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The Paradox of Anti-cancer Agents and Recurring Emergence of Drug Resistance

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Introduction

The singular challenge to effective cancer treatments based on previous and current strategies is the emergence of drug resistance. Accumulated evidence from decades of cancer treatments with various therapies has clearly and unequivocally highlighted that development of resistance over a "latent" time period is an inherent and default property of cancer cells [1]. As would be expected, drug resistance plays a prominent role in cancer-related mortality. How cancer-targeting effects provided by therapies become manipulated into a vehicle that initiates or promotes resistance is complex, and largely unknown. The cytotoxic nature of chemotherapy or radiotherapy, as well as specific gene or signaling abrogation offered by targeted therapies results in a tumor microenvironment that would be detrimental to "normal" non-cancer cells. Healthy cells would rapidly succumb to the damages mediated by anti-cancer therapies, however while such effects may impede tumor cells for a while, it eventually instigates cellular changes that result in resistance. The complex mechanism(s) of drug resistance is exacerbated further by the unpredictable manner of its emergence. Individualistic and highly dynamic nature of cancer cells, plus lack of standardized detection platforms complicates even further the how, the when and the where of drug resistant development [2], and poses a challenge of providing robust strategies against it.

Anti-cancer agents and drug resistance: The paradox

The same agents that are designed to attack tumor cells in order to provide response are linked with the processes that trigger or promote failure and loss of sensitivity to the drugs. This paradox place a considerable challenge in finding innovative ways of targeting cancer cells. How can treatments be fashioned to provide maximum efficacy that obliterate potential recovery of malignant cells whilst minimizing adverse effects to neighboring, non-cancer cells? Based on different modalities and varying mechanisms of drug action, combination therapies allow for differential and/or additive anti-tumor effects that truncate the adjustments associated with adaptations employed by cancer cells. Therefore, it is highly likely that chronic treatments with a singular agent result in specific alterations that facilitate drug resistance by cancer cells. Cellular perturbations that result from drug-specific alteration(s) in response to chronic treatments may hold important clues to the development of resistance or decreased drug efficacy. Drug-resistant cancer cells are associated with perturbations that include, genetic aberrations, metabolic alterations, distorted cellular redox hemostasis, as well as cell cycle dysregulation [1, 3]. Existence of such a chaotic tumor environment feeds directly into the fundamental operations of malignant cells, which is typified by genetic aberrations and dysregulated signaling events [1, 3]. From the foregoing, it is obvious that while the search for novel drug targets and mechanisms of action should be encouraged, the limited benefits that is usually offered provide only a partial solution. It therefore appears that the limiting factor to optimum efficacy of anti-cancer agents is time. The response of cancer cells to drugs occur for a limited time interval after which decreased sensitivity or complete loss of response becomes inevitable. Therefore, the goal of emerging cancer therapies must focus on the effective ability to completely destroy malignant cells without recourse to latent time-lag that allows recovery, cellular adjustments and resistance. In the same vein, existing treatment modalities should consider drug alternation strategies (as single agents or in combination) that disrupts cancer cells getting "acclimatized" and well-adjusted to a specific agent(s). Chronic drug combination strategies may perhaps provide desired outcomes if targeted cancer cells are effectively destroyed. Failure to do so will allow residual cancer cells to develop survival mechanisms against the drug combination, and eventually become resistant. In other words, the time-dependent requirement of drug resistance is not limited to only treatments with a single drug, but can also occur with drug combinations.

Cancer Immunotherapy: A solution to cancer drug resistance?

While research on cancer immunotherapy has witnessed a resurgence in recent years, the concept is not entirely new [4]. For decades, the idea of bolstering the immune system in order to better position and prepare it for adequate response against foreign agents in the body has been a potential and attractive cancer strategy. Priming the immune system facilitates memory, recognition of cancer cells as "foreign" and rapid build-up of killer T-cells to attack such cells [4]. Several vaccines have previously and successfully been implemented against various infectious diseases using this strategy. Adopting a similar approach geared at enhancing the immune system against cancer cells is therefore a major step in the right direction. However, critical to the success of cancer vaccines or therapies designed to boost the immune system against cancer is the identification of distinct antigens or factors that are specific to tumors. Such factors must be flagged as "non-self" in order for primed immune cells to recognize and provide an appropriate response that will hopefully destroy the cancer cells. In the case of cancer, immunotherapy will provide a significant departure from the manner in which tumors are traditionally treated. Rather than directly targeting malignant tumors, immunotherapy empowers the immune system to recognize cancer cells as "non-self" and hence attack and destroy such cells. In theory, such a model may ensure that cancer cells can be recognized and targeted by immune cells irrespective of dynamic changes inherent within tumors. It further ensures that the enabling environment that promotes the initiation, development or accentuation of drug resistance due to anti-cancer agents is minimal. A third advantage of immunotherapy is the ability of immune cells based on memory to recognize cancer cells if and when they do arise again. Although it is still too early to make comprehensive conclusions, emerging data appears to support the notion that relative success is being achieved by immunotherapy.

Opdivo (nivolumab): A case study of cancer immunotherapy drug

Opdivo (nivolumab) is a recently approved FDA and EU immunotherapy drug against metastatic melanoma and lung adenocarcinoma. It has been heralded as a major advance in cancer therapy. Several other immune-oncology drugs are in the pipeline which include antibodies developed against specific immune signaling targets. This approach may provide efficacy against many cancer types, and preliminary data from several studies indicate modest to significant benefits with respect to overall survival and safety profile. Nivolumab is a human IgG4 inhibitor against the programmed death 1 (PD-1) receptor. Tumor-expressed ligands, namely, PD-L1 and PD-L2 bind to PD-1 receptor on activated T-cells, thereby attenuating or disrupting T-cell-mediated immune response. This represents a mechanism by which tumor cells evade immune recognition, by-passing detection and destruction by the immune system. As a humanized antibody, nivolumab acts an inhibitory immune check-point by disrupting signaling events mediated by PD-1 receptor, thereby restoring anti-tumor immune functions [5-8]. The basic principle of nivolumab is geared towards removal of the hindrance instigated by cancer cells which serves as a mechanism of evading immune recognition. Specifically, in a recent study that compared overall survival rates between nivolumab versus docetaxel in nonsquamous non-small-cell lung cancer (NSCLC) patients following failure of platinum-based chemotherapy, progression-free survival (PFS) at the endpoint was negligible (3.2 months vs. 4.3 months, respectively; 5). However within a year of the treatments, nivolimab demonstrated a 51% PFS rate compared to 39% with docetaxel [5]. Furthermore, drug-related adverse effects were ~10% in the nivolumab group compared with 54% in docetaxel patients [5]. Another study that compared nivolumab versus everolimus in advanced renal-cell carcinoma demonstrated improved benefits in overall survival, as well as objective response and safety profile [6]. Everolimus is an mTOR inhibitor and is usually employed as a second-line therapy in the treatment of advanced renal-cell carcinoma [6]. While PD1-PD-L1 expression and interaction is thought to represent immune response to tumor cells, a study of nivolumab in patients with advanced squamous-cell NSCLC, showed that overall survival, objective response rate (ORR) and PFS were significantly better compared with docetaxel group, and the benefit was independent of PD-L1 expression [7]. Nivolumab has also been shown to demonstrate substantial therapeutic activity and safety profile in patients with relapsed or refractory Hodgkin's lymphoma [8]. While most of these studies were undertaken in advanced and/or previously treated tumors, there is evidence that nivolumab may also be effective against previously untreated tumors. For example, among previously untreated patients who had metastatic melanoma without a BRAF mutation, nivolumab demonstrated significant improvements in overall survival and PFS in comparison to dacarbazine [9]. In advanced melanoma and previously untreated patients that possessed wild-type BRAF mutation, nivolumab showed similar benefits in combination with monotherapy drug, Yervoy (ipilimumab) [10]. Patients with BRAF wild-type tumors, demonstrated an ORR of 61% in the group that received both ipilimumab and nivolumab (combination group) compared to 11% in patients that received ipilimumab and placebo (ipilimumab-monotherapy) [10]. While several differences exist between cancer-types, emerging data suggest that overall survival rates and other secondary endpoints, including ORR, PFS, and safety profile provides compelling evidence to the efficacy of the immune-oncology drug, nivolumab. While it is still too early to conclude, these encouraging studies suggest that immune-boosting anti-cancer therapies may provide the best chance of effective targeting of advanced-stage cancers that have failed to respond to first-line or previous therapies, or even previously untreated tumors. However, whether immunotherapy drugs eventually fail to provide action against cancer cells, or immune system become desensitized by the drugs remains be seen.

Conclusion

To outsmart stealth and resilient cancer cells, novel ways of therapeutic targeting must be devised that are amenable to the changing and dynamic nature of cancer cells. One way to achieve

this goal may include cancer immunotherapy. Cancer immunology is not an entirely new concept, but has gained momentum in recent years. It presents increasing chances of success based on technological advances and increased knowledge in the biology of immune cells and system. Perhaps a combination of immunotherapy with traditional anti-cancer agents may provide optimum therapeutic strategies to defeat cancer, and cancer drug resistance. Ability to achieve optimum benefits from such combinations whilst keeping secondary effects that result in the development of resistance to the nearest minimum may be a feasible target.

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