Antiangiogenesis Effects of Chemotherapy

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Mechanisms of Tumor Vascular Development

Angiogenesis

Vasculogenesis

CD45- CEP
CD45+
Myeloid Progenitor Cells Promote Vasculogenesis


Li et al, *FASEB J* 2006
Recruitment of myeloid DC progenitors promotes tumor vascularization and growth

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Discovery of mouse vascular DCs

CD11c

Matrigel

Discovery of Human Vascular DCs

Chemotherapy Targets Tumor Endothelium

Maximal Tolerated Dose ➞

Low Dose Metronomic ➞

Browder et al, Cancer Res 2000
LDM Chemotherapy Overcomes Tumor Resistance

Browder et al, *Cancer Res* 2000
LDM Chemotherapy Targets Tumor Angiogenesis

Bocci et al, Cancer Res 2002

Maraveyas et al, Br J Ca 2005
CEP Predict Response to Antiangiogenesis Therapy

CD13+/VEGFR-2+/CD45-/c-kit (CD117)+

Shaked, et al Cancer Cell 2005
LDM Chemotherapy Targets Tumor Vasculogenesis

Bertolini et al, Cancer Res 2003
LDM Chemotherapy Suppresses Multiple Pathways

Shaked et al, *Blood* 2005
Metronomic chemotherapy acts through multiple mechanisms

- Reduction of tumor/systemic VEGF-A levels
- Increase in endogenous antiangiogenic factors
- Direct inhibition of angiogenic sprouting
- Direct killing of tumor endothelial cells
- Suppression of circulating endothelial progenitor cells (CEP)
- Suppression of circulating endothelial cells (CEC)
- Suppression of recruitment and function of CEP and/or CEC in tumors.
LDM Chemotherapy Moves to the Clinic

Cisplatin, paclitaxel, topotecan, etoposide, vincristine, vinblastine, doxorubicin, mitoxantrone, 6-mercaptopurine, 9-amino-20(S)-camptothecin, camptosar, combrestatin A-4

Paclitaxel at 60 mg/m² + carboplatin (AUC = 2) q 3 weeks / 4 weeks

Watanabe et al, Gyn Oncol 2005
Challenges with LDM Chemotherapy

• Identify the optimal biological dose of LDM (in the clinic LDM chemotherapy doses arbitrarily chosen as 10-40% of MTD).

• Identify metrics of efficacy

• Identify optimal combinations

• Identify tumor/patient variables that affect response
What is the optimal LDM CMT dose?

The highest dose that can be delivered metronomically without causing bone marrow disruption (or other major toxicity) (Maraveyas et al, *Br J Cancer* 2005; Shaked, *Blood* 2005).
Rapid Screening Requires Reliable Pharmacodynamic Markers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Disadvantages</th>
<th>Advantages</th>
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<tr>
<td>Microvascular Density</td>
<td>Invasive, Inter-observer variability</td>
<td>Predictive of response</td>
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<tr>
<td>Tumor VEGF-A</td>
<td>Invasive, Inter-observer variability</td>
<td>Standardized</td>
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<tr>
<td>Tumor Response (RECIST)</td>
<td>Not predictive of time to progression</td>
<td>Potentially reliable</td>
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<td>Tumor Blood Flow (DCE-MRI)</td>
<td>Expensive</td>
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<tr>
<td>Circulating VEGF-A</td>
<td>Not predictive of response to therapy</td>
<td>Cheap, non invasive</td>
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<tr>
<td>Circulating Endothelial Cells</td>
<td>Standardization needed</td>
<td>Cheap, non invasive</td>
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<tr>
<td>Circulating Endothelial Progenitors</td>
<td>Standardization needed</td>
<td>Cheap, non invasive</td>
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CEC Predict Response to LDM Chemotherapy and Outcome

CD45-/CD31+/P1H12+/CD133-

Mancuso et al, Blood 2006

MTX PO 2.5 mg BID 2X/wk + CY PO 50 mg QD +/- THL PO 200 mg/dQD
Unlike cytotoxic therapies, antiangiogenic therapies may not result in a measurable decrease in tumor size.

The clinical endpoints to define therapeutic success of LDM chemotherapy may be quite different than for MTD chemotherapy.

Objective response rates may markedly underestimate the clinical benefit resulting from disease stabilization, increased progression-free or overall survival, and increased quality of life or palliation.
Bevacizumab + Cytotoxic Chemotherapy in Metastatic Colorectal Cancer:

Survival benefit irrespectively of objective response

Identification of combinations

Because of its low toxicity, metronomic chemotherapy is ideally suited for long-term combination with other drugs.

Antiangiogenic drugs, vascular disrupting agents and immunotherapy are attractive candidates.

How to triage drugs?

How to screen combinations / schedules?
LDM + Antiangiogenesis Therapy

Klement et al, *Clin Cancer Res* 2002
LDM + Antiangiogenesis Therapy

cisplatin 20 mg/m² weekly on d 1 +
SU-5416 145 mg/m² q 2 weeks, on d 1 and 3

The Promise of LDM Chemotherapy

• Optimize biological dose of LDM

• Validate metrics of efficacy

• Optimize combinations – antiangiogenesis, VDA, immunotherapy, targeted therapy

• Identify tumor/patient variables that affect response