Editorial

Metronomic chemotherapy: an alternative and effective means of chemotherapy, ideal for developing countries.

In recent times Metronomic chemotherapy has emerged as one of the most promising chemotherapy regimen and has become a viable alternative to conventional regimes which has serious side affects and risk of drug resistance. It was in 2000, when two cancer research groups published a remarkable observation, in tumor-bearing rodents, low-dose chemotherapy, too low to evoke side effects or have a meaningful direct impact on tumor cells, when given on a daily or near-daily schedule, could markedly retard tumor growth [1,2]. This happened even in tumours which were resistant to chemotherapeutic drugs employed. The mechanism of such response was later ascribed to the chemotherapy drugs slowing or preventing angiogenesis.

Tumour cells secret angiogenic substances, which cause rapid proliferation of extremely fragile endothelial cells to form new blood vessels in the tumour. Whereas the endothelial cells lining established vessels only rarely multiply, are stabilized by growth factors provided by neighboring cells, and are rarely killed by clinically feasible doses of chemotherapy drugs. The endothelial cells in the newly formed vessels, on the other hand, are extremely sensitive to killing by chemotherapeutic drugs, much more so than most cancer cells. Thus, when low-dose chemotherapy is administered on a daily schedule the continual death of endothelial cells attempting to form new blood vessels can substantially disrupt the angiogenic process, slowing it down notably.

Other researchers also noticed that traditional cytotoxic chemotherapy medicines, also had some anti-angiogenic activity when administered at low levels. This led to the concept of metronomic chemotherapy (known as "metronomic" because it is regular and even like the beat of a metronome): giving people long-term chemotherapeutic agents at relatively low doses, and with no drug-free breaks. The doses are low enough that side effects are not a major problem.

The metronomic chemotherapy philosophy stands as a different philosophy from the maximum tolerated dose (MTD) method typically used in conventional chemotherapy regimes, which employ higher doses of drugs often limited largely by the body's capacity to handle the side effects, and for limited campaigns of several weeks in order to avoid drug resistance and avoid harming the body's organs beyond a certain limit. Metronomic chemotherapy uses the conventional cytotoxic drugs but counts on them to stop or slow blood vessel growth. In other words, metronomic chemotherapy keeps on working when conventional therapy fails. So, there is hardly any drug resistance. However, the tumour may also increase production of pro-angiogenic factors that promote endothelial cells survival. This explains why cancers, which initially regress in response to metronomic therapy sometimes grow back despite continuing therapy. The cancer confers this relative resistance; not the endothelial cells themselves.

Another benefit of metronomic chemotherapy is that it tends to selectively kill a population of immune cells, called "T-reg" cells, that function to suppress the activity of immune cells capable of attacking the tumor. These are the natural killer (NK) cells and T-cytotoxic cells [3]. T-reg cells often congregate within tumors and secrete hormone-like factors that "turn off" the immune cells trying to attack the cancer. Thus, metronomic chemotherapy has emerged as a useful adjuvant to therapeutic strategies intended to boost the tumor-killing capacity of NK and T-cytotoxic cells [4,5].

Metronomic chemotherapy can also be useful when used in conjunction with conventional chemotherapy [6]. Another merit of this regimen is that it is essentially free of annoying side effects. Only a mild suppression of white cell count was observed in a small minority of the treated patients.

Another strategy cancer researchers are looking into is to cause the cancer to go dormant. This means the body still has cancer cells in it, but the cancer is not growing or a threat to overall health. It has been known since the 1970s that tumors without blood vessels can be dormant. There are suggestions that metronomic chemotherapy can help induce tumor dormancy, although this hasn't been proven.

One study has shown long-term responses of patients with metastatic breast cancer to a metronomic regimen involving daily cyclophosphamide (50mg) and two weekly doses of methotrexate (5mg per dose) [7,8]. 32% of the patients achieved either a complete or partial remission, or a stabilization of disease lasting at least 24 weeks. In about 16% of patients, no tumor progression was noted for over a year. Even in the patients in whom progression did occur, it seems likely that the therapy was often slowing the spread of the disease.

Since metronomic therapy is directed against endothelial cells, not cancer cells, a metronomic regimen that works well with one type of cancer should work well with all types of cancer dependent on angiogenesis for growth.

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