Cancer Log-Kill Revisited

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INTRODUCTION

At the root of science lie basic rules, if we can discover or deduce them. This is not an abstract project but practical; if we can understand the why then perhaps we can rationally intervene. One of the unifying unsolved problems in physics is the hypothetical “Theory of Everything.” In a similar vein, we can ask whether our own field contains such hidden fundamental truths and, if so, how we can use them to develop better therapies and outcomes for our patients. Modern oncology has developed as drugs and translational science have matured over the 50 years since ASCO’s founding, but almost from that beginning tumor modeling has been a key tool. Through this general approach Norton and Simon changed our understanding of cancer biology and response to therapy when they described the fit of Gompertzian curves to both clinical and animal observations of tumor growth. The practical relevance of these insights has only grown with the development of DNA sequencing promising a raft of new targets (and drugs). In that regard, Larry Norton’s contribution to this year’s Educational Book reminds us to always think creatively about the fundamental problems of tumor growth and metastases as well as therapeutic response. Demonstrating the creativity and thoughtfulness that have marked his remarkable career, he now incorporates a newer concept of self-seeding to further explain why Gompertzian growth occurs and, in the process, provides a novel potential therapeutic target. As you read his elegantly presented discussion, consider how this understanding, wisely applied to the modern era of targeted therapies, might speed the availability of better treatments. But even more instructive is his personal model—not only the Norton-Simon Hypothesis—of how to live and approach science, biology, patients and their families, as well as the broader community. He shows that with energy, enthusiasm, optimism, intellect, and hard work we can make the world better.

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The best drugs in the world are useless (or worse) if they are not used properly. As cancer researchers globally pursue the prospect and promise of personalized, precision medicine—perfecting the match between the individual patient’s disease and the drug by focusing on the molecules actually causing that patient’s disease—we must not lose sight of this simple fact. Indeed, modern science should be leading us beyond the best choices of drugs for the individual patient to include the best doses and schedules and durations of therapy. Only then would the full potential of mechanism-based therapeutics be realizable.

The pioneers of medical oncology were cognizant of the need to optimize dose and schedule. Indeed, they may have been more sensitive to this issue than are we in our contemporary social environment. Now, it is widely recognized that cancer can be treated successfully with medicines. Daily advances continue to fuel our enthusiasm. Then, the early medical oncologists were confronted with a zeitgeist antagonistic to the concept that cancer could be treated medically. Hence, minimizing toxicity while maximizing efficacy was critical for the very survival of their nascent field! (For example: I recall a humiliating episode early in my own career. I entered the room a few minutes late for Grand Rounds in a major teaching hospital and was greeted by the leader—a renowned internist—with the laughter-inducing admonition “What were you doing, Larry, saving lives?”)

We recall that in the early days everyone knew with absolute certainty that cancer was a disease entirely defined by aberrant cell division. (Spoiler alert: Below we will reconsider this idea.) It logically follows, then, that the proper targets for the killing of cancer cells should be the molecules critical for mitosis. Such targeting, according to this theory would not only be necessary for optimal therapeutics, but—and this may be the greatest weakness of the theory—sufficient. Over the decades this line of reasoning has produced our current armamentarium of cancer drugs, including many modern targeted therapies.

But normal cells also divide. So how does one use potent...
antimitotic drugs and still minimize toxicity while maximizing efficacy? To answer this question the trailblazers made the critical decision not to develop cancer drugs simply by trial-and-error. They thought, quite correctly, that that would be too risky in addition to being too inefficient. Instead they turned toward mathematical thinking. They reasoned that cancer is not a static process: the mitotic cycle takes time; cell numbers build up over time. Mathematical tools are essential if one is to seek an understanding of fluxes in numbers over time and space.

It is important to note here that mathematical thinking is no more about numbers themselves and symbolic equations than music about the printed notes on a sheet of paper. In both cases what appears on the page is just a guide for deeper and more meaningful concepts, actions, and events. And the mathematical thinking of the founders of medical oncology was both deep and meaningful.

The most influential of these efforts was the product of a team of brilliant researchers at the Southern Research Institute in Birmingham, Alabama, under the visionary support of the United States National Cancer Institute. Among the many discoveries attributable to these scientists was a concept of cancer cell killing called the “log-kill hypothesis”. In essence it expresses the observation that when the growth of a cancer is exponential—increasing by a constant fraction of itself every fixed unit of time—then in the presence of effective anticancer drugs it also shrinks by a constant fraction of itself. (The connection to “log” is that a constant fraction reduces the cell number by one log to the base ten, a “one-log kill.”)

This discovery is profound because it is actually counterintuitive. If it were just a matter of drug molecules occupying receptor sites on individual cancer cells, one would expect that a fixed amount of drug would kill a fixed number of cells, not a fixed proportion of the cells. So there must be something else at play here. Mathematical logic leads one to suspect that something else has to do with the tumor’s growth rate: constant fraction growth leads to constant fractional cell killing. Moreover, if one combines two or more agents that do not interfere with each other, the log kills are additive. For example, if one drug can kill 90% of the cells and another call kill 90% of the cells, using them both would kill 99%, a two-log kill.

The log-kill hypothesis almost immediately generated many ideas concerning the best way to discover, test, and use anticancer drugs. The importance of this is more than merely historic. So many of our approaches to cancer medicine today utilize these principles. And therein lies the rub: if the log-kill hypothesis is wrong (or, better said, incomplete) then many of our contemporary approaches might well be suboptimal.

These principles include:

- the inverse relationship between tumor size and curability, which motivates many postsurvival surveillance programs and justifies postoperative adjuvant and especially neoadjuvant drug therapy as well;
- positive dose-response relationships, which encourage using tumor volume shrinkage as a primary measure of treatment efficacy and motivate treatment at maximum tolerated dose levels, including high-dose chemotherapy with bone marrow reinfusion as rescue; and
- the additively of log kills numbers, which motivates combination chemotherapy.

We owe many clinical advances over the decades to the application of the log-kill hypothesis. However, its strict translatability from mouse to human is perhaps not incontrovertible. The value of postsurgery surveillance (providing the opportunity to give systemic therapy at very small metastatic tumor sizes) is not well established. Postoperative adjuvant therapy works for breast cancer, but it is not universally curative as log kill might have predicted. In addition, preoperative use of the same agents as in the postoperative setting does not improve ultimate outcomes, even though one thereby treats smaller micrometastatic foci. Yes, in the neoadjuvant treatment of primary breast cancer, patients who attain pathologic complete remission do better than those who do not. But regimens causing a high rate of pathologic complete remission are not necessarily better overall than those with lower rates. Using tumor volume shrinkage as a criterion for selecting and approving new agents has had a more modest effect on survival than on response rates. And high dose chemotherapy for many diseases including breast cancer has been especially disappointing. Even combination chemotherapy, as fundamental a concept as has ever influenced cancer medicine, is now being challenged regarding its universal superiority over sequential single agents.

So how could an idea that worked so well in mice work not quite as well in humans? About thirty years ago my colleagues and I started wrestling with this enigma by asking how log kill applied to cancers that grew by other than exponential kinetics. In particular, we were drawn to the Gompertzian growth curve since others had already shown that this was the more common pattern in nature. (In other words, murine leukemia, the basis for the log-kill hypothesis, was a rare exception.)

In Gompertzian growth as the mass of cells gets larger it increases by a constantly decreasing proportion of itself over any chosen time interval. Very tiny cancers may double in size over a certain time interval while that same cancer, when large, may grow hardly at all over that same interval. What we found experimentally was that the proportion of cells killed by an effective therapy was not independent of tumor size, as stated by the log-kill hypothesis, but rather inversely proportional to it: A high fraction of the cells in faster-growing, small tumors could be killed by a given drug at a certain dose level that had very little effect on larger, slowly growing masses of otherwise identical cancer cells. Others termed this the “Norton-Simon Hypothesis” for a given drug and a given dose level the cell kill is proportional to the growth rate that would be expected for an unperturbed tumor of that size.

Our hypothesis led immediately to several novel ideas. Nevertheless, these ideas, although mathematically logical, took several decades to prove true in the management of
might cast light on these two puzzles. Indeed the solution without specifying the mechanism for this effect. Both hypotheses link growth rate to anticancer efficacy, but tiny cancers, which should be inordinately sensitive to treatment, are not always eradicated by drug therapy. In addition, some other maneuvers reduce the density of treatment. The availability of granulocyte growth factors then allowed us to take the concept of dose density to an even higher level by permitting treatment each 2 weeks rather than the conventional three with agents such as doxorubicin plus cyclophosphamide (this combination being rational in that both agents are given at their optimal level) followed sequentially by paclitaxel. Paclitaxel could also be given weekly—another dose-dense regimen—with equal efficacy and less toxicity. Most recently the superiority of dose dense regimens in the adjuvant treatment of breast cancer was confirmed by an independent trial. Trastuzumab for the treatment of HER2 over-expressing disease can be safely integrated into such a regimen with good effect. This means that comparisons with anthracycline-free trastuzumab-plus-chemotherapy regimens are difficult to interpret when the anthracycline-containing control arm is not given in a dose-dense fashion. Moreover, since trastuzumab may be given with paclitaxel without curtailing the efficacy of the chemotherapy, the Norton-Simon Hypothesis predicted that the combination would be more effective that the sequential use, which has also been confirmed by clinical trial.

More sophisticated applications of the model have discovered that not only does efficacy not rise strictly with dose, but that the effect of treatment does not increase linearly with duration of exposure either. For example, 2 weeks of daily capecitabine are less that twice as effective a 1 week of exposure, but more toxic than a regimen giving 1 week on and 1 week off. The reason may well be that exposure to an agent induces its own transient resistance by a variety of means including release from feedback inhibitor of alternative signal-transduction pathways. Hence, our increasing knowledge of anticancer mechanisms is adding considerably to the basic ideas underlying the log-kill hypothesis and its minor modification, the Norton-Simon Hypothesis.

But mysteries remain: both hypothesis fail to explain why tiny cancers, which should be inordinately sensitive to treatment, are not always eradicated by drug therapy. In addition, both hypotheses link growth rate to anticancer efficacy, but without specifying the mechanism for this effect. Lately, a series of investigations in the laboratory of Joan Massagué has produced a new concept of malignancy that might cast light on these two puzzles. Indeed the solution might be linked mechanistically and might also explain the etiology of Gompertzian growth.

In a clinically relevant animal model of breast cancer it was observed that the expression of genes that mediate lung metastases also make the cancers grow faster in the mammary fat pad, the primary site of implantation. This faster growth was not associated with a higher percent of dividing cells in comparison with nonmetastatic, slowly growing cell lines with different gene expression profiles. To solve the riddle of how a mass could be growing faster without a higher percentage of dividing cells we offered the hypothesis of self-seeding. That is, in addition to the cells being metastatic (distant seeding) to the lung they were also metastatic (self seeding) back to the fat pad of origin. Indeed, this was proven to be true in several experimental models. The faster growth rate is because the mass in the fat pad is not one unit but a collection of units—a conglomerate— and X units growing at rate Y each grows X times faster than one unit growing at rate Y. Moreover, the seeds bring with them new marrow-derived endothelial blood vessel precursors and leukocytes with growth-promoting properties.

This hypothesis explains many otherwise arcane clinical observations. One is the need for radiation therapy to the breast after lumpectomy of a breast cancer with clear margins: blood-borne self-seeds have contaminated noncontiguous breast tissue. The hypothesis also provides a mechanism for Gompertzian growth: seeding from the outside-in must happen at the surface of a mass, and the ratio of the surface to the volume of a solid object decreases as that object grows larger. That is, a small mass means a large surface area relative to volume, which means faster growth (relative to tumor size) than a large mass with a smaller ratio. The endothelial cells and leukocytes in contact with the seeds are the biologic basis for this phenomenon.

If Gompertzian growth rate is because of self-seeding and cancer cell killing is proportional to growth rate, is it possible that one of the main effects of chemotherapy is the disruption of the cancer-microenvironment interaction? We examined this in another experimental system and found that indeed the chemical communication between the three species was definable and was perturbed by chemotherapy. That tiny cancers many not yet have established such environmental interactions might make them impervious to their disruption. This could be considered a new slant on the drug-resistant stem cell hypothesis.

Seeding could influence drug resistance in another way. A case of metastatic lung cancer was recently published where drug resistance in all sites was documented to be because of the identical mutation. The only rational explanation for this observation is that this mutation arose in one site, and then seeded the others. Some sites may be better recipients of cancer seeds, some better at releasing them, which could inform patterns of both anatomic metastases and drug resistance. It is also possible that mobile stromal cells could alter over time, biologically or even genetically, promoting both growth and drug resistance.

These latter thoughts bring us back to the central thesis of
this essay. The log-kill hypothesis and its progeny were based on observations that the choice of drug and its dose level and its schedule, all of these, were important in optimizing anticancer therapy. The choice of drug, in other words, was necessary, but not sufficient to get the best results. Now, our rapidly improving knowledge of cancer biology and of cancer genetics is beginning to tell us why dose and schedule are important. To some degree these advances challenge the venerable concept of cancer as only a disease of abnormal mitosis. Cell migration over time and space, tissue geometry, and the kinetics of growth and volume regression—all topics that are grist for the mathematician’s mill—may play key roles. It is both a hope and an expectation that these ideas may be pointing us toward the ultimate in personalized medicine: not just the right drug or drugs for the individual case, but those therapies delivered the right way.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

References

28. Budd GT, Barlow EW, Moore H, et al. Comparison of two schedules of
paclitaxel as adjuvant therapy for breast cancer. *J Clin Oncol.* 2013;31: (suppl; abstr CRA1008).


42. Norton L. Cancer stem cells, EMT, and seeding: A rose is a rose is a rose? *Oncology (Williston Park).* 2011;25:30, 32.

