Current Clinical Trials of Molecularly Targeted Agents in Children With Cancer, Part 2

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A number of molecularly targeted agents directed at critical cell survival and cell proliferation pathways have recently entered clinical evaluation in children with cancer. These agents offer the potential for more effective anticancer therapy while simultaneously diminishing acute and long-term toxic effects. Systematic evaluations of targeted agents are essential to achieving continued improvements in outcome for children with cancer. Brief summaries of the rationale for conducting studies of several agents in children are provided below. Following these summaries is a listing of phase I, phase I/II, phase II, and pilot studies of these and other agents in pediatric populations.

Clinical Trials Referral Resource is designed to serve as a ready reference for oncologists to help identify clinical trials that might be suitable for their patients. We hope it will also enhance accrual to clinical trials by informing practicing oncologists of ongoing protocols. Currently in the United States less than 10% of eligible adult patients are entered into clinical trials. The result is a delay in answering important therapeutic and scientific questions and disseminating therapeutic advances to the general oncology community.

It should be emphasized that including a specific trial does not imply that it is more important than another trial. Among the criteria for selection are that the trial is addressing an important question and is not expected to close in the immediate future (less than 1 year), and that initial staging or laboratory tests required for patient eligibility are widely practiced and available. Information on other protocols can be accessed via Physician’s Data Query (PDQ).* We emphasize that this is an attempt to encourage referral of patients to these trials. We are specifically not soliciting additional members for the cooperative groups, nor are we suggesting how practicing oncologists should be treating patients who are not in a study.

This month’s installment of Clinical Trials Referral Resource, a continuation of the article begun in the previous issue, is devoted to current clinical trials of molecularly targeted agents for children with cancer.

For patient entry information, see the individual trials.

G3139

G3139 (bcl-2 antisense, Genasense) is an 18-mer phosphorothioate oligonucleotide antisense molecule that binds to the first six codons of human bcl-2 mRNA and reduces expression of the bcl-2 gene by preventing translation and production of the encoded protein.[1] By reducing levels of bcl-2 protein, G3139 increases the activation of the apoptotic pathway in response to various stimuli such as chemotherapy, irradiation, or other DNA-damaging events. Tumor xenograft models have demonstrated single-agent activity of G3139 against follicular lymphoma cell lines[1] and against a neuroendocrine malignancy (ie, Merkel cell carcinoma).[2] In xenograft models in which G3139 was...
tested in combination with chemotherapy, enhanced antitumor activity was observed for
cyclophosphamide (Cytoxan, Neosar) against non-Hodgkin lymphoma,[3] for dacarabazine
(DTIC-Dome) against melanoma,[4] and for cisplatin against gastric carcinoma.[5]
G3139 has been studied in adults with cancer, both as a single agent[6] and in combination with
chemotherapy.[7,8] Because antisense-mediated down-regulation of bcl-2 levels requires several
days, G3139 is administered intravenously as a single agent for 4 to 7 days prior to the initiation of
chemotherapy.
G3139 has been generally well tolerated, and serum levels in excess of those associated with bcl-2
down-regulation and potentiation of chemotherapy have been achieved. Combinations of G3139 with
chemotherapy have not produced substantial increases in toxicity compared to those expected for
chemotherapy alone. Down-regulation of bcl-2 in peripheral blood mononuclear cells and in tumor
cells has been observed in adult studies.[6,8]
G3139 may eventually have utility against several pediatric cancers in which bcl-2 may be
associated with treatment resistance, including neuroblastoma,[9,10] synovial sarcoma,[11,12]
acute lymphoblastic leukemia,[13,14] and acute myeloid leukemia.[15,16] G3139 is being evaluated
in combination with doxorubicin and cyclophosphamide in a pediatric solid tumor phase I study
(ADVL0211) that should begin enrollment in the first quarter of 2002.

**ZD1839**

ZD1839 (Iressa) is an orally available agent that selectively inhibits the tyrosine kinase activity of the
epidermal growth factor receptor (EGFr).[17] ZD1839 inhibits ligand-induced EGFr
autophosphorylation, leading generally to a cytostatic effect.[17] In preclinical models, oral dosing
occasionally causes tumor regression but more generally causes growth inhibition of
EGFr-expressing tumor xenografts.[18,19] The antitumor activity of a variety of conventional
chemotherapeutic agents can be potentiated when combined with ZD1839.[18,19]
Phase I trials of ZD1839 demonstrated that the agent is well tolerated at doses that suppress EGFr
phosphorylation in surrogate tissues.[20] When ZD1839 is administered daily, the most common
toxicities observed are grade 1/2 diarrhea and a distinctive acneiform skin rash.[17] The
pharmacokinetics of ZD1839 justify administration on a once-daily schedule. ZD1839 has induced
responses in patients with colorectal, ovarian, non-small-cell lung cancer, head and neck, renal, and
hormone-resistant prostate cancers.[17,21,22] It has been safely combined with several
conventional chemotherapy agents, including cisplatin/gemcitabine (Gemzar)[23] and
fluorouracil/leucovorin.[24] Another EGFr inhibitor, cetuximab (IMC-C225, Erbitux) has been safely
administered in combination with cisplatin,[25,26] irinotecan (CPT-11, Camptosar),[27] and radiation
therapy,[28] further supporting the feasibility of combining this class of agent with conventional
anticancer treatments.
The expression of EGFr in neuroblastoma,[29,30] rhabdomyosarcoma,[29,31] osteosarcoma,[32] and
glioma[33] provides the rationale for studying ZD1839 in children. A pediatric phase I trial of ZD1839
(ADVLO016) in children with solid tumors is scheduled to begin in the first quarter of 2002. For
children with high-grade gliomas (either supratentorial or brainstem), the Pediatric Brain Tumor
Consortium is conducting a phase I study of ZD1839 in combination with radiation therapy
(PBTC-007).

**Rituximab**

Rituximab (Rituxan) is a mouse/human chimeric antibody that targets the CD20 antigen, which is
present exclusively on B cells (pre-B and mature B lymphocytes) and on most B-cell
lymphomas.[34,35] Rituximab kills cells via several mechanisms, including antibody-dependent
cellular toxicity, activation of the complement cascade,[36,37] and modulation of signaling pathways
leading to apoptosis.[38,39] In preclinical models, rituximab enhances the activity of chemotherapy
agents.[40-43]
Rituximab was first shown to be active against low-grade or follicular non-Hodgkin lymphoma[44]
and was subsequently found to be active against diffuse large-cell lymphoma.[45] Toxicities
attributed to rituximab are generally mild and most often associated with the first infusion. An acute
tumor lysis syndrome, likely related to cytokine release, has occurred in patients with high
circulating lymphocyte count or large tumor burden.[46-48] Rituximab has been safely combined
with standard CHOP chemotherapy (cyclophosphamide, doxorubicin HCl, vincristine [Oncovin],
prednisone),[49,50] with no substantial increase in toxicity above that associated with the CHOP
regimen alone.
A randomized trial in elderly adults with diffuse large-cell lymphoma comparing CHOP to CHOP plus rituximab demonstrated significantly higher event-free survival and survival rates in patients receiving rituximab plus chemotherapy.[51] Rituximab has also been safely combined with an intensive chemotherapy regimen used to treat Burkitt lymphoma.[52]

Among the lymphomas that occur in children, diffuse large-cell lymphoma and Burkitt lymphoma both express high levels of CD20.[53-57] Rituximab induces apoptosis in Burkitt lymphoma cell lines,[38,39] and anti-CD20 monoclonal antibodies are active in a Burkitt lymphoma xenograft model.[58] There are anecdotal reports of children with recurrent Burkitt lymphoma[59] and children with post-transplant lymphoproliferative disease responding to rituximab.[60]

A Children’s Oncology Group pilot study (ANHL01P1) combining rituximab with standard chemotherapy agents in children with newly diagnosed Burkitt lymphoma and diffuse large-cell lymphoma should begin accrual in the second quarter of 2002. A second Children’s Oncology Group study (ANHL0121) will combine rituximab with ICE (ifosfamide [Ifex], carboplatin [Paraplatin], etoposide) in children with recurrent Burkitt lymphoma and diffuse large-cell lymphoma. Rituximab plus ICE chemotherapy has shown substantial activity in adults with recurrent high-grade B-cell lymphomas.[61] The ANHL0121 study should open in the third quarter of 2002.

**IDEC-Y2B8**

Yttrium-90-ibritumomab tiuxetan (IDEC-Y2B8, 90Y-Zevalin) is also to be studied in children with recurrent B-cell lymphomas. Ibritumomab is a murine IgG1 kappa immunoglobulin that, like rituximab, reacts with the CD20 antigen. It is covalently attached to the chelator tiuxetan, which can then secure either the pure beta emitter yttrium-90 for therapeutic applications or secure indium-111 for imaging/dosimetry.[62]

A randomized trial in adults with relapsed or refractory low-grade, follicular, or CD20+ transformed B-cell non-Hodgkin lymphoma compared weekly rituximab (four doses) to a regimen in which a single dose of IDEC-Y2B8 was preceded by two doses of rituximab to clear peripheral B-cells and improve biodistribution of IDEC-Y2B8.[62] Patients receiving IDEC-Y2B8 had a higher response rate compared to those receiving rituximab alone.[63] A pediatric phase I study of IDEC-Y2B8 (ADVL0013) in children with recurrent B-cell lymphomas should begin accruing patients in the third quarter of 2002.

**In Summary**

The clinical trials of the molecularly targeted agents described above and those described in last month’s issue of Oncology represent necessary early steps towards rationalizing therapy for children with cancer. Realizing the potential benefits of targeted therapies will require increased understanding of the biology of pediatric cancers, as well as systematic clinical evaluations of targeted agents. Eventual success will require the concerted efforts of molecular biologists elucidating key survival and cell death pathways in specific childhood cancers, of preclinical researchers using animal models to prioritize new agents for evaluation in children, and of clinicians implementing well-conceived development plans for those agents selected for study in children.

**Phase II**

**Title:** A Phase II Study of Ifosfamide, Carboplatin, Etoposide, and Rituximab as Retrieval Therapy for Relapsed/Refractory NHL—A COG Study  
**Protocol Number:** ANHL0121  
**Participating Institutions:** Children’s Oncology Group  
**Contact:** Judith Everett, (626) 447-0064, ext 116

**Phase I/II**

**Title:** A Phase I/II Trial of ZD1839 (Iressa) and Radiation in Pediatric Patients Newly Diagnosed With Brain Stem Tumors or Incompletely Resected Supratentorial Malignant Gliomas With Phase II Limited to Brain Stem Tumors  
**Protocol Number:** PBTC-007  
**Participating Institutions:** Pediatric Brain Tumor Consortium  
**Contact:** J. Russell Geyer, (206) 526-2106
Phase I

**Title:** Phase I Study of Rituximab Followed By Yttrium Y 90 Ibritumomab Tiuxetan With or Without Autologous Peripheral Blood Stem Cell Transplantation in Children With Recurrent or Refractory CD20-Positive Lymphoma  
**Protocol Number:** COG-ADVLO013  
**Participating Institutions:** Children’s Oncology Group  
**Contact:** Judith Everett, (626) 447-0064, ext 116  
**Latest Information:** [http://www.cancer.gov/clinical_trials/](http://www.cancer.gov/clinical_trials/)

**Title:** A Phase I Study of ZD1839 (Iressa), an Oral Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor, in Children With Refractory Solid Tumors  
**Protocol Number:** ADVL0016  
**Participating Institutions:** Children’s Oncology Group  
**Contact:** Judith Everett, (626) 447-0064, ext 116  
**Title:** A Phase I Trial of BCL-2 Antisense Combined With Cytotoxic Chemotherapy in Relapsed Childhood Solid Tumors  
**Protocol Number:** ADVL0211  
**Participating Institutions:** Children’s Oncology Group  
**Contact:** Judith Everett, (626) 447-0064, ext 116

Pilot Studies

**Title:** A Pilot Study to Determine the Toxicity of the Addition of Rituximab to the Induction and Consolidation Phases and the Addition of Rasburicase to the Reduction Phase in Children With Newly Diagnosed Advanced B-Cell Leukemia/Lymphoma Treated with LMB/FAB Therapy  
**Protocol Number:** ANHL01P1  
**Participating Institutions:** Children’s Oncology Group  
**Contact:** Judith Everett, (626) 447-0064, ext 116

Other Agents of Interest in Clinical Trials

**Title:** Phase II Study of Gemcitabine in Children With Relapsed or Refractory Acute Lymphoblastic Leukemia or Acute Myelogenous Leukemia  
**Protocol Number:** CCG-A0999, COG-ADVLO022  
**Participating Institutions:** Children’s Oncology Group  
**Contact:** Judith Everett, (626) 447-0064, ext 116; for a complete listing of study contacts, click [here](http://www.cancer.gov/clinical_trials/)

**Title:** Phase II Study of Compound 506U78 in Patients with Refractory T-Cell Malignancies  
**Protocol Number:** CCG-P9673, POG-9673  
**Participating Institutions:** Children’s Oncology Group  
**Contact:** Judith Everett, (626) 447-0064, ext 116; for a complete listing of study contacts, click [here](http://www.cancer.gov/clinical_trials/)

**Title:** Phase II Study of Rebeccamycin Analogue in Children With Solid Tumors or Non-Hodgkin's Lymphoma  
**Protocol Number:** COG-P9963  
**Participating Institutions:** Children’s Oncology Group  
**Contact:** Judith Everett, (626) 447-0064, ext 116; for a complete listing of study contacts, click [here](http://www.cancer.gov/clinical_trials/)

**Title:** Phase I Study of Flavopiridol in Children With Relapsed or Refractory Solid Tumors or Lymphomas  
**Protocol Number:** CCG-AO972, COG-ADVLO017, NCI-A0972  
**Participating Institutions:** Children’s Oncology Group  
**Contact:** Judith Everett, (626) 447-0064, ext 116; for a complete listing of study contacts, click [here](http://www.cancer.gov/clinical_trials/)

**Title:** Phase I Study of hu14.18-Interleukin-2 Fusion Protein in Children With Refractory or Recurrent Neuroblastoma or Other GD2-Positive Tumors  
**Protocol Number:** ADVL0018  
**Participating Institutions:** Children’s Oncology Group  
**Contact:** Judith Everett, (626) 447-0064, ext 116; for a complete listing of study contacts, click [here](http://www.cancer.gov/clinical_trials/)
Title: Phase II Pilot Study of Modified Multiagent Berlin-Frankfurt-Muenster-86 Chemotherapy With or Without 506U78 in Patients With Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia
Protocol Number: COG-AALL00P2
Participating Institutions: Children's Oncology Group
Contact: Judith Everett, (626) 447-0064, ext 116; for a complete listing of study contacts, click here
Latest Information: http://www.cancer.gov/clinical_trials/

References:


63. Witzig TE, White CA, Gordon LI, et al: Final results of a randomized controlled study of the Zevalin radioimmunotherapy regimen vs a standard course of rituximab immunotherapy for B-cell NHL

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