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A Change of Treatment Strategy against Cancer: Can Cancer be Controlled rather than Cured?

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Cancer results from uncontrolled growth of mutated cells in the body. It is characterized by a rapid proliferation of genetically altered cells, invasion of adjacent tissues by creating a network of anarchical blood vessels (angiogenesis) and metastasis, the spreading of malignancy in other parts of the body. Cancer is one of the world's leading causes of death. About 14% of the world population dies of cancer every year. By now, the methods that have been used to detect and manage cancer lack effectiveness and specificity, and most of the anticancer drugs induce multiple side effects. Furthermore, the absence of satisfying modality for treatment monitoring and feedbacks slows down the decision making process to change the strategy for the management of cancer when the previous treatment fails [1].

Systemic administration of cytotoxic drugs is the primary treatment strategy for patients with disseminated cancer. Even though many effective anticancer drugs are available, the amplitude and durability of cancer response to chemotherapy are limited because of cancer cell resistance. It can arise due to either the intrinsic properties of the cancer cells or factors in the microenvironment [2,3]. The phenotype multiple drug resistance (MDR) is defined as the resistance of tumor cells to the cytostatic or cytotoxic actions of multiple, structurally unrelated and functionally divergent drugs commonly used in cancer chemotherapy [4].

When chemotherapy is used to treat cancer, drugs are often administered in therapeutic doses with intervals of about one or more weeks between repeated courses. This is because many of drugs cause damage to proliferating hematological bone marrow precursor cells, and it takes about one or more weeks for the adequate repopulation of bone marrow stem cells and their genetic descendant to occur [5]. The overall treatment time allows the repopulation of normal cells, but at the same time, repopulation of surviving cancer cells also occurs. Moreover, the number of cancer with high resistance actually increases more, making the elimination process to fail.

Cancer cell repopulation might also limit the effectiveness of chemotherapy since they may develop MDR phenotypes, which presents significant obstacles in providing effective cancer chemotherapy. MDR is termed "intrinsic" when the disease becomes resistant to treatment upon relapse [5,6]. Thus, drug resistance arises as a result of temporal and spatial heterogeneity in cancers that typically contain both multiple cellular subpopulations and microenvironments. Cellular damage by chemotherapy sets in the motion of phenomena that not only results in cancer cell death, but also in promotion of phenotypic and micro environmental alterations that may lead to evolution of resistance and cancer relapse.

Since cellular and micro environmental dynamics are typical nonlinear systems, it is very difficult to predict or control. In contrast, cancer chemotherapy is typically imposed in a rigid fashion, with drug types, doses, and intervals fixed by protocol and altered only in the event of excessive clinical toxicity in patients. Thus, although the cancer is a dynamic system that evolves during treatment, therapeutic strategies tend to remain relatively static.

Cancer micro-circulation is affected by impaired, multidirectional and intermittent blood flow, impaired interstitial fluid drainage, increased interstitial fluid pressure and increased vascular permeability [7]. While an inefficient blood stream may be considered as a flaw of solid tumors, evidence of the impact of poor oxygenation on cancer biology suggests that the cancer vasculature may in fact be a powerful protective net against complete eradication by cancer chemotherapy. For example, through detection of molecular markers of hypoxia and pO_2 measurements, it has been reported that increasing levels of prostate tumor hypoxia within prostatic tissue correlated significantly with increasing clinical stage and patient age [8]. Moreover, evidence has connected cancer aggressiveness and poor patient survival with small vessel density in many human malignancies including prostate cancer [9].

Furthermore, it is necessary to consider tumor dormancy in control of cancer. Clinical cancer dormancy is defined as an unusually long time between the removal of the primary tumor and subsequent relapse in a patient who has been clinically disease-free [10]. Following the treatment, patients may enter complete remission in which persistent cells represent the minimal residual disease (MRD) state. Experimental and clinical data suggest that the absolute quantity of MRD is extremely low. Tumor dormancy would then result from equilibrium between MRD and the patient rather than from cellular quiescence. Such long-term equilibrium may be due to several conditions. The host could control the tumor outgrowth, the tumor cells could resist the host defenses, or the microenvironment may not present an optimal environment for tumor growth (e.g. limited angiogenesis), there may also be a lack of angiogenesis there may also be a lack of appropriate extracellular matrix to stimulate adhesion molecules [11].

Replicative and quiescent cells could also coexist if replicative cells are only being destroyed by the host defense system. Very few cancer cells can persist for years or decades under these hostile conditions that include continuous exposure to host stress, maintenance treatment, autologous anti-tumor immune response, and nonpermissive microenvironments [12]. Therefore, efforts to eliminate cancers, i.e., under hostile condition may actually hasten the emergence of resistance and tumor recurrence from tumor dormancy state.

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Eradicating the large, diverse and adaptive populations found in most cancers presents a formidable challenge. One cubic centimeter of cancer mass contains about 10^9 transformed cells and weighs about 1 gram. Variable cell division and differences in genetic lineages and micro environmental selection pressures mean that the cells within tumor are diverse in both genetic make-up and observable characteristics. Additionally, tumors are complex ecosystems that include normal cells as well as the regions of low blood flow and oxygen content where cancer cells are relatively protected from chemotherapy. If blood flow is poor, for example, so is the delivery of the toxic drugs [8,9,13].

The typical goal in cancer therapy is to kill as many tumor cells as possible under the assumption that it will, at best, cure the disease or at worst, keep the patients alive for as long as possible. Indeed, for more than 50 years, oncologists have tried to find ways to administer ever-larger doses of ever-more cytotoxic therapy. But, regardless of concentration or cleverness of design, cancerous cells also have adapted to therapy as in MDR patterns [13]. *In vivo* experiment based-computer simulations and recently developed mathematical models of tumor evolutionary dynamics suggest that efforts to eliminate cancers may actually hasten the emergence of resistance and cancer relapse, thus reducing patients' chances of survival [14].

The reason for this hypothesis arises from a component of cancer biology not ordinarily investigated; the cost of resistance to treatment. Cancer cells pay a price when they evolve resistance to a particular treatment. For example, to cope with chemotherapy, cancer cells may increase their rate of DNA repair, or actively pump the drug out across the cell membrane. In targeted therapies, in which drugs interfere with the molecular signaling needed for proliferation and survival, a cell might adapt by activating alternative pathways to defend the attack of chemotherapy.

All these strategies use up energy that would otherwise be available for invasion into normal tissues or proliferation, which as a result reduce the fitness of the cell. The fact that cancer cells must pay a price for resistance is supported by several observations [15-17]. Moreover, although resistant cells are commonly found in tumors that haven't yet been exposed to treatment, they generally occur in small numbers [18]. This hypothesis suggests that in the absence of therapy, cancer cells which haven't evolved resistance will proliferate at the expense of the less-fit resistance ones. And, when a large number of the sensitive cells are killed, for instance by aggressive therapies, the resistant types are able to proliferate in uncontrolled patterns. This means that high dose of chemotherapy might actually increase the likelihood of a tumor becoming unresponsive to further therapy.

Therefore, a therapeutic strategy explicitly designed to maintain a stable, tolerable tumor volume without breaking balance between sensitive and resistant tumor cell could increase patient's survival by allowing sensitive cells to suppress the growth of resistant ones. As a matter of fact, mice that were treated with human ovarian cancer cells showed longer survival time with a drug dose continuously adjusted to maintain a stable tumor volume than mice with conventional high-dose chemotherapy [14].

Designing therapies to sustain a stable tumor mass rather than eradicate all cancer cells will require a long-term, multilayered strategy that looks beyond the immediate cytotoxic effects of any one treatment. Even now, many oncologists agree with the principle that therapeutic strategies aimed at controlling cancer are proven to be more effective and possible than trying to cure it. However, the idea of not killing the maximum number of tumor cells possible and living along with tumor will be difficult for both physicians and patients to accept in real clinical practices.

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