



Chula
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Metronomic Chemotherapy in Pediatric Oncology

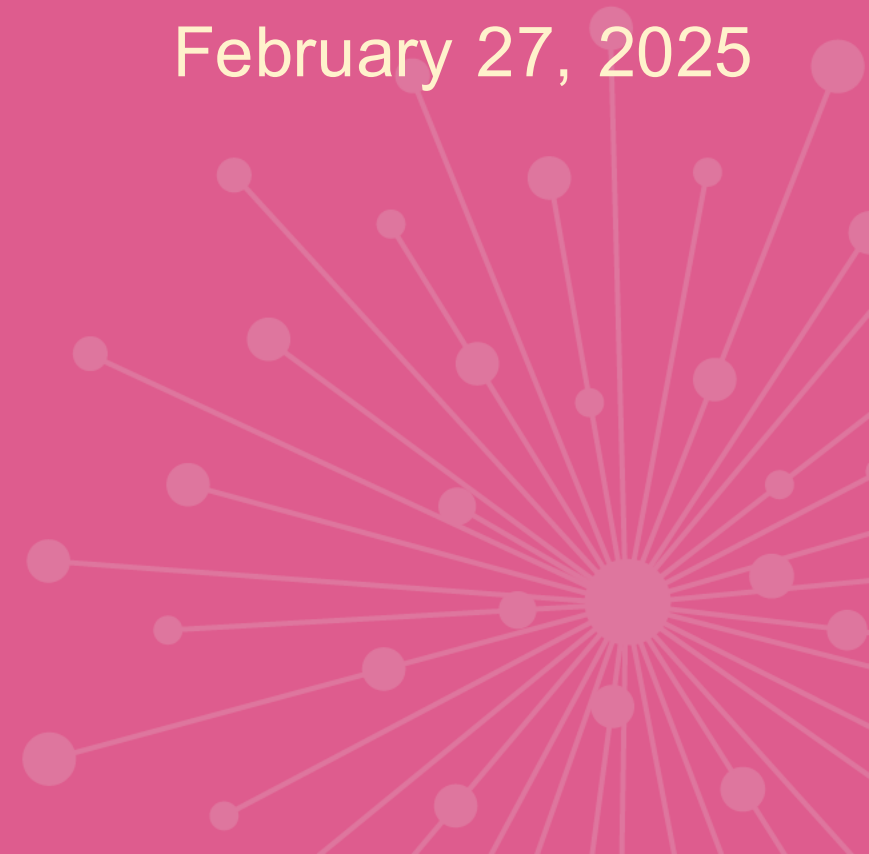
February 27, 2025

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Department of Pediatrics, Faculty of Medicine

Chulalongkorn University



Metronomic chemotherapy in pediatric oncology – *Raising an unwanted child?*



INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
HONOLULU, HAWAII, USA | OCTOBER 17-20, 2024

**56TH CONGRESS OF THE
INTERNATIONAL SOCIETY OF
PAEDIATRIC ONCOLOGY
HONOLULU, HAWAII, USA
OCTOBER 17-20, 2024**

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Pediatric Oncology Department, University Hospital
Brno, Masaryk University, Faculty of Medicine
Czech Republic, EU



In conjunction with:



Masaryk University
Faculty of Medicine



Chemotherapy and Its Beginning

SCIENCE

Vol. 103, No. 2675

Friday, April 5, 1946

The Biological Actions and Therapeutic Applications of the B-Chloroethyl Amines and Sulfides

Alfred Gilman, Major, and Frederick S. Philips, 1st Lieutenant, SnC, AUS
Pharmacology Section, Medical Division, CWS, Edgewood Arsenal, Maryland

Science 103: 409-436, 1946

The fact that agents classified as "confidential" were involved in the above studies has heretofore precluded the possibility of presenting the results in the open literature. (Page 409)

The first clinical trial of the nitrogen mustards (65) was conducted on a group of six patients in the terminal stages of various neoplastic diseases. In two cases of lymphosarcoma in which X-ray therapy had been discontinued, a rapid dissolution of large tumor masses followed a course of injections. The results were sufficiently encouraging to warrant further clinical experimentation. To date approximately 150 patients have been treated by several groups of investigators (66-68). (Page 414)

Chemistry Called Newest Weapon in Cancer Battle

"Chemistry" is the newest weapon in science's arsenal in the battle against cancer, says Dr. Sidney Farber, 51-year-old world-famed cancer authority, today visiting the University of California's San Francisco Medical Center.

Farber, scientific director of Harvard University's Children's Cancer Research Foundation, told a group of Bay Area reporters yesterday that use of chemicals to combat cancer presently plays the role of "last resort."

"Surgery and radiology are still the most effective treatments for cancer," Farber stressed. "After that, or in cases such as leukemia where radiation is ineffective, chemicals are used on humans."

The use of chemicals for cancer is a new field, Farber explained. The recent discovery of a family of chemical compounds known as dihydrotriazines by Farber and the Harvard Medical school staff has greatly aided in cancer fighting research.

EXPLAINS REACTION

Farber explained in general terms how the 75 compounds making up the dihydrotriazine family effect cancer.

"Essentially, these compounds, in theory, destroy the chemical processes in the cancer cell that are necessary for cell division," he said.

The use of chemicals—referred to as chemotherapy—actually started at the Harvard Medical Center about seven years ago, Farber stated.

"It is yet too early to be able to make any sort of a statement that this approach is even the answer to any one of the 250 forms of cancer," he explained.

"Further," he continued, "chemotherapy is not ready for use outside of the research laboratory."

The scientist said that to date



Dr. Sidney Farber, director of Harvard University's Children's Cancer Research Foundation, who is visiting in the Bay area.

the great bulk of research has been confined to lower animals—mostly mice—and that the technique involves the use of combinations of chemicals.

OBJECTIVE TOLD

The hope for a single chemical that will strike at a key process in the cancer cell system of living is one Farber and his associates continually seek, he said.

Farber claimed that experiments to date have shown that cancer in mice has been arrested for various periods through the chemical therapy process.

"Fragments of information we needed when we started this study seven years ago, are beginning to come to light now," Farber explained. "We do not know enough about the chemical processes that take place inside, and are necessary for the

life of the cancer cell," he continued.

The world-famed scientist shares his fame with famous brothers, three of whom are residents of the Bay area.

The eldest of the Farbers is 55-year-old Dr. Seymour Farber, who is a professor of medicine at the University of California and graduated from the same college from which Dr. Sidney Farber graduated.

Next is Dr. Jason Farber, a prominent Oakland specialist and a former member of the Stanford Medical Center's teaching staff.

WINS RECOGNITION

Dr. Seymour Farber gained national fame with his sputum test for cancer of the lung. He is presently a member of the University of California's medical center staff.

The youngest Farber is Eugene Farber, 30, who is a Stanford University Center's department of pathology.

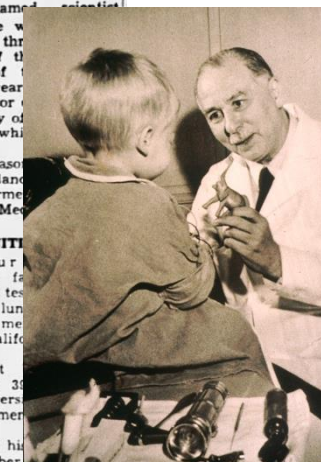
In addition to his duties as director of research at the Children's Hospital, and as a consultant for all research involving children, Dr. Farber is also a consultant for the National Cancer Institute.

Farber will give a series of lectures on cancer discovery in the Bay area doctors at the Medical Center through May 15.

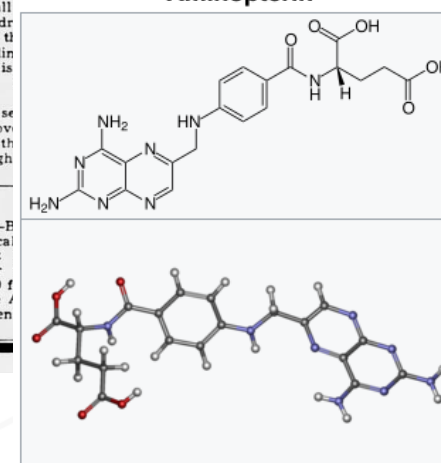
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Berkeley Building

BERKELEY, Jan. 8.—Permits for the week-long construction valued at \$100,000 were issued for the building of a new dwelling costing \$10,000 for Wong at 1350 Stannage. The remainder represents pairs and alterations.

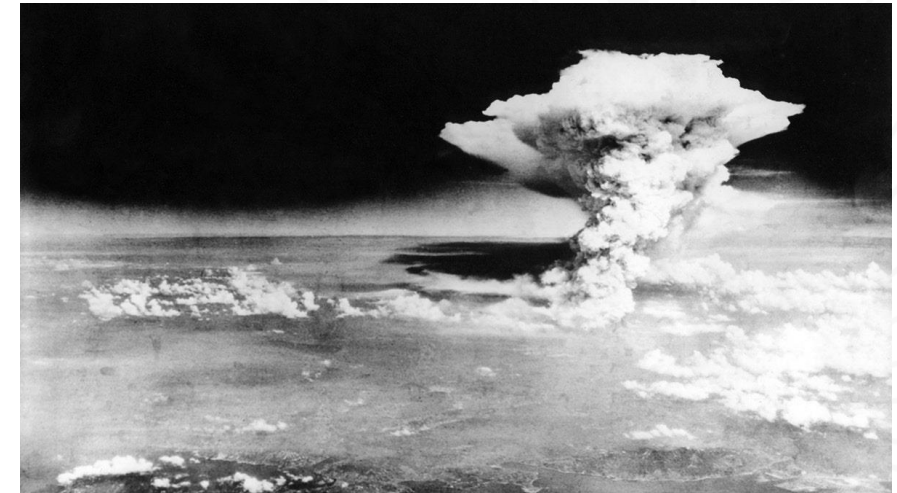
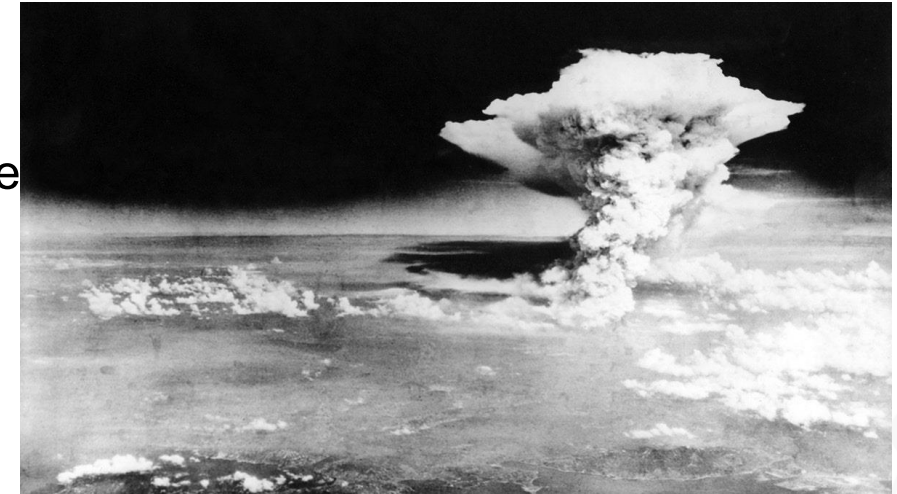


Aminopterin

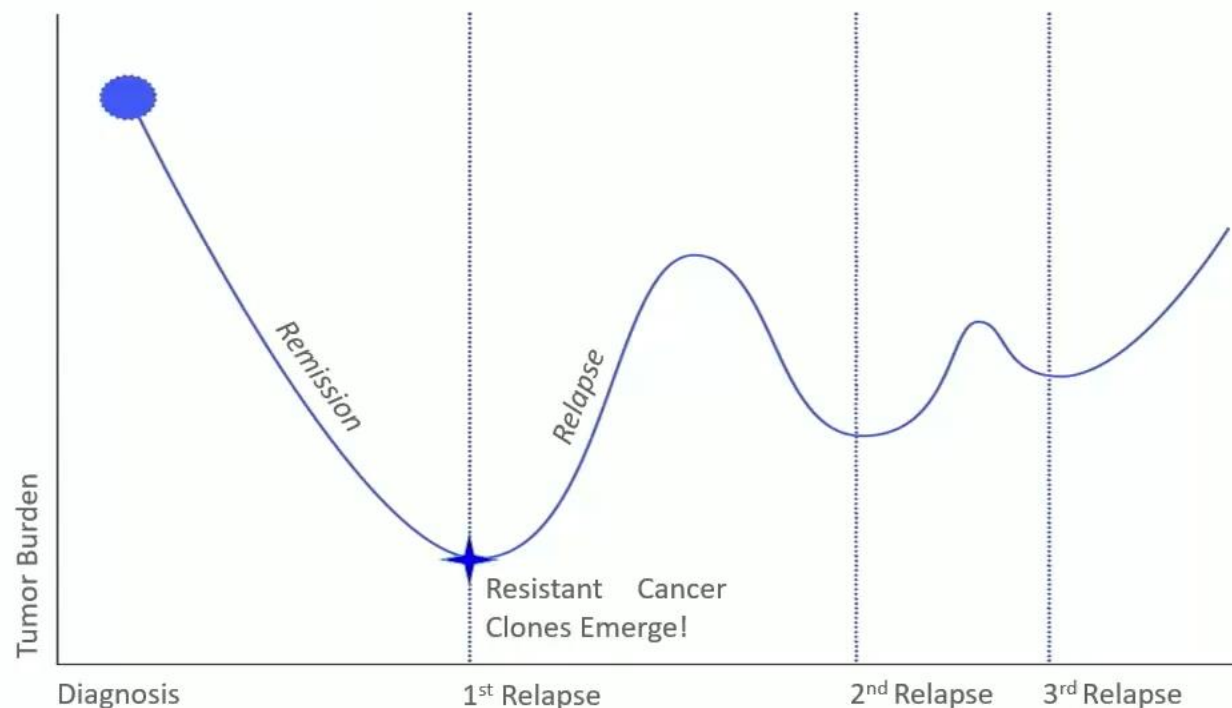


Maximum Tolerated Dose (MTD) based chemotherapy

- High-Dose Strategy
 - To kill the maximum cancer cells using the highest tolerable dose
- Dose-Limiting Toxicity (DLT)
 - Determined in early-phase clinical trials
- Cytotoxic Effect
- Fixed dose cycles
 - Repeating cycles to allow for recovery from side effects.
- Common in standard pediatric oncology protocols.



Traditional MTD based Cancer Therapy



Is characterized by cycles of **remission** and **relapse**, with **poor quality of life** for the patient and the family.

Lot of such therapies lack durable responses, despite good initial response.

For too many cancers, too many patients still die within first few years of diagnosis...



Metronomic Chemotherapy

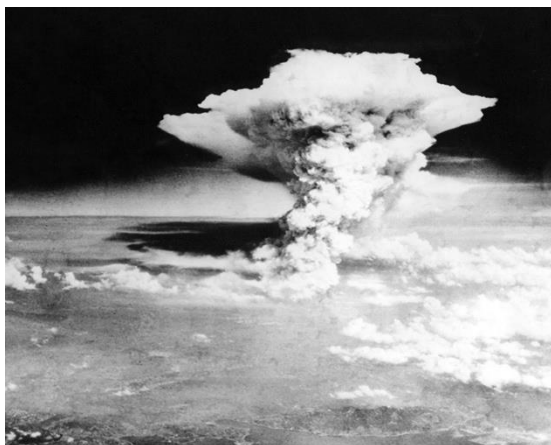


Metronomic Chemotherapy

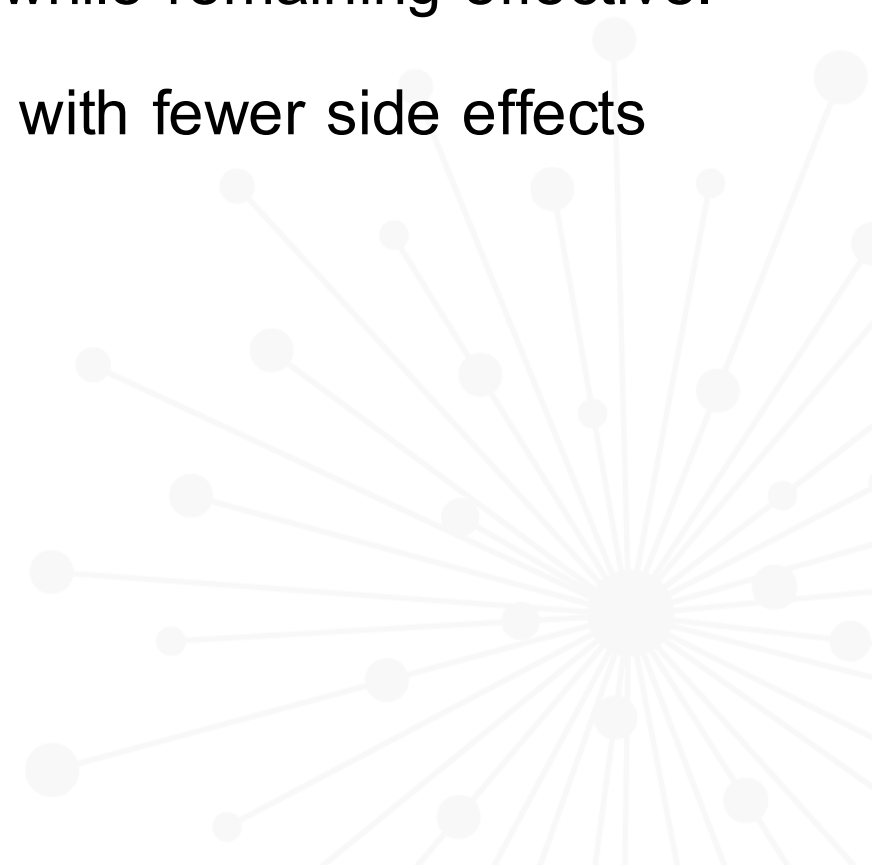


- Frequent, regular administration of chemotherapeutic drugs
- Maintains a low but active drug concentration over long periods
- It aims to reduce excessive toxicities while remaining effective.
- Potential benefits in cancer treatment with fewer side effects

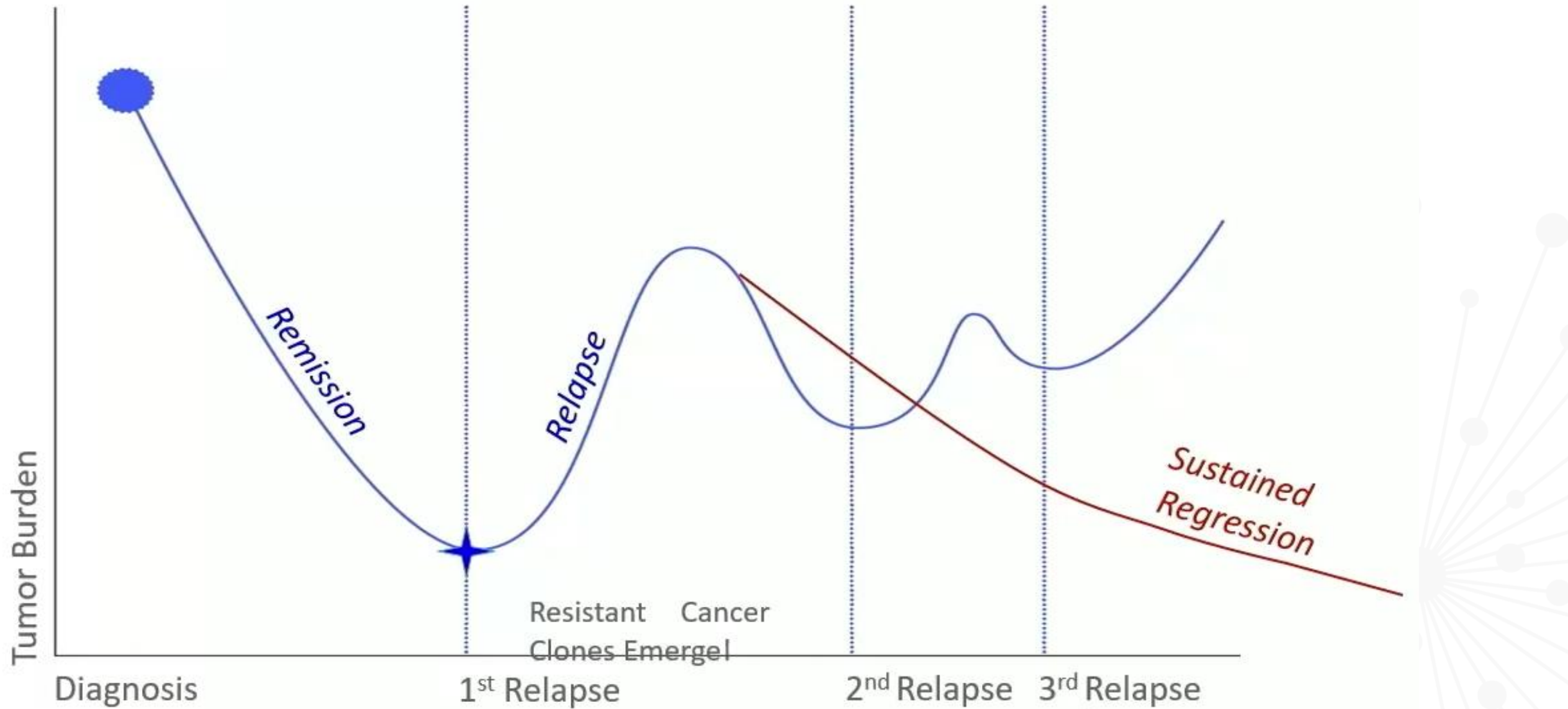
MTD



Metronomic Chemotherapy

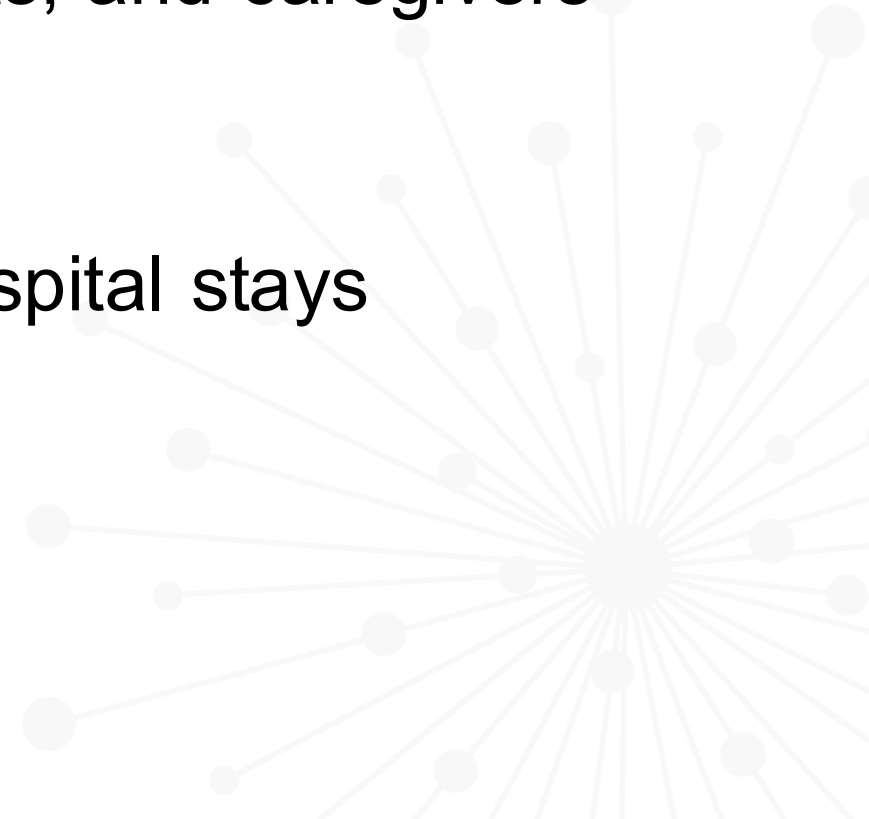


Metronomic Chemotherapy (MC)



Advantages of Metronomic Chemotherapy

- Low toxicity, making it safer for long-term use
- Oral administration allows for easier at-home treatment
- Improves quality of life for children, parents, and caregivers
- Reduces the economic burden
- Feasible for prolonged therapy without hospital stays



Mechanism of Metronomic Chemotherapy

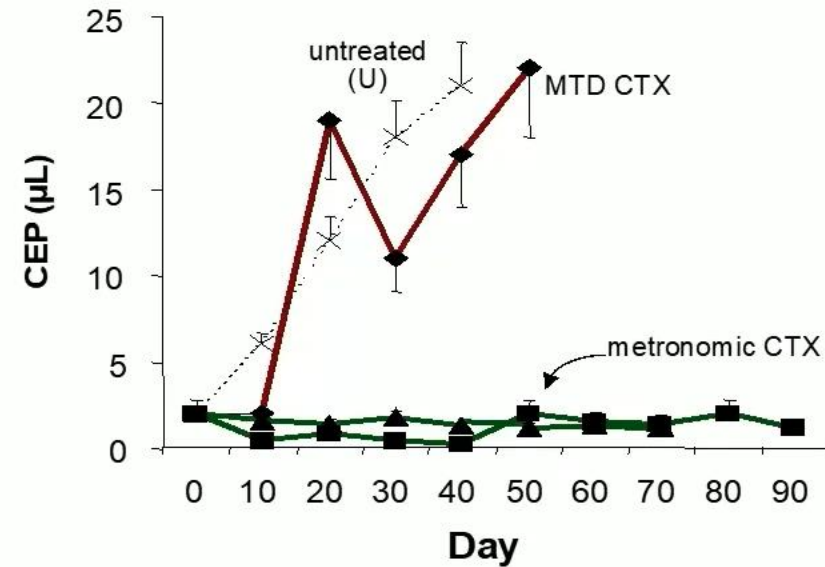
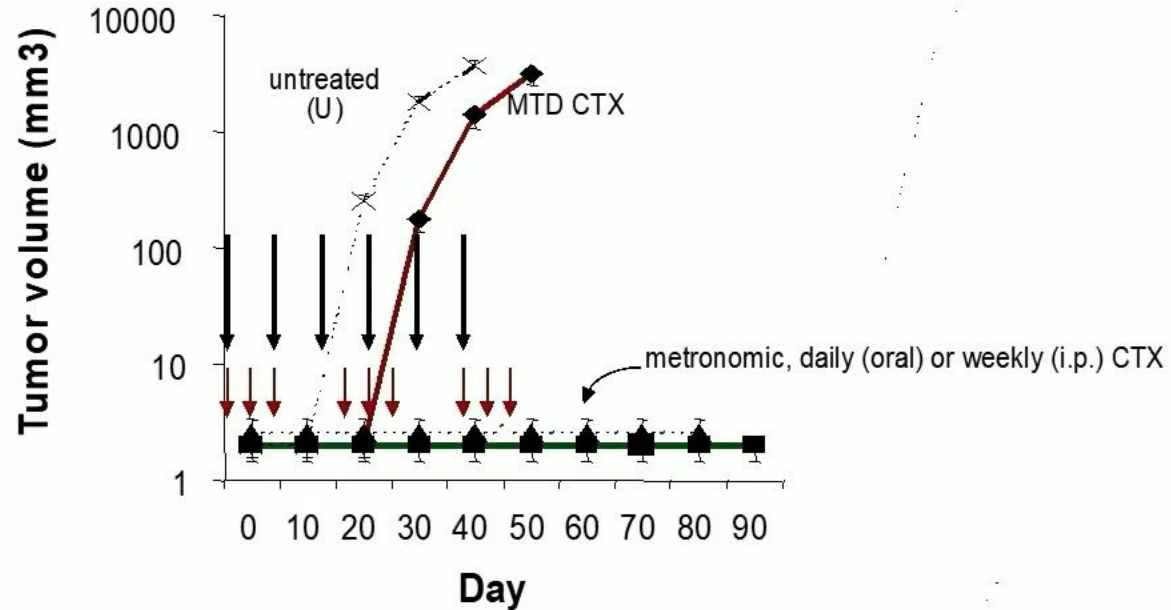


The Mechanisms of Action of Metronomic Chemotherapy (1)

Animal Models

NOD/SCID mice injected cells derived from an EBV+ Burkitt's lymphoma

Treated with CTX at the **MTD** or a **Metronomic low-dose** scheduled dose



Cancer Research, 63: 4342-4346, 2003

Maximum tolerable dose and low-dose metronomic chemotherapy have opposite effects on the mobilization and viability of circulating endothelial progenitor cells **F. Bertolini, S. Paul, P. Mancuso, S. Monestiroli, A. Gobbi, Y. Shaked, and R.S. Kerbel**



The Mechanisms of Action of Metronomic Chemotherapy (2)

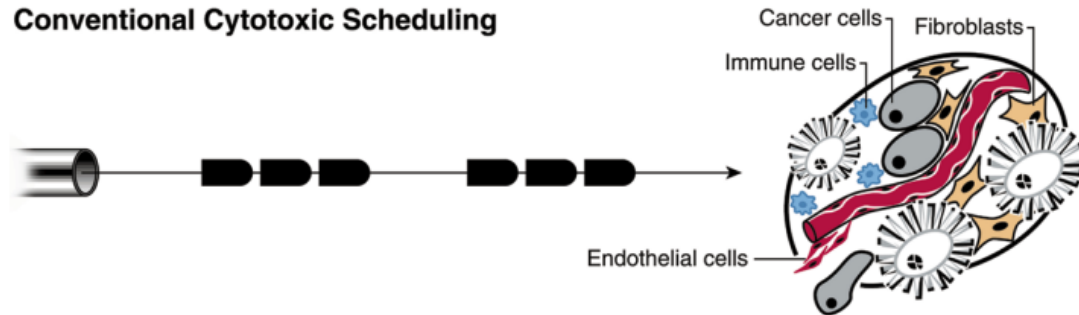
JCI The Journal of Clinical Investigation

Less is more, regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice

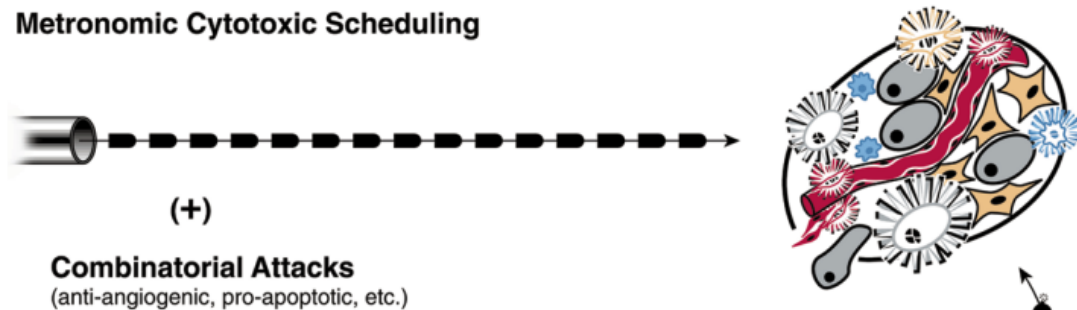
Douglas Hanahan, ... , Gabriele Bergers, Emily Bergsland

J Clin Invest. 2000;105(8):1045-1047. <https://doi.org/10.1172/JCI9872>.

Conventional Cytotoxic Scheduling



Metronomic Cytotoxic Scheduling



Combinatorial Attacks

(anti-angiogenic, pro-apoptotic, etc.)

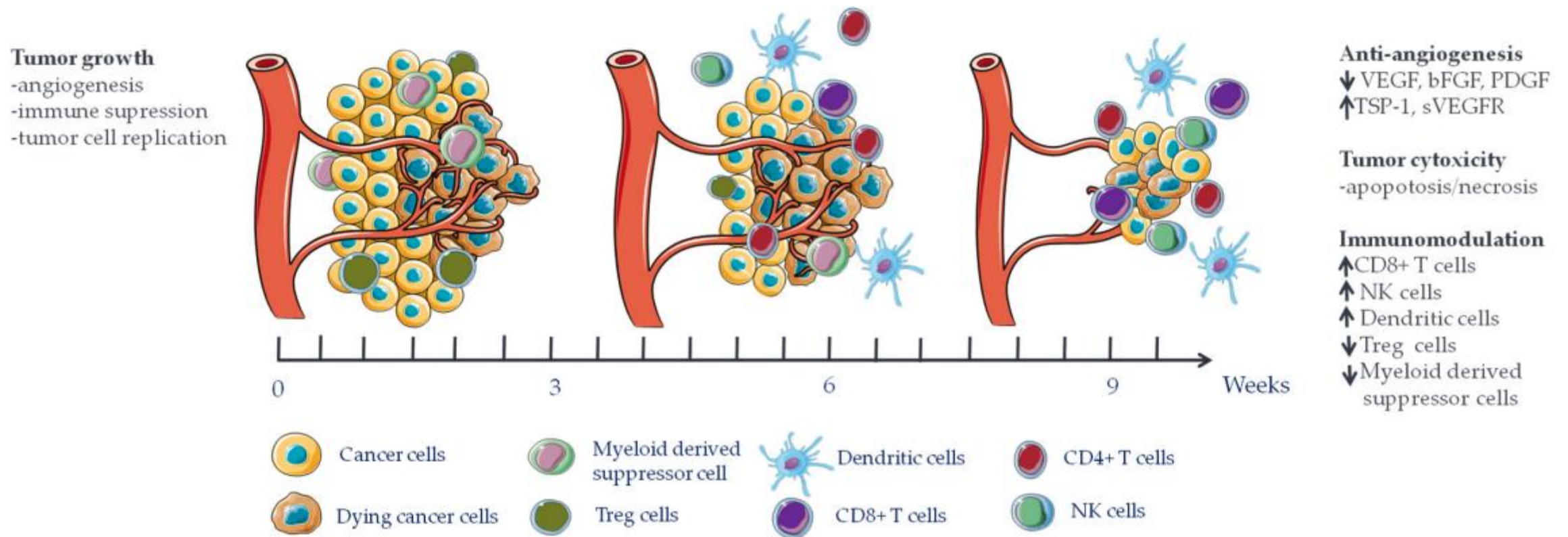


- Inhibition of endothelial cell proliferation
- Selective inhibition of endothelial cell migration
- Increased thrombospondin-1 a natural angiogenesis inhibitor.
- Indirect tumor destruction
 - **Causes hypoxia and nutrient starvation, which can kill both drug-naïve and drug-resistant cancer cells.**

Nature Reviews Cancer volume 4, pages423–436 (2004)

Nature Reviews Clinical Oncology volume 7, pages455–465 (2010)

The Mechanisms of Action of Metronomic Chemotherapy (3)



1. **Reduction of immunosuppressive cells:** Depletes Regulatory T Cells (Tregs)

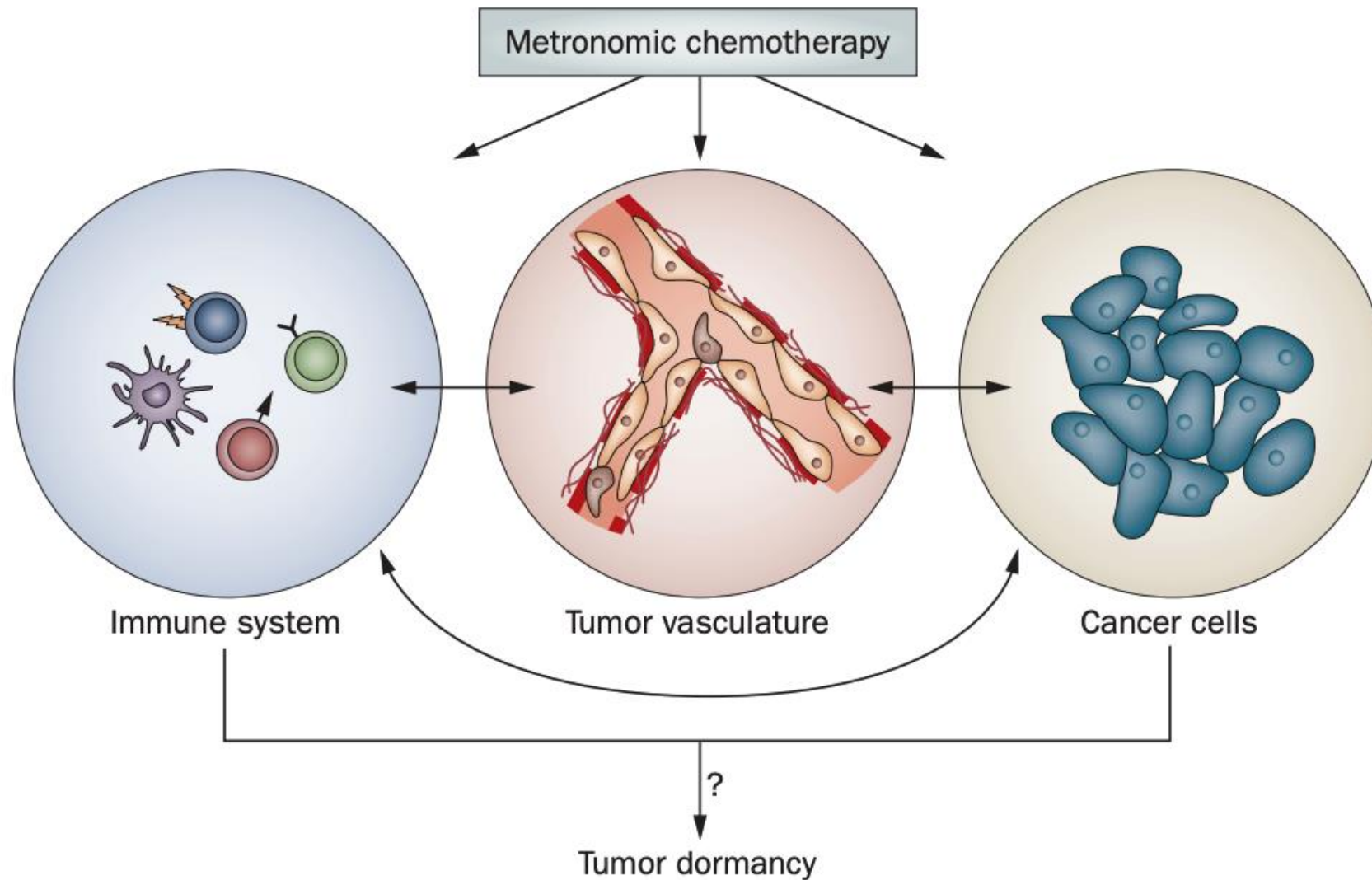
2. **Activation of effector immune cells:**

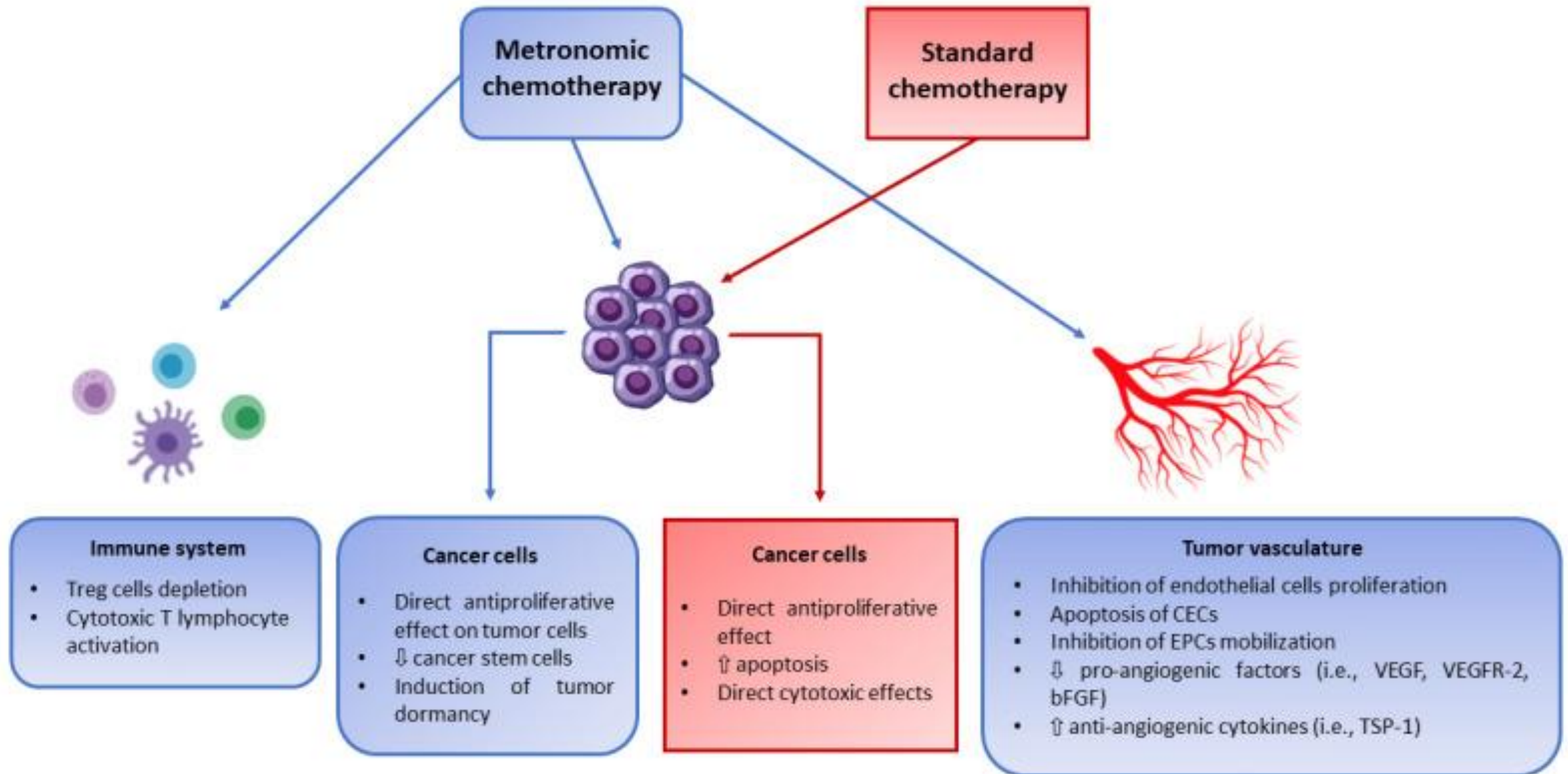
- Enhances cytotoxic T-cell function:
- Increases natural killer (NK) cell activity:

Nature Reviews Cancer volume 4, pages423–436 (2004)

Nature Reviews Clinical Oncology volume 7, pages455–465 (2010)

The Mechanisms of Action of Metronomic Chemotherapy (4)





Clinical Use of Metronomic Chemotherapy in Pediatric Oncology



- **Palliative treatment in advanced or refractory disease**
 - Relapsed Ewing sarcoma, rhabdomyosarcoma, osteosarcoma, neuroblastoma
 - Common regimens: low-dose cyclophosphamide, etoposide, vinorelbine, valproic acid, vinblastine, methotrexate
 - Disease stabilization with manageable toxicity
- **Maintenance therapy after standard treatment to prolongs remission, delays relapse**



Metronomic Chemotherapy in ThaiPOG current protocol (1)

Page 6 of 7

Patient's name _____ Age _____ Sex _____
Hospital _____ HN _____ BW _____ Ht _____ BSA _____

Phase V: SR-MAINTENANCE (12 weeks/cycle)

Start Maintenance cycle I on Day 57 of DI or when ANC $\geq 750/\mu\text{L}$ and Plt $\geq 75,000/\mu\text{L}$, whichever occurs later.

Repeat maintenance chemotherapy for the total duration of 20 months (female) and 32 months (male).

Date start maintenance _____ END of therapy date: _____

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
Day	1	8	15	22	29	36	43	50	57	64	71	78	85
Medication:													
VCR _____ mg IV	V				V				V				
PRED _____ mg po BID	PPPPP				PPPPP				PPPPP				
6-MP _____ mg PO daily													
MTX _____ mg PO	M	M	M	M	M	M	M	M	M	M	M	M	
IT-MTX _____ mg	T												
Investigation:													
CBC/diff	+				+				+				
CSF cell count/ cytopsin	+												
BUN, Cr, TB, DB, AST, ALT	+												
Drug	Dosage												Days
Prednisolone (PRED)	20 mg/m ² /dose PO BID												Days 1-5, 29-33, 57-61
Vincristine (VCR)	1.5 mg/m ² /dose IV push (Max 2 mg)												Day 1, 29, 57
6-MP	50 mg/m ² /dose PO daily (hs)												Day 1-84
Methotrexate (MTX)	20 mg/m ² /dose PO weekly												Day 1 then weekly until Day 78
Intrathecal Methotrexate(IT MTX)	Age (yrs)												Dose
	1-1.99												8 mg
	2-2.99												10 mg
	3-8.99												12 mg
	≥ 9 (but <30 kg)												12 mg
	≥ 9												15 mg

Note:

Maintenance with 13 Cis-retinoic acid

Given dose/day	Drug	Dosage
.....mg	13-cis-retinoic acid	80 mg/m ² /dose PO BID (total 160 mg/m ² /day)

Cycle	Cycle week	Treatment	Date given	Remarks
1	1-2	13-cis-retinoic acid		NSE and/or VMA
	3-4	Off		
2	5-6	13-cis-retinoic acid		
	7-8	Off		
3	9-10	13-cis-retinoic acid		NSE and/or VMA
	11-12	Off		
4	13-14	13-cis-retinoic acid		
	15-16	Off		
5	17-18	13-cis-retinoic acid		NSE and/or VMA
	19-20	Off		
6	21-22	13-cis-retinoic acid		
	23-24	Off		
7	25-26	13-cis-retinoic acid		NSE and/or VMA
	27-28	Off		
8	29-30	13-cis-retinoic acid		
	31-32	Off		
9	33-34	13-cis-retinoic acid		NSE and/or VMA
	35-36	Off		
10	37-38	13-cis-retinoic acid		
	39-40	Off		
11	41-42	13-cis-retinoic acid		NSE and/or VMA
	43-44	Off		
12	45-46	13-cis-retinoic acid		
	47-48	Off		

Metronomic Chemotherapy in ThaiPOG current protocol (2)

Treatment protocol for Low Grade Glioma [ThaiPOG-LGG-1801]

Protocol name ThaiPOG-LGG-1801

Protocol for Low grade glioma

Reference J Clin Oncol. 2016 Oct 10;34(29):3537-3543

Open Date April 2018

Patient's name..... Sex..... HN.....

Age (yy/mm/dd)..... BW.....kg Ht.....cm BSA.....m²

Eligible criteria

- ☐ Chemotherapy naïve symptomatic low grade glioma with tissue diagnosis
- ☐ Pathologically confirmed low grade glioma with tumor progression after initial observation
- ☐ Chemotherapy naïve low grade glioma with incomplete surgical resection (<95% tumor removal or residual tumor > 1.5 cm²) associated with
 - risk of neurological impairment with progression OR
 - radiographic evidence of tumor progression
- ☐ Radiologically typical optic pathway tumor with or without surgical resection
- ☐ NF 1 with radiographically progressive optic pathway tumor without tissue diagnosis

Dose and schedule

Drug	Dose	Desired dose	Schedule
Vinblastine	_____ mg	6 mg/m ² /dose IV push (Max 10 mg/dose) or 0.2 mg/kg/dose if BSA < 0.6 m ²	Weekly for 70 weeks

- Ondansetron can be given 5 mg/m² IV push prn for N/V (max 8 mg/dose)
- CBC weekly, result need to be checked before giving each chemotherapy in the first 6 weeks, after the first 6 weeks, dosage can be adjusted based on the CBC result of the prior week
- Dose adjustment
 - If ANC > 750/mm³ and platelet count > 75,000/mm³ continue same dose
 - If ANC 500-750/mm³ and platelet count 50,000-75,000/mm³, reduce dose to 5 mg/m² or by 20% of the previous prescribed dose
 - If ANC < 500/mm³ or platelet count < 50,000/mm³, withhold vinblastine until blood count recover (ANC >750/mm³ and platelet >75,000/mm³), then restart at 5 mg/m²/dose
- Once the drug dose has been decreased there will be no drug dose escalation.
- LFT, BUN, Cr q 6 weeks
- Chemotherapy will be given as a weekly schedule (every 7 ± 2 days), with total duration of treatment 70 weeks

Patient's name..... Sex..... HN.....

Age (yy/mm/dd)..... BW.....kg Ht.....cm BSA.....m²

Date start treatment

Week	Date given	Vinblastine		ANC	Platelet	Remark
		Desired dose (mg/m ²)	Actual dose (mg)			
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						

Patient's name..... Sex..... HN.....

Current agents use for Metronomic Chemotherapy in Pediatric Oncology

Drug	Common dose range	Common dose frequency
Cyclophosphamide	25–50 mg/m ² or 2.5 mg/kg	Days 1–21, followed by a 1-week period of rest
Etoposide	25–50 mg/m ²	Days 1–21, followed by a 1-week period of rest
Celecoxib	100 mg, divided bid (<20 kg)	Daily
	200 mg, divided bid (20–50 kg)	
	400 mg, divided bid (>50 kg)	
Vinblastine	3 mg/m ²	Weekly
Methotrexate	10–15 mg/m ²	Twice a week for 3–4 weeks
Vincristine	1.5 mg/m ²	Weekly for 4 weeks
Vinorelbine	25–60 mg/m ²	Weekly for 3 weeks
Topotecan	1.4 or 0.22 mg/m ²	Days 1–5 or daily
Thalidomide	3–24 mg/kg	Days 1–21 or daily
Fenofibrate	90–100 mg/m ²	Daily
Valproic acid	20 mg/kg	Daily
Isotretinoin	100 mg/m ²	Days 1–14, followed by a 2-week period of rest
Temozolomide	30 mg/m ²	Daily
Pazopanib	160 mg/m ²	Daily since day 2
Zoledronic acid	2.4 mg/m ²	Day 1
Cholecalciferol	300 kU/m ²	Day 1
Vitamin D3	1500 U/m ²	Days 1–78
Bevacizumab	10 mg/kg	Every 14 days
Nivolumab	3 mg/kg/dose	Days 1, 15

Cyclophosphamide (CTX)

- Low-dose CTX inhibits endothelial proliferation and downregulates VEGF.
- Selectively depletes regulatory T cells (Tregs), enhancing cytotoxic T-cell and NK-cell activity.
- Improves antigen presentation by dendritic cells.
- Direct Cytotoxicity

Etoposide (VP-16)

- Inhibits topoisomerase II, preventing DNA repair and replication in cancer cells.
- Induces apoptosis in tumor cells at low, continuous doses.
- Disrupts tumor vasculature, reducing oxygen and nutrient supply.
- Reduces levels of VEGF and bFGF, key angiogenic factors.
- Increases the activity of cytotoxic T lymphocytes (CTLs).
- Works synergistically with low-dose CTX to reduce immunosuppressive Tregs

Oral Etoposide for Refractory and Relapsed Neuroblastoma

Authors: [Brian H. Kushner](#), [Kim Kramer](#), and [Nai-Kong V. Cheung](#) | [AUTHORS INFO & AFFILIATIONS](#)

Publication: Journal of Clinical Oncology • [Volume 17, Number 10](#) • <https://doi.org/10.1200/JCO.1999.17.10.3221>

- Oral etoposide (50 mg/m², 21 consecutive days)
- 20 neuroblastoma children
- Low-dose oral etoposide showed antineoplastic activity in pediatric neuroblastoma patients (9/11 patients) with tumor burden after high-dose chemotherapy.
- Toxicity & Tolerability:
 - Minimal myelosuppression (no neutropenia or need for transfusions).
 - Little immunosuppression
 - No major organ toxicity

Metro-SMHOP 01: Metronomics combination with cyclophosphamide-etoposide and valproic acid for refractory and relapsing pediatric malignancies

Received: 5 November 2019

Revised: 5 May 2020

Accepted: 26 May 2020

DOI: 10.1002/pbc.28508

GLOBAL ONCOLOGY: RESEARCH ARTICLE

Pediatric
Blood &
Cancer

SOCIÉTÉ INTERNATIONALE
D'ONCOLOGIE PÉDIATRIQUE
SIO
INTERNATIONAL SOCIETY
OF PEDIATRIC ONCOLOGY

aspho
The American Society of
Pediatric Hematology/Oncology

WILEY

28-day cycles with a 1-week break after Day 21 for Cyclophosphamide & Etoposide

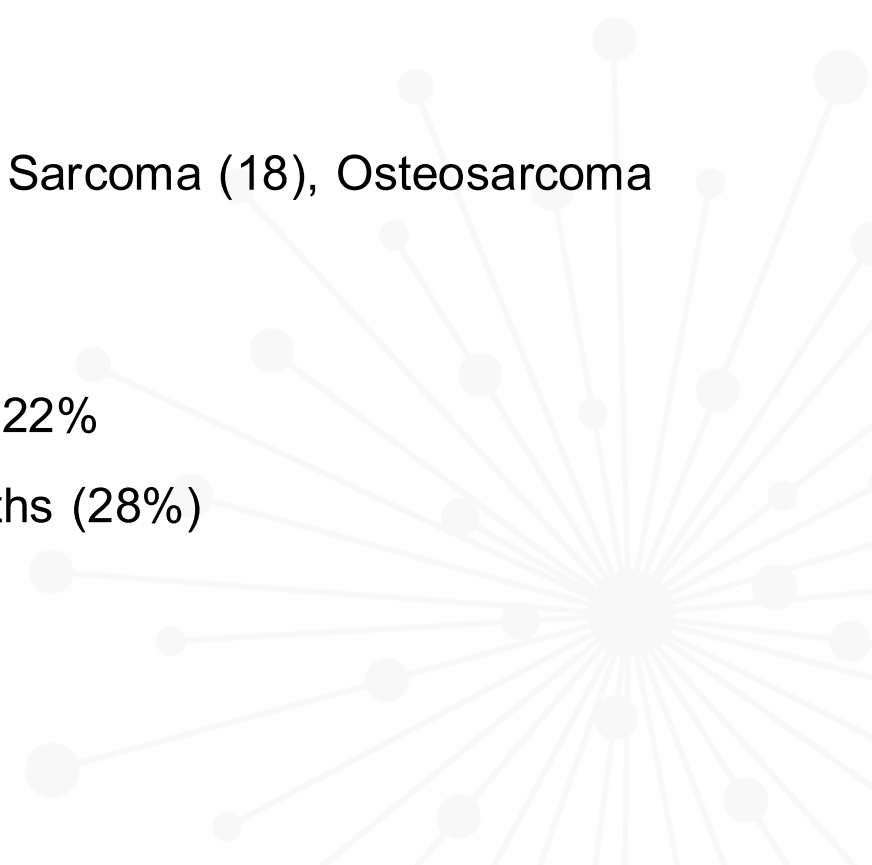
- Cyclophosphamide 30 mg/m² (Days 1–21, daily oral)
- Etoposide 25 mg/m² (Days 1–21, daily oral)
- Valproic Acid 20 mg/kg (Days 1–28, daily oral)

Results:

- 98 children (median age: 8 years) with Neuroblastoma (24), Ewing Sarcoma (18), Osteosarcoma (14), Rhabdomyosarcoma (14), Miscellaneous tumors (28)
- Median treatment cycles received 6 (range 1–18)
- 1-year Progression-Free Survival 19% with 1-year Overall Survival 22%
- Tumor response: Complete (3%), Partial (11%), Stable for >6 months (28%)

Conclusions:

- Well-tolerated three-drug metronomic regimen
- Associated with tumor response and prolonged stabilization



Metro-SMHOP 01: Metronomics combination with cyclophosphamide-etoposide and valproic acid for refractory and relapsing pediatric malignancies

Received: 5 November 2019 | Revised: 5 May 2020 | Accepted: 26 May 2020
DOI: 10.1002/pbc.28508

GLOBAL ONCOLOGY: RESEARCH ARTICLE



TABLE 2 Outcomes by tumors types and number of previous lines of chemotherapy

Stratum	N	Treatment lines prior to MC	CR	Response PR	SD	PD
Neuroblastome	24	1 (1-2)	-	1	4	19
Ewing sarcoma	18	1 (1-2)	1	4	3	10
Osteosarcoma	14	1	-	-	-	14
Rhabdomyosarcoma	14	1(1-3)	1	2	4	7
MGT	4	1	-	-	1	3
Hodgkin lymphoma	4	1 (1-3)	-	1	1	2
Wilms tumor	4	1 (1-2)	-	-	-	4

CR, complete response; MGT, malignant germ-cell tumors; PD, progressive disease, PR, partial response; SD, stable disease.



- Histone DeAcetylase (HDAC) Inhibition: increased acetylation of histones and non-histone proteins.
- Epigenetic reprogramming, reactivation of tumor suppressor genes, and inhibition of tumor growth.
- Anti-angiogenic effects: reduces VEGF expression and inhibits endothelial cell proliferation
- Immune Modulation: increasing MHC class I expression, improving tumor antigen presentation.
- Regulates T-cell activity and increases the cytotoxic effects of immune cells.
- Promotes differentiation of cancer cells, reducing stemness and promoting apoptosis

Synergistic Effects with Other Metronomic Agents:

- VPA enhances tumor cell sensitivity and reduces resistance with low-dose chemotherapy (e.g., cyclophosphamide, etoposide).

Semi-synthetic vinca alkaloid

- Enhances vascular normalization, improving drug delivery and immune infiltration.
- Reduces regulatory T cells (Tregs), restoring cytotoxic CD8+ T-cell activity.
- Stimulates natural killer (NK) cell function, enhancing tumor immune surveillance.
- Direct Tumor Cytotoxicity: Inhibits microtubule polymerization, disrupting mitotic spindle formation

Synergistic Potential with Other Metronomic Agents

- Vinorelbine + Cyclophosphamide: neuroblastoma, Ewing sarcoma, and rhabdomyosarcoma.
- Effective in low-grade gliomas and refractory brain tumors, often combined with bevacizumab.
- Oral vinorelbine (low-dose, frequent administration) offers a convenient option with reduced toxicity compared to conventional high-dose schedules.

- 117 patients (median age: 12 years)
- VNL 25 mg/m² IV (Days 1, 8, 15) + CPM 25 mg/m² orally (daily) in 28-day cycles
- Tumor response is assessed every two cycles.

Results

- Rhabdomyosarcoma (RMS) (n=50): ORR 36% (8% CR, 28% PR)
- Ewing's Sarcoma ORR 13%
- Non-RMS Soft Tissue Sarcoma & Neuroblastoma: ORR 6%
- No response in Osteosarcoma & Medulloblastoma
- Grade 3/4 Neutropenia (38%), Peripheral Neuropathy (3%), No hemorrhagic cystitis

Conclusion

- VNL + CPM showed promising efficacy in **RMS** with acceptable toxicity



Vinorelbine and continuous low-dose cyclophosphamide as maintenance chemotherapy in patients with high-risk rhabdomyosarcoma (RMS 2005): a multicentre, open-label, randomised, phase 3 trial

Gianni Bisogno, Gian Luca De Salvo, Christophe Bergeron, Soledad Gallego Melcón, Johannes H Merks, Anna Kelsey, Helene Martelli, Veronique Minard-Colin, Daniel Orbach, Heidi Glosli, Julia Chisholm, Michela Casanova, Ilaria Zanetti, Christine Devalck, Myriam Ben-Arush, Peter Mudry, Sima Ferman, Meriel Jenney*, Andrea Ferrari*, for the European paediatric Soft tissue sarcoma Study Group

Summary

Lancet Oncol 2019; 20: 1566–75
Published Online

Background For more than three decades, standard treatment for rhabdomyosarcoma in Europe has included 6 months of chemotherapy. The European paediatric Soft tissue sarcoma Study Group (EpSSG) aimed to investigate

the first randomized trial to show some improvement in survival with maintenance chemotherapy (six cycles of intravenous vinorelbine 25 mg/m² on days 1, 8, and 15, and daily oral cyclophosphamide 25 mg/m² on days 1–28)

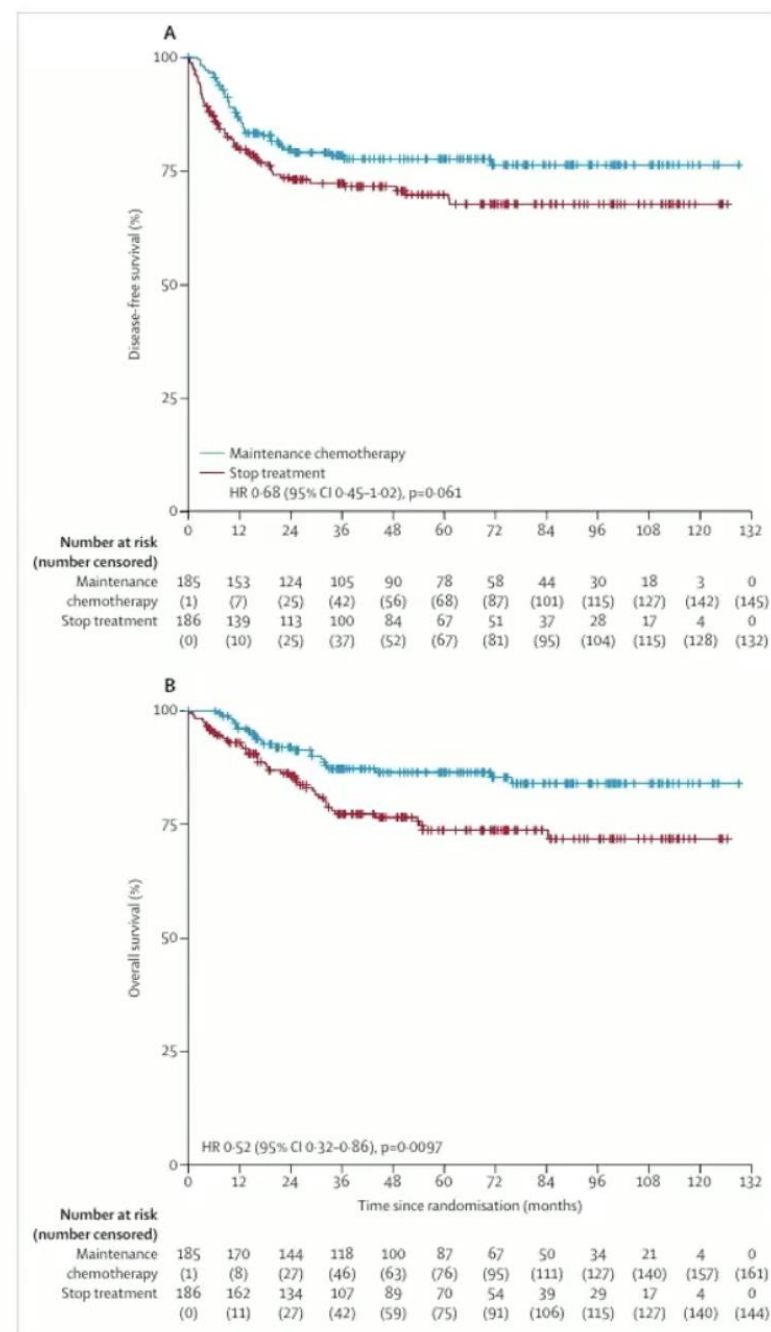


Figure 2: Kaplan-Meier estimates of disease-free survival (A) and overall survival (B)

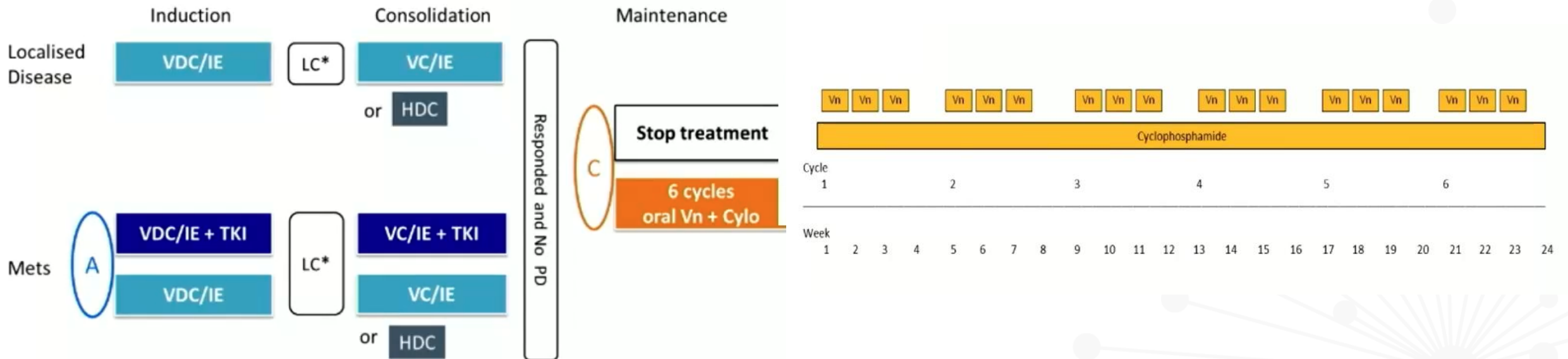
Vinorelbine and continuous low-dose cyclophosphamide as a Maintenance chemotherapy in patients with high-risk RMS

- A multicenter, open-label, randomized, phase 3 trial
- 371 patients HR-RMS after standard treatment
- Randomized (1:1) to stop/receive maintenance chemotherapy in **six 4-week cycles** of
 - Vinorelbine 25 mg/m² IV (Days 1, 8, 15)
 - Cyclophosphamide 25 mg/m² oral (Days 1–28)
- 5-year DFS: 77.6% (Maintenance) vs. 69.8% (No maintenance) (HR 0.68, p=0.061)
- **5-year OS: 86.5% (Maintenance) vs. 73.7% (No maintenance) (HR 0.52, p=0.0097)**
- Toxicity profile: grade 3–4 leucopenia (75%), neutropenia (82%), Anemia (10%), thrombocytopenia (1%), infection (31%)
- A new standard of care for HR-RMS in western pediatric oncology group

INTER-EWING-1 is an opened clinical trial



Can the addition of 6 cycles of maintenance chemotherapy of vinorelbine and cyclophosphamide improve patient outcomes? (Randomization C)



Mets = metastatic including lung mets; No PD= no progressive disease; TKI= Tyrosine Kinase Inhibitor; LC= Local control (* see separate schema for radiotherapy) HDC = High dose chemotherapy; A= randomisation A; C= randomisation C.

Administered at **low, frequent doses**, it exerts anti-angiogenic, immune-modulating, and direct cytotoxic effects while minimizing toxicity.

Synergistic Potential with Other Metronomic Agents

- **Vinblastine + Bevacizumab (anti-VEGF)**: Effective in **relapsed/refractory pediatric brain tumors (low-grade gliomas, ependymomas)**.
- **Vinblastine + Cyclophosphamide/Etoposide** is used in **pediatric sarcomas and neuroblastoma**.
- **Vinblastine + Valproic Acid (HDACi)**

Low-dose **weekly vinblastine** is well tolerated, with **minimal myelosuppression and neurotoxicity** compared to conventional dosing.



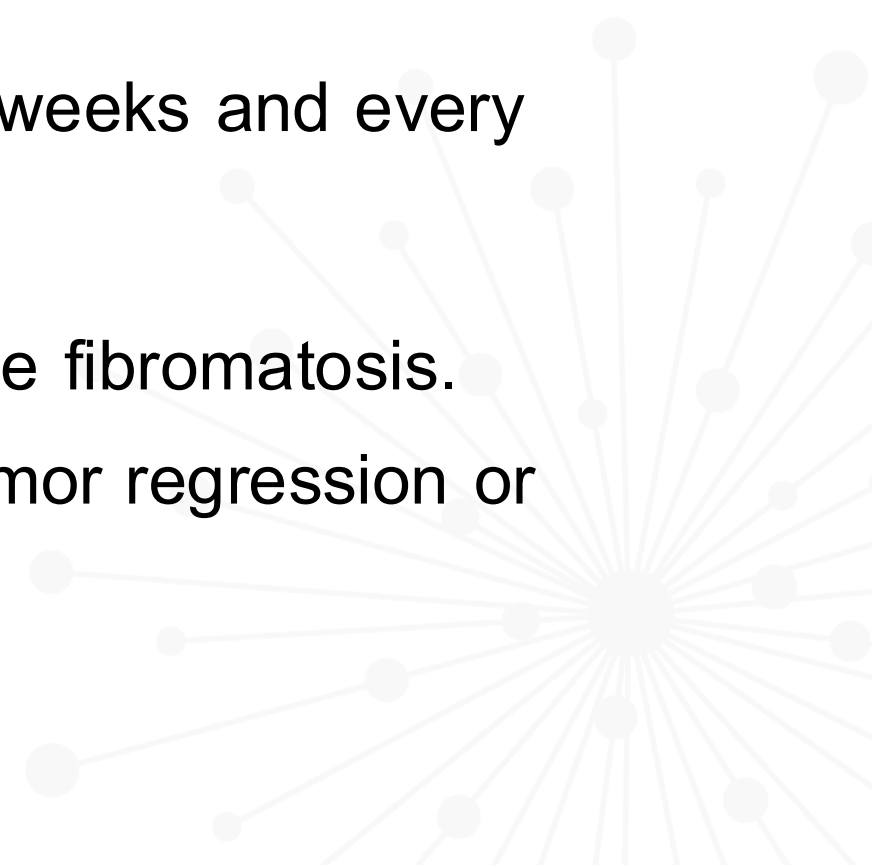
Vinblastine and Methotrexate for Desmoid Fibromatosis in Children: Results of a Pediatric Oncology Group Phase II Trial

Stephen X. Skapek, William S. Ferguson, Linda Granowetter, Meenakshi Devidas, Antonio R. Perez-Atayde, Louis P. Dehner, Fredric A. Hoffer, Roseanne Speights, Mark C. Gebhardt, Gary V. Dahl, and Holcombe E. Grier

VOLUME 25 • NUMBER 5 • FEBRUARY 10 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

- Vinblastine (5 mg/m² /dose) and Methotrexate (30 mg/m² / dose) were administered intravenously.
 - Vbl and Mtx were administered weekly for 26 weeks and every other week for 26 weeks.
 - It is well tolerated in children with desmoid-type fibromatosis. Furthermore, this combination can promote tumor regression or block tumor growth in most children.
- 

Sustained Survival Benefit in Recurrent Medulloblastoma by a Metronomic Antiangiogenic Regimen A Nonrandomized Controlled Trial

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IMPORTANCE Medulloblastoma recurrence in patients who have previously received irradiation has a dismal prognosis and lacks a standard salvage regimen.

OBJECTIVE To evaluate the response rate of pediatric patients with medulloblastoma recurrence using an antiangiogenic metronomic combinatorial approach (Medulloblastoma European Multitarget Metronomic Anti-Angiogenic Trial [MEMMAT]).

DESIGN, SETTING, AND PARTICIPANTS This phase 2, investigator-initiated, multicenter nonrandomized controlled trial assessed 40 patients with relapsed or refractory medulloblastoma without a ventriculoperitoneal shunt who were younger than 20 years at original diagnosis. Patients were enrolled between April 1, 2014, and March 31, 2021.

INTERVENTIONS Treatment consisted of daily oral thalidomide, fenofibrate, celecoxib, and alternating 21-day cycles of low-dose (metronomic) oral etoposide and cyclophosphamide, supplemented by intravenous bevacizumab and intraventricular therapy consisting of alternating etoposide and cytarabine.

- Treatment consisted of
 - Daily oral thalidomide, fenofibrate, celecoxib
 - Alternating 21-day cycles of oral etoposide and cyclophosphamide
 - Intravenous bevacizumab
 - Intraventricular therapy via an Ommaya reservoir consisting of alternating etoposide and cytarabine.

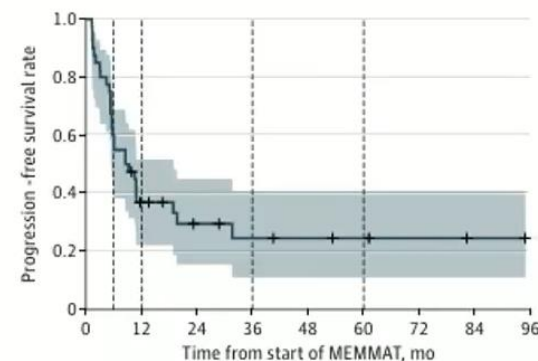
Sustained Survival Benefit in Recurrent Medulloblastoma by a Metronomic Antiangiogenic Regimen

A Nonrandomized Controlled Trial

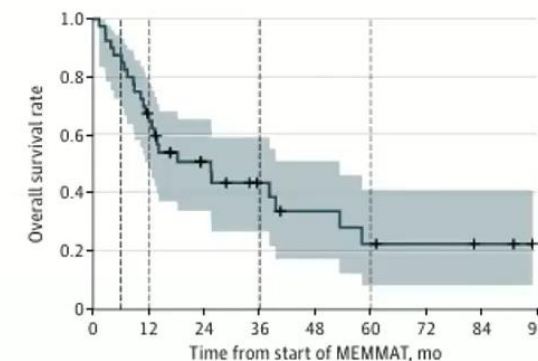
JAMA Oncol. 2023;9(12):1688-1695

Results Summary

- **Patients:** 40 enrolled (Median age: 10 years)
- **Efficacy:**
 - **Disease control** at 6 months: **57.5%**
 - **Response rate:** **45.0%**
 - **Median OS:** **25.5 months** (Range: 10.9–40.0)
 - **Median PFS:** **8.5 months** (Range: 1.7–15.4)
 - **3-year & 5-year PFS:** **24.6% ($\pm 7.9\%$)**
 - **3-year & 5-year OS:** **43.6% ($\pm 8.5\%$)** → **22.6% ($\pm 8.8\%$)**
- **Key Findings:**
 - No significant impact of **molecular subgroups** or **prior recurrences** on outcomes
 - **12-month progression-free patients** has **5-year PFS:** **66.7% ($\pm 16.1\%$)**
- **Safety:**
 - **Well tolerated**, but **Grade 3–4 AEs** included **myelosuppression**, **infections**, **seizures**, **headaches**
 - **1 fatal case:** heavily pretreated patient developed **secondary AML**

A Progression-free survival

No. at risk (censored) 40 (0) 13 (2) 7 (6) 5 (7) 4 (8) 3 (9) 2 (10) 1 (11)

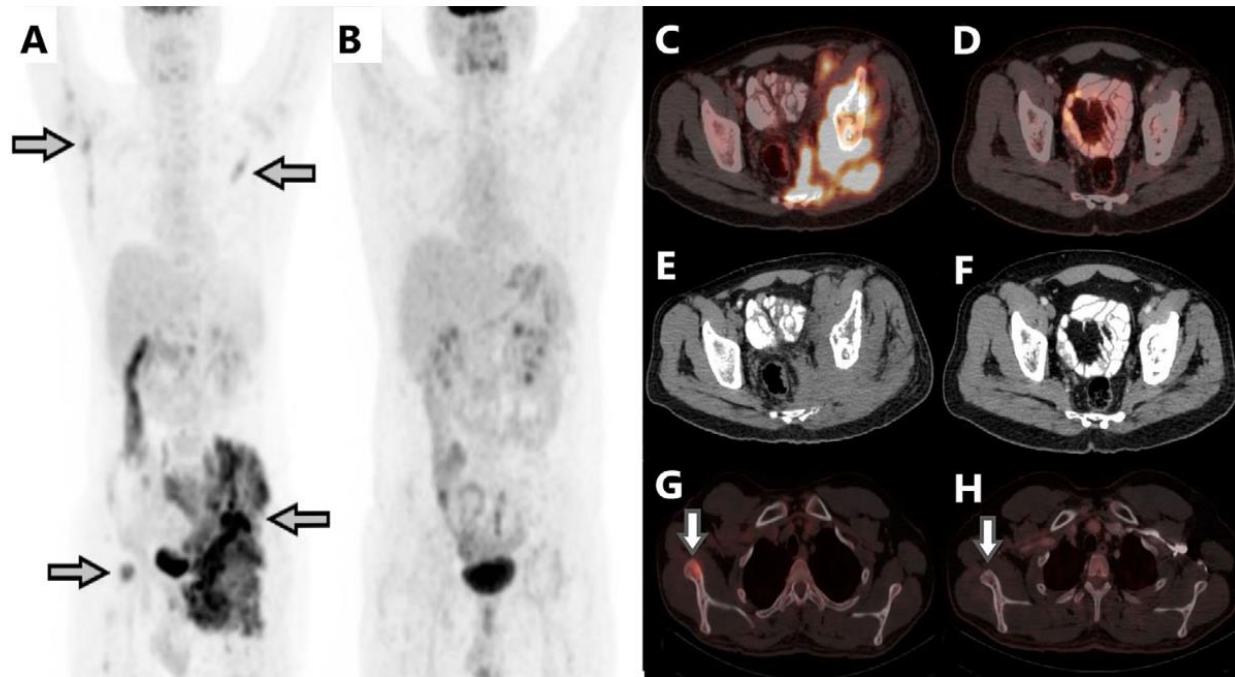
B Overall survival

No. at risk (censored) 40 (0) 26 (1) 14 (7) 9 (10) 6 (11) 4 (11) 3 (12) 2 (13)

The shaded areas represent 95% CIs; vertical dashed lines indicate the 6-month, 12-month, 36-month, and 60-month time points; and crosses represent censored participants. MEMMAT indicates Medulloblastoma European Multitarget Metronomic Anti-Angiogenic Trial.

- Thalidomide
 - Glutamic acid derivate with immunomodulatory and sleep-promoting characteristics
 - Anti-angiogenic: teratogenicity related to an inhibition of blood vessel growth
- Fenofibrate peroxisome proliferator-activated receptor-alpha (PPAR- α) agonist,
 - Primarily used as a lipid-lowering agent.
 - Shifts cancer cell metabolism from glycolysis to fatty acid oxidation, reducing energy availability.
 - Depletes cancer stem cells (CSCs) by inhibiting lipid synthesis.
 - Suppresses glucose uptake via downregulation of GLUT transporters, starving tumor cells.
- Celecoxib (COX-2 Inhibitor)
 - Inhibits COX-2-mediated prostaglandin E2 (PGE2) production, which suppresses tumor-driven angiogenesis.
 - Downregulates VEGF and bFGF, reducing tumor vascularization.

Widely disseminated metastatic Ewing sarcoma: Sustained, complete metabolic response to first-line oral metronomic chemotherapy



- Metastatic EWS
- Treat the patient with palliative intent.
- He received palliative radiotherapy (8 Gy, single fraction) to the primary site for severe pain.
- He was started on an OMCT protocol consisting of
 - cyclophosphamide, etoposide both at 50 mg/m² once daily dose (capping at 50 mg) for 21 days
 - tamoxifen (20 mg/m² with cap at 20 mg twice daily) repeated every 28 days
- Treatment course 1.5 years



Chula
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