

Advances in Drug Development

Section Editor: **Mark J. Ratain, MD**

Current Developments in Oncology Drug Research

Metronomic Chemotherapy: Teaching Old Drugs New Tricks?

Nicholas Vogelzang, MD
Director
Nevada Cancer Institute

What is metronomic chemotherapy?

Metronomic means fluctuating chemotherapy. It is a process by which low doses of continuous-infusion chemotherapy are administered either orally or intravenously over prolonged or protracted periods of time in an attempt to inhibit the proliferation of endothelial cells, which repopulate malignant tumors.

How does metronomic chemotherapy differ from continuous-infusion chemotherapy?

Continuous-infusion chemotherapy, which is a very old approach to cancer, has been reinvented as “metronomic chemotherapy.” There is excitement around this term, which I believe is inaccurate because the word metronomic implies variability. It suggests that patients treated with metronomic chemotherapy receive a higher dose, then a lower dose, then a higher dose—a type of chronotherapy. In reality, patients receive a continuous “flat” dose. Even weekly chemotherapy, which is very popular with oncologists, is not metronomic chemotherapy. Metronomic chemotherapy is literally daily chemotherapy, or even continuous extended chemotherapy.

What were the results of studies you performed on low-dose continuous-infusion chemotherapy in the 1980s?

A number of the patients we treated were able to receive a cumulative dose of doxorubicin (Adriamycin, Pfizer) that was much higher than the bolus dose. For example, I treated an advanced sarcoma patient with a total of over 1,500 mg/m² of doxorubicin using a pump that delivered 2–3 mg/m² per day without evidence of cardiac toxicity; normally, a dose of 550 mg/m² will cause cardiac toxicity in 10–20% of patients. Remarkably, the tumor shrank or stayed stable while on therapy, but the tumor began to grow each time we stopped the chemotherapy.

In the mid-1980s, similar findings were reported for a number of drugs, including bleomycin (Blenoxane, Bristol-Myers Squibb), cytosine arabinoside, vinblastine (Velban, Lilly), and 5-fluorouracil.

How were the effects of continuous-infusion low-dose chemotherapy understood at the time of these studies?

We had always assumed that continuous-infusion chemotherapy was simply related to overcoming drug resistance; any time the cancer cells tried to divide, chemotherapy was present in their environment, thus the cells would be exposed to lethal drug levels and die. We called this type of drug resistance kinetic drug resistance. By giving the cancer continuous exposure to chemotherapy, you could kill the low-growth fraction of tumors. Most cancer cells only have 1–2% of their cells dividing at any given time, and some people have estimated the number to be much smaller than that. Therefore, the rationale for continuous-infusion chemotherapy in the 1980s and late 1970s was that it could inhibit the cancer cells anytime they tried to divide. Furthermore, continuous-infusion chemotherapy had a very different, generally milder, set of side effects.

What new data are the current studies adding to the literature?

A recent study found that metronomic (low-dose continuous) chemotherapy works through a potentially novel mechanism of action. Dr. Bocci and colleagues demonstrated that chemotherapy drugs administered to mice below the maximum tolerated dose—that is, using metronomic dosing—caused sustained antiangiogenic effects, presumably by targeting proliferating endothelial cells. These effects appeared to be in the absence of side effects. This finding is remarkable because it suggests a marked and selective sensitivity of activated endothelial cells to low-dose chemotherapy in the absence of direct anticancer effects of the agent.

This paper says that, in animals, low-dose chemotherapy induces production of thrombospondin-1, a potent and endothelial-specific inhibitor of angiogenesis. Bocci et al showed that knocking out thrombospondin in transgenic mice (thereby preventing them from making thrombospondin-1), led to the loss of the beneficial effects of low-dose cyclophosphamide. Furthermore, they hypothesized that the

effect of low-dose continuous-infusion chemotherapy may be mediated through its effect on the endothelial cells. However, we do not yet know whether this same effect will be seen in humans. We had previously assumed that continuous-infusion chemotherapy is able to overcome drug resistance because it ensures that there is chemotherapy in the environment of a cancer cell whenever it attempts to divide. This, along with an improved side effect profile, was the rationale for continuous-infusion chemotherapy in the 1970s and 1980s.

So Dr. Bocci and other researchers are now able to identify potential explanations for the responses seen with continuous-infusion chemotherapy?

That's correct. Rather than an effect on the tumor, as was thought, the effect is on the endothelial cell.

Given this understanding about continuous-infusion chemotherapy and endothelial cell mediation, what is the next step?

The mechanism by which such therapy is effective in human cancers needs to be proven. It needs to be determined if this is truly an effect on upregulating production of thrombospondin-1 or a direct effect on the tumor. All of the animal models suggest that it is a direct effect on the circulating endothelial cells, as do the circulating endothelial cell assays. But there needs to be more data to confirm these findings in humans.

What would be the implications for patient treatment if this mechanism was confirmed?

In that case, antithrombospondin-1 therapy could be used to the same effect as chemotherapy. In fact, Abbott already has a molecule that inhibits thrombospondin-1, called ABT-510. If that in fact is the mechanism by which therapy works, then ABT-510 should be an extremely effective drug. Other thrombospondin inhibitors are also being developed.

Has ABT-510 been explored in preclinical studies for cancer?

Yes, it was highly effective in preclinical studies. It is now in phase I–II studies, including one in renal cancer.

If continuous-infusion chemotherapy is able to control or shrink a tumor, but the tumor begins to grow again as soon as the therapy is halted, might this approach convert cancer to a chronic disease in which a patient would have a low dose of chemotherapy, perhaps every day?

I believe so. In preclinical models, there is now good evidence that continuous-infusion chemotherapy can overcome the resistance that has developed to bolus therapy. It is unclear whether this is really truly related to the thrombospondin or if it is just a different kinetic mechanism.

What are the potential drawbacks associated with low-dose, continuous-infusion therapy?

While this approach may be less toxic, it is also more com-

plicated: the physician has to hook the patient up to a pump, and a catheter is inserted into the chest or in their arm, which can get infected. For this reason, continuous-infusion therapy is less popular than bolus dosing, even though it is less toxic.

Might oral dosing be the solution to this problem?

Yes, but this hypothesis is not new. Low-dose, continuous oral chemotherapy is already used with cyclophosphamide for treating hormone refractory prostate cancer, and can be very effective in treating certain patients.

Are researchers developing slow-release oral drugs?

There are many drugs available now that use polymers for this purpose. For example, there have been studies done with paclitaxel (Taxol, Bristol-Myers Squibb) administered in a polymer, which allows once-weekly dosing but provides continuous infusion of the agent for the whole week. There are also pegylated forms of drugs, which continuously expose the patient to low doses of drugs. Liposomal doxorubicin (Doxil, Ortho Biotech) is effectively a form of continuous-infusion doxorubicin, which may explain why it is at least as effective as doxorubicin.

How would you summarize the study of metronomic chemotherapy?

The overwhelming problem is that current cancer therapy has severe limitations that must be overcome for us to effectively treat established cancers. We need either new drugs or better ways to use old drugs. One of the better ways to use old drugs may include giving them by continuous-infusion or metronomic chemotherapy. Because of the complexity of pumps and catheters, a better solution might be oral drugs, which many pharmaceutical companies are developing. In this way you can teach an old drug new tricks, rather than only focusing on the development of new agents.

Suggested Reading

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