18.4 mL/kg</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>DLTs</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>

(Table 2; ref. 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% confidence interval, 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 bleeding 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 suggests 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 drug (10). While the MTD of 2.5 mg/kg was unable to sustain free concentrations in excess of complexed aflibercept for the duration of the dosing interval, possibly due to an ongoing compensatory increase 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.

Despite the 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 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 and pediatric populations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C.H. Chau, W.D. Figg
Writing, review, and/or revision of the manuscript: C.H. Chau, W.D. Figg

Grant Support

This work was supported by the Intramural Research Program of the National Cancer Institute, and the NIH.

Received July 26, 2012; accepted July 31, 2012; published OnlineFirst August 6, 2012.

References


Aflibercept in Pediatric Solid Tumors: Moving Beyond the Trap
Cindy H. Chau and William D. Figg


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-12-2212

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2012/09/12/1078-0432.CCR-12-2212.DC1

Cited articles
This article cites 10 articles, 7 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/18/18/4868.full#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.