METRONOMIC CHEMOTHERAPY CHANGING THE PARADIGM THAT MORE IS BETTER

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INTRODUCTION

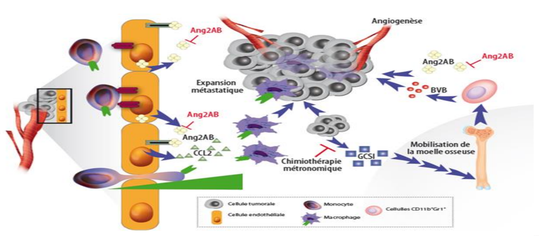
Chemotherapy regimens reflect a controversy that is by now historical: between efficacy in tumour killing and lack of toxicity, which way should the scale be tipped? On one side is the ability of chemotherapeutic drugs to disrupt the dna of tumour cells, rendering them unable to replicate and finally killing them, with a befitting corollary: "the higher the dose, the better."
The introduction of the maximum tolerated dose (mtd) in usual treatment protocols made necessary the imposition of rest periods between cycles of therapy—a practice that not only involves re-growth of tumour cells, but also growth of selected clones resistant to the therapy. Hence, the therapeutic success obtained during the first cycles of treatment reverts in the direction of growth of more malignant metastatic tumours with no therapeutic response.
This name makes reference to the chronic, equally spaced administration of (generally) low doses of various chemotherapeutic drugs without extended rest periods.

MATERIALS AND METHODS

1 . Metronomic Chemotherapy in the Experimental Setting

As with any other experimental therapy, metronomic chemotherapy (MCT) built its foundations with plenty of experimental work, beginning with the pioneering work in the Folkman and Kerbel laboratories. Browder and colleagues demonstrated that standard chemotherapeutic drugs such as cyclophosphamide can also be used as anti-angiogenic agents. The administration of cyclophosphamide in doses lower than the MTD, at shorter intervals and without extended rest periods, showed results better than those obtained with the MTD schedule in the treatment of two cyclophosphamide- resistant tumours, Lewis lung carcinoma and the murine mammary carcinoma cell line EMT-6 .

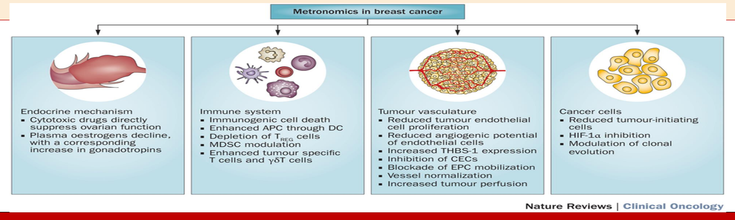
They also eradicated the drug-sensitive Lewis lung carcinoma and the L1210 leukemia using the same therapy. This schedule of cyclophosphamide administered in combination with a specific anti-angiogenic agent (TNP-470) eliminated most drug-resistant Lewis lung carcinomas. Nevertheless, despite being lower than the MTD, the dose of cyclophosphamide was still high, and the experimental animals received palliative care to ameliorate gastrointestinal dysfunction and weight loss.



RESULTS

2 . How Does Metronomic Chemotherapy Work?

Angiogenesis is a normal process that has essential roles in development, reproduction, and tissue repair. On the other hand, pathologic angiogenesis is closely involved in diabetic retinopathy, chronic inflammation, and tumour formation. Angiogenesis plays a critical role in the growth and metastatic spread of tumours .
The angiogenic switch occurs when levels of angiogenesis stimulators such as vegf and basic fibroblast growth factor (bfgf) exceed those of angiogenesis inhibitors such as thrombospondin-1 (tsp-1)
The angiogenic polypeptide vegf is detected in many malignant tumours . Several in vitro and in vivostudies demonstrated that vegf can be considered a marker of the angiogenesis process . Interestingly, a decrease in serum levels of vegf was observed in patients with advanced breast cancer treated with metronomic low-dose cyclophosphamide . Similarly, a metronomic chemotherapy regimen of weekly platinum and daily oral etoposide in patients with high-risk non-small-cell lung cancer showed a decrease in vegf levels during treatment .

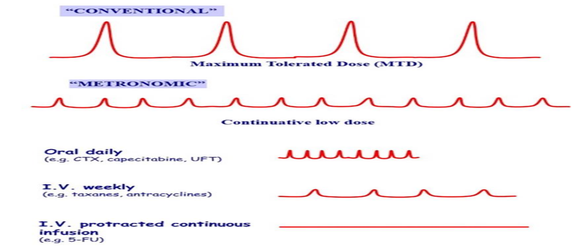


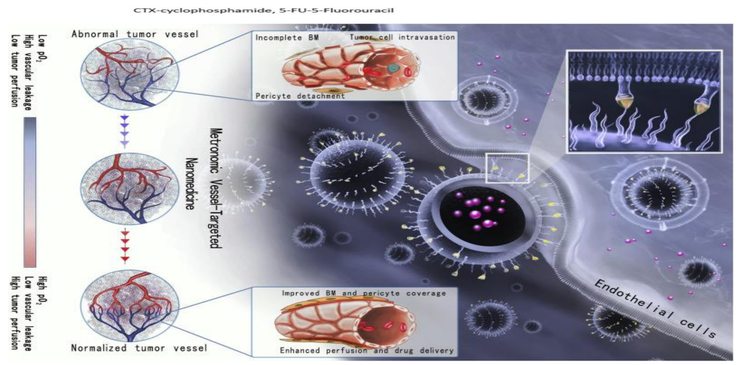
RESULTS

In children with recurrent refractory solid tumours treated with celecoxib and metronomic vinblastine or cyclophosphamide, Stempak and colleagues observed substantial inter-patient variability, but no significant relationship between stable disease or disease progression and the serum concentrations of these markers during the course of therapy. These findings are not entirely unexpected, because a vast number of inducers and inhibitors act in concert to tightly regulate angiogenesis.

A number of recent experimental observations suggest that the growth of some types of cancer may depend on vasculogenesis (that is, progenitor cell–dependent generation of new blood vessels) and not just angiogenesis (that is, mature endothelial cell–dependent generation of new blood vessels). Circulating endothelial cells (cecs) are seldom found in the blood of healthy individuals (an exception is the increase by a factor of 1.5–2 seen in women during the active menstrual phase associated with uterine vascular remodelling).

Another mechanism responsible for the antitumour effect of mct with certain chemotherapeutic drugs could be the stimulation of the immune response, because metronomic administration of oral cyclophosphamide in advanced cancer patients induces a profound and selective reduction in circulating regulatory T cells (Tregs). This effect is associated with suppression of Treg inhibitory functions on conventional T and natural killer cells, leading to restoration of peripheral T-cell proliferation and innate killing activities .





CONCLUSIONS

The novelty of this treatment modality lies not only in its antitumour efficacy with very low toxicity, but also in a cell target switch, now aiming at tumour endothelial cells. The knowledge acquired in the experimental field of metronomic chemotherapy, plus the increasing experience that is being obtained in the clinical setting, will help to lead a change in the design of therapeutic protocols against cancer.
The data so far obtained induced us and other authors to begin a changing of our way of thinking about cancer treatment. To date, the aim of chemotherapy has been to achieve complete tumour suppression, a goal reached only exceptionally. We now know that all tumour cells cannot be consistently eliminated by high dosing schemes. The repeated administration of mtd, which induces important remissions, is generally followed by recurrences with the developWe can now focus on cancer therapy from a different angle. With low-dose chemotherapy, it may be possible to obtain a therapeutic effect in the clinical setting similar to that obtained experimentallyment of tumours even more malignant.
A change from the apparently remote therapeutic objective of killing all tumour cells to the more pragmatic objective of diminishing tumour burden as much as possible and maintaining that diminishment over time can now be considered. This goal might be achieved by administering drugs in a low-dose metronomic schedule over time.

REFERENCES

NCI Dictionary of Cancer Terms
http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/chemotherapy-and-other-drug-therapies/chemotherapy/getting-chemotherapy/?region=on#ixzz4QkvTSXg1
http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/chemotherapy-and-other-drug-therapies/chemotherapy/after-chemotherapy/?region=on#ixzz4Qkve02sB
http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/chemotherapy-and-other-drug-therapies/chemotherapy/after-chemotherapy/?region=on
http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/chemotherapy-and-other-drug-therapies/chemotherapy/getting-chemotherapy/?region=on
https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=46609
https://getpalliativecare.org/whatis/pediatric/
https://www.google.com/#q=metronomic+chemotherapy

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