

Metronomic Therapy

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Metronomic Therapy

It makes sense and is patient friendly.

Metronomic

Anti-Angiogenic

Low Dose

Continuous

Tumor Complexity

Early Experimental and Animal Models

1. Homogeneous cell population i.e. single cell type
2. Synchronous growth
3. Log phase
(100% cells are proliferative)

vs. Reality – Solid Tumors (Adults)

1. Multiple cell types
(highly mutated)
2. Not synchronous
3. Not in log phase
(<10% cells are proliferative)

Standard Systemic Therapy

Mechanism of action

1. Damage DNA
2. Microtubule inhibitors

Is More Better?

(but dumb)

1. The more you give, the more you kill; is this true?
2. Is there a dose response curve? (for solid tumors)
3. Acceptance of MTD, DLT.
4. The Ultimate High Dose:
bone marrow transplant and
stem cell support, proven not to work.

Standard Therapy

Method of Administration

In single doses or short courses

At highest doses possible (MTD) or DLT

Requires long breaks (as long as 2 – 3 weeks)

Progress has been modest

Usually associated with significant toxicity

Is More Better ?

Made possible by two decades of:

1. Better supportive care
2. More effective antibiotics
3. Blood cell replacement therapy
 - a. RBC
 - b. Platelets
4. Cytokines
 - a. Erythropoietin
 - b. G - CSF
 - c. GM – CSF

Toxicity Associated with Standard Rx at MTD

Myelosuppression

Hair loss

Damage to intestinal mucosa

Nausea and vomiting

Mucositis

Hand-Foot Syndrome

Long term effect on:

- Heart

- Kidney

- Nervous system

- Reproductive organs

Results of in vitro Models to Study the Effects of Chemotherapy on Cell Kill

S-phase specific agents are:

- a. Not cytotoxic to resting cells
- b. Effective above some minimal concentration
- c. Low doses given frequently are maximally effective

Results of in vitro Models to Study the Effects of Chemotherapy on Cell Kill

Cell cycle nonspecific agents

A single maximum tolerated dose rendered a very high percentage of leukemia cells nonviable if given on every 2 day or every 4 day schedule.

Formula for Cell Kill

$$\text{Cell Kill} = K^{-CT}$$

T = Time of exposure

C = Concentration

C is reflected by the Dose

T is dependent on Frequency

Rethinking the “Cell-Kill Paradigm”

$$\text{Cell Kill} = K^{-CT}$$

If C is kept constant

T = duration of drug exposure

Prolong exposure using lower doses

Examples

5 FU

Cyclophosphamide

Etoposide

Taxotere

Methotrexate

Success of Metronomic Therapy

The smallest amount of drug that will deliver 100% lethal dose (LD 100) to a susceptible cell population.

Once an LD 100 concentration is reached for a susceptible cell, the critical variable then becomes time; i.e. duration of exposure

High Dose vs. Low Dose

Which is Better?

LD 10,000 for one day

or

LD 100 for 100 days

The product CXT is the same.

What is a Tumor Mass?

Endothelial cells

Inflammatory cells

Tumor cells

Connective tissue

Metronomic Chemotherapy

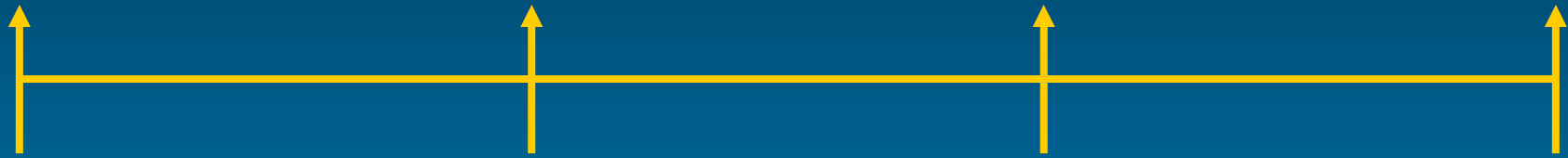
1. Reduces toxicity.
2. Eliminates the need for growth factors.
3. May be superior to MTD schedules in prolonging survival.
4. Main targets are the proliferating endothelial cells of tumor vasculature. It is therefore anti-angiogenic.
5. Redefining the target of chemotherapy.

Potential Benefits of Anti-Angiogenic Therapy

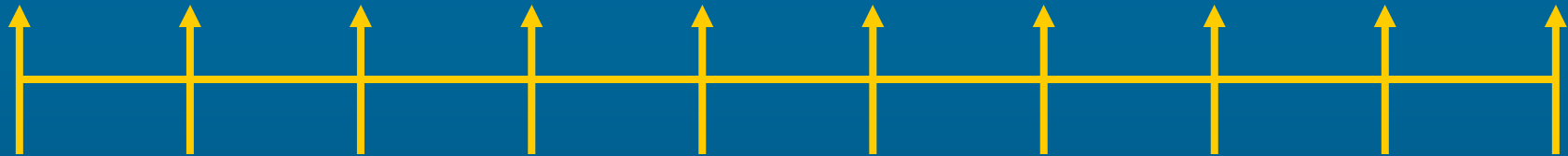
1. Host vascular endothelial cells are genetically stable, i.e. nonmutated.
2. Less drug resistance.
3. Almost every class of chemotherapeutic agents has anti-angiogenic properties.
4. Acquired tumor drug resistance could be reversed by shifting focus of Rx from tumor to drug sensitive tumor endothelium.

Different Therapeutic Regimens

A. MTD pulsatile chemotherapy (every 3 weeks)



B. Metronomic chemotherapy – lower dose on a weekly basis



C. Metronomic chemotherapy – lower dose on a daily basis



Metronomic Dosing Advantages

1. Drugs are “old-timers”
2. Inexpensive
3. Safe
4. Minimal to no toxicity
5. Synergy with targeted non-toxic agents

Sensitivity of Human Vascular Endothelial Cells to Metronomic Therapy

Drug(s)	Results
Methotrexate	Human endothelial cells inhibited by low concentrations of drug (5×10^{-9} M)
Paclitaxel	Inhibition of endothelial-cell chemotoxins and invasiveness detected after several hours incubation with drug concentrations as low as 10pM
Vinblastine	Human endothelial cells inhibited by ultra-low concentrations
Paclitaxel and Vinblastine	Human umbilical endothelial cells inhibited with IC_{50} values in the range of 0.4-0.5 nM
Paclitaxel, cyclophosphamide and epothilone B	Daily exposure to drugs over 6 days resulted in inhibition of human endothelial-cell proliferation with IC_{50} values in the range of 50-100 pM
Paclitaxel	Paclitaxel (over 3 days) selectively inhibits proliferation of human endothelial cells at ultra-low concentrations (0.1-100 pM) with an IC_{50} value of 0.1pM
Paclitaxel and docetaxel	Endothelial cells found to be 10-100 times more sensitive than tumor cells; docetaxel 10 times more effective than paclitaxel

Clinical Trials Involving Metronomic Chemotherapy

Patient Population	Drug treatment
Advanced, refractory melanoma; pilot study of 12 patients (completed)	Daily low-dose (500 mg) oral treosulfan and daily rofecoxib (Vioxx), 25 mg
Advanced, refractory prostate cancer; Phase II trial of 32 patients (completed)	Daily low-dose , oral cyclophosphamide (50 mg) and daily low-dose dexamethasone (1 mg)
Advanced, refractory breast cancer; Phase II trial of 64 patients (completed)	Daily low-dose, oral cyclophosphamide (50 mg) and oral low-dose methotrexate twice per week
Advanced or metastatic ovarian carcinoma (underway)	Daily low-dose cyclophosphamide (50 mg) plus bevacizumab, 10 mg/kg every 2 weeks
Advanced, metastatic breast cancer (underway)	Daily low-dose, oral cyclophosphamide (50 mg), oral low-dose methotrexate twice per week (10 mg) and bevacizumab 10 mg/kg every 2 weeks
Recurrent and Metastatic chemo-resistant squamous cell carcinoma of the head and neck (pilot study; completed)	Daily oral low-dose (2.5 mg) methotrexate and 400 mg celecoxib twice per day
Relapsed , refractory non-Hodgkins lymphoma (ongoing)	Oral low-dose (50 mg) cyclophosphamide and 400 mg celecoxib twice per day
Metastatic renal cell carcinoma (completed)	Daily oral low-dose (50 mg) cyclophosphamide and 400 mg celecoxib twice/day
Hepatocellular Carcinoma	Oral low-dose (50 mg) cyclophosphamide and 400 mg celecoxib twice per day
Refractory solid tumors in children and adults (completed)	Daily low-dose oral cyclophosphamide for 3 weeks followed by daily low-dose oral etoposide for 3 weeks, which is repeated chronically, combined with daily oral low-dose thalidomide and daily oral low-dose celecoxib
Pancreatic carcinoma	Oral low-dose (50 mg) cyclophosphamide and 400 mg celecoxib twice per day

Clinical Examples of Metronomic Rx

Disease

Drug

Lung cancer

Etoposide

Ovarian cancer

Taxane

Breast cancer

Taxane

Lymphoblastic leukemia

Methotrexate, 6 MP

Colon cancer and
Pancreatic cancer

5 FU

“Randomized, Controlled Trial Irinotecan plus Infusional, Bolus, or Oral Fluoropyrimidines in First-Line Treatment of Metastatic Colorectal Cancer: Results From the BICC-C Study”

C.S. Fuchs et al.

117 Patients Randomly Assigned



57 Arm A

60 Arm B

(FOLFIRI + bevacizumab)

(mFOLFOX6 + bevacizumab)



56 treated

59 treated

Results

FOLFIRI+ Bev

mFL + Bev

PFS

11.2 months

8.3 months

Overall Median

>25 months

19.2 months

At 12 months

87%

60%

“Early Results of Weekly Metronomic Dosing of Paclitaxel, Oxaliplatin, Leucovorin and 5Fu (POLF) in the Treatment of Metastatic Pancreatic Cancer” B.M. Chue et al.

Results

50% Reduction of CA 19-9	100% of Patients
Response Major	43% of Patients
Response Minor	57% of Patients
Survival Median	10.4 months

ASCO GI Symposium Jan 2007

Best Objective Tumor Response (WHO criteria) in Patients With Locally Advanced Unresectable Pancreas Cancer With Measurable Disease Treated With the Combination of Fluorouracil, Leucovorin, Mitomycin and Dipyridamole (N=47)

Outcome	No. of Patients	%
Complete response	2	4
Partial response	10*	26
Stable disease/no response	15	32
Disease progression	7	15
Inadequate assessment	13	28

*Unconfirmed in five patients

“Phase II Trial of Infusional Fluorouracil, Leucovorin, Mitomycin and Dipyridamole in Locally Advanced Unresectable Pancreatic Adenocarcinoma: SWOG S9700”

W.H. Isacoff et al.

Results

Survival

% Alive

At 1 Year

54

At 2 Years

16

Median os

13.8 months

Cooperative Group Trials in Patients with Localized Pancreatic Cancer Since 1979

Study	Treatment	Median Survival
GITSG	60 Gy alone	22.9 weeks
	40 Gy + 5 Fu	36.5 weeks
	60 Gy + 5 Fu	49.4 weeks
GITSG	60 Gy + 5 Fu	37.0 weeks
	40 Gy + Adriamycin	33.0 weeks
GITSG	54 Gy + 5 Fu then SMF	42.0 weeks
ECOG	40 Gy + 5 Fu	8.3 months
GERCOL	FU/Leucovorin/Gem Or Gem/Ox followed by 55 Gy +FU	11.4 months
NCCTG	50.4 Gy + Gemcitabine And Cisplatin twice weekly Followed by Gemcitabine	10.2 months
RTOG	5.4 Gy + weekly paclitaxel	11.0 months
SWOGS 9700	5 Fu(Ci)/LV/Mito-C/D	13.8 months