

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Use of Dose-dense Chemotherapy in the Management of Breast Cancer

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H&O Could you explain the Norton-Simon hypothesis of dose-dense chemotherapy for breast cancer?

LN This hypothesis is a convergence of a few different ideas. The underlying philosophy is that a kinetic process requires a kinetic solution. When a target is changing over time, one has to take those kinetics into account in planning an approach. As an analogy, when shooting a clay pigeon flying through the air, you aim not where it is when you pull the trigger, but where it will be when the buckshot reaches it. You take into account its speed and trajectory, which is a kinetic determination. In medicine, we often treat using a static view, but cancers are always growing, and we need to plan accordingly. However, it's not enough to use a gestalt approach based on an imprecise sense of cancer cell growth patterns. Quantitative measurement and calculations are necessary to determine the best treatment strategy. We need to understand the mathematics of tumor growth, and this understanding is the basis of the Norton-Simon hypothesis.

H&O What models exist for predicting tumor growth and how have you used them?

LN This work started with Howard Skipper, Frank Schabel, and their colleagues at Southern Research Institute in Birmingham. They developed a simple model of tumor growth that was profoundly important for the development of the field. From this model of tumor growth, they determined that the best way to treat tumors is to use drugs in combination and to use them in equally spaced cycles of equal intensity. Much of what we do in medical oncology is based on these principles. The problem is that this model led to two predictions, one of which

is not true. The first prediction is that if you shrink the tumor you improve prognosis, which is true. The other prediction is that giving the drugs for long enough and at an adequate dosage should lead to tumor eradication, but this has turned out to be false. As Richard Simon and I reported, tumors do not grow by this simple pattern of growth. Rather, tumors grow by a slightly more complex pattern that was discovered by Benjamin Gompertz in the first quarter of the nineteenth century. Combining the Gompertzian model with the Skipper-Schabel model produces the Norton-Simon model.

H&O What are the predictions of the Norton-Simon model?

LN Norton-Simon model calculations led to predictions that were initially somewhat counterintuitive. For example, it predicted it was not necessarily better to use drugs in combination. Instead, it was more important to use the optimal dose that causes regression of the tumor. Additionally, modifying doses to force a combination is less useful than using the drugs sequentially, which would accomplish optimal cell kill. That prediction has been tested in a number of clinical trials and has been found to be accurate. The second prediction occurred much later, at the same time that the granulocyte colony-stimulating factor pegfilgrastim (Neulasta, Amgen) was developed. The availability of pegfilgrastim enabled us to consider the possibility of using drugs more often because bone marrow toxicity could be ameliorated.

This line of thought is the genesis of the concept of density. If you treat a patient every 2 weeks, the overall treatment is more dense than if you treat every 3 weeks (ie, 4 doses given every 3 weeks is less dense than 4 doses given every 2 weeks). Adding the notion of density into the Norton-Simon model led to the prediction that dose-dense therapy should be profoundly more effective. That prediction began a series of clinical trials that culminated in a successful study, started in 1997 by the Cancer and Leukemia Group B (CALGB) and the American Breast Intergroup—CALGB 9741—that showed that giving the drugs more densely made a significant difference, particularly in estrogen receptor (ER)-negative breast cancer. The benefit of this approach in ER-positive disease is not quite as clear because it takes longer to see the chemotherapy

effect in the presence of tamoxifen and other hormone therapy. For example, 15-year data recently published in the *Lancet* demonstrated more benefit from chemotherapy in ER-positive disease than would have been predicted from observations over shorter follow-up periods. We fully expect that this will also be seen in the dose-density trials as we follow the ER-positive cases longer.

H&O What are the common misconceptions about dose-dense therapy?

LN Many people have the misconception that dose-dense chemotherapy for breast cancer is more toxic than standard-dose chemotherapy because the word “density” seems to imply toxicity. However, this method is actually less toxic. In normal tissues, duration of therapy is a very important factor for toxicity, whereas in cancers the density of therapy is the most important factor. It is important to separate the toxicity of chemotherapy from the efficacy. This misconception may be due to the terminology; if the approach were called “toxicity-reduced therapy,” it may be more widely accepted.

The second misconception is that the concept is closely tied to the drugs we used to test it. We used doxorubicin, cyclophosphamide, and paclitaxel to test the approach initially, but the findings in no way depend upon these specific drugs. The strategy itself is valid independent of the medications used to test it and should apply for any cancer in which cells grow in a Gompertzian fashion. Normal scientific procedures should lead to tests of dose-dense therapy for other diseases and approaches. Indeed, preliminary results seem to indicate that it works in malignant lymphoma

H&O Why do tumors grow in a Gompertzian fashion?

LN This question has been at the center of much exciting work in my career. The fundamental shift in thought that the Norton-Simon model purports is that cancer is not a disease of abnormal cell growth but rather a disease of abnormal cell mobility. Rather than being a singular disease, cancer is really a collection of little cancers stuck together. Each of the little cancers grows quickly and is more dense than the normal tissues from which it arises; the cells are close together, with more cells in a particular unit of volume, growing faster and enlarging at a faster rate than would a singular disease. One cancer growing to a given size is 10 times smaller than 10 cancers growing to that given size. Therefore, a collection of little cancers is going to behave in a very different fashion from a single cancer.

H&O How does this concept change the understanding of metastases?

LN This concept changes our notion of the relationship between tumor size and metastatic potential. Both the ability to grow big and to metastasize depend upon cell mobility. The classic notion that cancers metastasize because they grow big is probably not accurate. The correct explanation is that cancers are big because they metastasize themselves, a concept known as “self-seeding.” The ability for a tumor to spread locally is closely related to the ability to spread to other parts of the body. Our current thought is that the right way to exploit these concepts is to develop drugs that affect cell mobility in addition to drugs that affect cell proliferation. Excitingly, researchers are starting to identify gene targets so we can start to develop therapeutics to this end.

H&O Does this approach apply to first-line treatment of breast cancer only or is relapsed disease also part of the discussion?

LN The dose-dense concept was specifically designed for low-volume disease. Cell kill will be greater in advanced disease, but eradication with the currently available drugs is uncommon. The real advantage of dose-dense therapy is the ability to eradicate low-volume disease. Currently, studies are evaluating the concept of dose-dense chemotherapy in the adjuvant setting.

H&O What are the potential implications of the concept of cell mobility that you described above?

LN This new concept could have far-reaching implications in terms of designing drugs and understanding the growth of cancer. My collaborator Joan Massagué conducted compelling studies of the concept of metastasis-associated genes. Currently, we are conducting specific experiments not only to prove the concept but also to develop an array of targets that can lead to effective therapeutic intervention.

References

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