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Controversy and Consensus

Cancer Research

First Strike–Second Strike Strategies in Metastatic Cancer: Lessons from the Evolutionary Dynamics of Extinction

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Introductory Statement

While clinical cancer research has produced many highly effective drugs, the diversity and evolutionary capacity of most cancer populations remain insurmountable barriers to cure. Here, we propose that curative outcomes may, nevertheless, be achieved by sequencing therapies that are individually effective but noncurative. Basic principles for such an approach are derived from the eco-evolutionary dynamics of background extinctions in which a "first strike" reduces the size and heterogeneity of the population. When followed immediately by demographic and ecological "second strikes," the population can be reduced below some minimum threshold, leading inevitably to extinction. This strategy bears strong similarity to the empirically-derived curative therapy in childhood acute lymphocytic leukemia.

Introduction

For decades, cancer therapists have focused on development of new drugs as the most productive strategy to improve outcomes in treatment of disseminated, metastatic cancers. The successes and limitations of these efforts are evident in, for example, many classes of drugs (hormone-, chemo-, and immunotherapy, radiopharmaceuticals, angiogenesis inhibitors, etc.) available for treatment of metastatic prostate cancers (mPC). Yet, disseminated mPC, despite many effective systemic therapies, remains almost uniformly fatal. Although curative treatment for mPC may ultimately require newer and better drugs, we propose the barrier to cure in many metastatic cancers, including mPC, may not be insufficient agents but rather ineffective tactics. In particular, we hypothesize the key to improved outcomes may be the evolutionary dynamics observed in natural extinctions.

The similarity of cancer treatment to extinction dynamics has been previously noted (1). In many ways, conventional therapy, by applying treatment at maximum dose density, mimics the powerful application of evolutionary forces similar to the famous mass extinction of the dinosaurs by a single catastrophic event—the large meteor impact at the Cretaceous-Paleogene boundary [formerly known as the Cretaceous-Tertiary (K-T) boundary]. Although the goal of creating a mass extinction of cancer cells is intuitively appealing, the dinosaur analogy is actually a cautionary tale because the indiscriminant effects of the massive, global evolutionary force that caused extinction of all of the *Dinosauria* superorder also destroyed many non-dinosaur species. Similarly, application of a lethal perturbation to disseminated cancer cells through the administration of cytotoxic drugs will always be limited by toxicity to normal cells necessary for survival.

Nevertheless, 99% of all species that have existed on earth, many larger more diverse and more geographically dispersed than metastatic cancer populations, have become extinct. Some species extinctions were caused by a global "biotic crisis," but most were lost individually through subtle and relatively undramatic eco-evolutionary dynamics. Each of these "background extinctions" involved a unique sequence of events, but a general pattern is observed. The initial decline of a large, diverse, and geographically dispersed species generally begins with one or more demographic and ecological perturbations. Importantly, these events do not cause species extinction but rather reduce it to a small population with limited genetic diversity and fragmented ecological distribution. This surviving cohort is highly vulnerable because small, stochastic ecological, and demographic perturbations, which would have had little effect on the original population, can now drive it to extinction.

Here, we hypothesize that large, diverse, and spatially-dispersed metastatic cancers may be eradicated by strategic application of a sequence of drugs or drug combinations, none of which are individually curative. The specific sequence, similar to the dynamics of background extinctions, begins with a first strike to reduce the cancer population size and diversity, followed rapidly by additional eco-evolutionary perturbations to drive the vulnerable surviving population to its extinction threshold. Interestingly, this strategy appears to have been empirically-derived in the development of curative therapy for pediatric acute lymphoblastic leukemia (ALL).

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Cancer Evolution within a Host: From One Cell to Population Dynamics

In an evolutionary model, the cancer cell population within a host is a clade (i.e., descending from one cell or a small population of cell), but the heterogeneous intratumoral environment typically generates multiple ecological niches occupied by phenotypically and genetically distinct cancer cell "species." Cancer cells compete with each other in a dynamic environment with spatial and temporal fluctuations in nutrients as well as blood-borne growth factors while being "stalked" by the predatory cells of the host immune system. Adding to the eco-evolutionary complexity is the ability of the cancer cell to deploy niche-construction strategies such as angiogenesis, thus generating ecological as well as evolutionary heritability. Although cancer populations begin (probably) with one cell, proliferation of that individual will inevitably produce group dynamics (2) such as the Allee effect in which the cancer cell proliferation rate is an increasing function of the cell density. This "cooperative" interaction in which individual fitness increases with the number of individuals, perhaps related to stem cell dynamics, is observed in cultured cancer cells and in growth thresholds of small metastases (3). Perhaps the simplest example of an Allee is angiogenesis, which requires a loose cooperation of many cancer cells to generate a sufficient signal to generate new blood vessels. However, the Allee effect can also result from production of hormones or growth factors or other products by some cancer cells as a public good to promote proliferation and invasion or enhance mutual defense from immune attack. Thus, in general, small populations of cancer cells behave differently than large populations and will likely respond differently to at least some therapies (4). Furthermore, because of the Allee effect, cancer populations, similar to the dynamics found in conservation biology, may collapse and become extinct once they fall below some threshold, even without additional therapy. That is, although tumors may arise from a single cell, the development of aggregation dynamics within groups of cancer cells suggest an existing cancer population can become extinct without explicitly killing each constituent cell. The importance of group dynamics is evident in preclinical experiments in which the probability of tumor formation in both immunocompetent and immunosuppressed mice is directly related to the number of cells injected.

Cancer Treatment and the Evolutionary Dynamics of Extinction

Up to a billion cancer cells can occupy each gram of tumor and many metastatic human cancers reach a total tumor burden well in excess of 100 g. Eliminating this large, diverse, and spatially dispersed population (roughly equivalent to the size and diversity of the global mouse population), without destroying the native cellular species necessary for host survival, is clearly a daunting task. For over a century, cancer therapists have largely focused on drug development as the best means to achieve this goal. The ideal cancer drug is a "magic bullet" that eradicates all cancer cells and spares all normal ones. Unfortunately, even highly targeted therapies frequently cause significant toxicity to normal host cells so that magic bullets, equivalent to antibiotics in bacterial infections, remain elusive.

Thus, most cancer treatments represent a trade-off between the benefit of killing as many cancer cells as possible and the potentially lethal toxicity to normal cells necessary for host survival. Currently, the vast majority of cancer drugs receive regulatory approval based on single-agent efficacy in clinical trials that typically enroll patients with measurable (and, therefore, usually advanced) disease. The successes and limitations of these efforts are evident in treatments for mPC. Currently, oncologists can select from and combine a wide number of drugs that can cause demographic perturbations of the population (hormone and chemotherapy drugs), disrupt its habitat (angiogenesis inhibitors), or introduce a predator (immunotherapy). Yet, the vast majority of men with mPC that has disseminated to bone and lymph nodes are not cured because cancer cells have remarkable ability to evolve resistance. In many cases, it appears that the phenotypic and environmental diversity of large, disseminated cancer population, building upon the vast information stored in the human genome, has produced a resistant population prior to therapy. In addition, it is likely that some of the cancer phenotypes can also rapidly deploy defensive strategies available within the genome, such as xenobiotic metabolism. Regardless of the specific dynamics, it is clear in mPC, as with most other common human cancers, that eradicating a large, genetically diverse, geographically disseminated, and evolutionarily nimble population of cancer cells by a single drug or combination of drugs is not currently achievable.

The Evolutionary Dynamics of Extinction

When cancer treatment applies toxic drugs at maximum tolerated dose (MTD), it mimics in many ways the powerful ecological forces that produce mass extinctions. But, decades of experience have demonstrated this approach is largely ineffective in producing the extinction of most metastatic cancers. Why? One obvious limitation, also apparent in mass extinctions, is that large global perturbations are inherently indiscriminant. Thus, for example, K-T event did not kill only dinosaurs but, in fact, resulted in extinction of many other populations. Similarly, the cytotoxic effects of cancer treatment will also affect normal cells so that treatment is often constrained by the danger of causing potentially fatal collateral damage to normal cells.

In contrast, consider the heath hen (*Tympanuchus cupido cupido*), a large chicken-like bird populous on the east coast of North America when European settlers first arrived. Throughout the colonial period, the heath hen population steadily declined due to hunting (the heath hen may have been the "turkey" at the first Thanksgiving) and habitat disruption from expanding settlements. By 1870, just 50 heath hens remained, all restricted to a small refuge on the island of Martha's Vineyard. With protection from the local community, their relatively small population rebounded to about 2,000 by 1915. However, the next few years brought stochastic perturbations. A fire destroyed part of their breeding area, several winters were unusually harsh, and an infectious poultry disease appeared. The last heath hen died in 1932.

The heath hen's decline from a large, spatially dispersed, heterogeneous population is a well-documented, well-studied background extinction that illustrates two important ecological and evolutionary concepts: (i) the role of multiple sequential perturbations in extinction divided into "first strike–second strike" (5) strategies; (ii) the concept of minimum viable population (MVP).

The "first strike" is typically one or several events that greatly reduce the size, spatial distribution, and diversity of an initially

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large and heterogeneous population. For the heath hen, the first strike involved habitat loss and over-hunting but did not eliminate the entire population. Rather, it reduced a large, diverse, and geographically dispersed population to one that was isolated, small, and with limited genotypic and phenotypic diversity. The final extinction was the result of small perturbations that would have been inconsequential to the original population. These dynamics of small surviving populations at increased risk of extinction are often expressed as an MVP. This is the number of individuals necessary for population survival or, stated differently, population size below which extinction is inevitable. As noted below, cancer populations following response to therapy are often reduced to isolated small colonies so that the MVP applies to each colony rather than the global tumor population. Populations at or near their MVP are subject to extinctions caused by demographic perturbations (changes in birth and death rate) and ecological disruption that might, for example, reduce local blood flow. Interestingly, empirical and theoretical studies in nature have shown MVPs were most strongly related to environmental variations (6). Finally, as demonstrated in the heath hen extinction, perturbations of populations near their MVP are entirely random, while in cancers, the therapist can also apply demographic and ecological stresses in the form of therapy and can do so systematically and strategically.

Extinction Dynamics in Cancer Therapy

These dynamics are probably observable clinically in adjuvant cancer therapy. For example, when pediatric patients with clinically localized osteosarcoma were treated with only surgical resection, about 80% developed lethal metastases within 2 years. However, if chemotherapy was administered after surgery, the development of metastases fell to as low as 10% (7). In an ecoevolutionary context, it is likely that clinically unobservable micrometastases at or near their MVPs are present in nearly all patients with osteosarcoma. Untreated, some of these microtumors undergo extinction, whereas others stochastically expand to form a clinical tumor in about 80% of patients. Adjuvant treatment following the surgical first strike reduces the number of cancer cells in each metastatic site, pushing them closer to and frequently below their MVP. This increases the probability of extinction and decreases the probability that the small cancer colonies will grow to clinically evident metastases.

Cancer Therapy Using a "First Strike–Second Strike" Strategy

The "first strike–second strike" approach would require two major changes in common oncologic practices. First, the treating physician will need to switch therapy despite the high level of efficacy in the first strike agents. Second, the physician needs to apply treatment even in the absence of visible tumor (i.e., "measurable disease") so that the effects of treatment cannot be assessed with current technology.

Importantly, there is a precedent for this in pediatric ALL in which a highly successful, empirically derived curative therapy has been developed through a number of clinical trials over several decades. Typically, pediatric ALL treatment begins with an initial "induction" therapy that is followed immediately by a "treatment intensification" using new agents and then by an "intermediate dose intensification" and then by "maintenance," also using different agents. In the context of background extinctions, the initial induction treatment represents a first strike followed quickly by a second strike ("treatment intensification"), third strike ("delayed intensification"), and fourth strike ("maintenance"). In effect, the optimal therapy predicted by the background extinction model and evidenced in the ALL treatment is to use the first strike to deliver substantial damage to the tumor population and then simply continue to "kick them when they are down."

First Strike–Second Strike Strategies in mPC

In a prior clinical study (8), we demonstrated integration of evolutionary dynamics into mPC second-line therapy with abiraterone can improve outcomes. Here, we consider first-line hormone therapy in mPC with ADT, which is typically administered at MTD until tumor progression (PSA increase and increased size on radiographs). However, within the context of our first strike–second strike theoretical model, continuing ADT after PSA normalization is unlikely to further reduce the population size, because the only remaining cells will be resistant. Furthermore, because therapy is changed only when the progressive tumor is measurable, the new treatment is applied to a larger population with fewer extinction vulnerabilities than when the PSA was at its nadir. Can the dynamics of background extinction be adapted for the treatment of mPC?

Clearly, ADT is an effective first strike that greatly reduces the cancer population's size and diversity (i.e., strongly selecting for "castrate-resistant" phenotypes). Microscopy of surviving tumor populations following neoadjuvant ADT therapy demonstrates "habitat disruption," with small clusters of cancer cells "floating" in large regions of necrosis (9). Such isolated pockets are ecologically vulnerable because the surrounding necrosis or fibrosis limits blood flow and their cell populations may initially be too small to promote angiogenesis. They are also evolutionarily subject to a number of Allee effects similar to those observed in background extinctions and, therefore, vulnerable to unpredictable habitat disruption (environmental stochasticity) and demographic stochasticity (increased death rate or decreased proliferation rate) due to random perturbations or, more importantly, application of new treatments. Furthermore, in the absence of survival-enhancing Allee effects such as "safety in numbers" when subjected to the predatory activities of the immune system or "dilution effects" of multiple cellular "sinks" that can reduce the effective concentration of a treatment drug, the small cancer cell populations that survive the first strike may be more susceptible to some treatments (compared with the initial large population).

Ideally, extinction-producing therapies for mPC will use treatments with mechanisms of action and resistance different from the initial first strike with ADT. Importantly, optimal agents for this phase of therapy do not necessarily have to be effective as first strike drugs. In mPC, for example, both the Latitude and the Stampede studies (10) support observation in the CHAARTED (10) study that early combination of additional treatments with ADT can lead to improved outcome but not a cure. Based on the model we proposed, the clinical outcome can be improved further if the additional agent (e.g., docetaxel) is given as a second strike immediately following normalization of PSA by ADT. In the CHAARTED study, for example, we would

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propose adding 12 weeks of abiraterone to ADT after maximal tumor reduction with ADT and then 6 cycles of docetaxel as second and third strikes, respectively. Additional perturbations might include habitat disruption through angiogenesis inhibitors, or introduction of a "predator" through immunotherapy. Although neither approach is currently very effective when treating large volumes of mPC, they may be sufficiently effective to push small, homogeneous surviving populations below their extinction boundary.

Conclusion

In summary, the traditional cancer treatment focus on new drugs development has successfully produced effective treatment options for nearly all cancers. However, magic bullets remain elusive for most metastatic diseases, and MTD therapies are limited by toxicity and the evolution of resistance. Observations from nature suggest optimal cancer treatment strategies may be found in the eco-evolutionary dynamics of extinctions in the Anthropocene era. Thus, strategic, sequential application of available drugs, similar to the events that drive background extinctions, may be sufficient to eradicate some currently incurable metastatic cancers.

Disclosure of Potential Conflicts of Interest

J. Zhang has received speakers bureau honoraria from Sanofi and is a consultant/advisory board member for Bayer, Astrazeneca, and Janssen Biotech. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: R.A. Gatenby, J.S. Brown
Development of methodology: R.A. Gatenby, J.S. Brown
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Zhang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.S. Brown
Writing, review, and/or revision of the manuscript: R.A. Gatenby, J. Zhang, J.S. Brown

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