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Darwinian Principles toward Multidrug-Resistant Cancer Cells

Mehmet Varol[*1,2]

[1]*Department of Biology, Faculty of Science, Yunusemre Campus, Anadolu University, Eskisehir TR26470, Turkey*

[2]*Department of Molecular Biology and Genetics, Kotekli Campus, Mugla Sitki Kocman University, Mugla TR 48000, Turkey*

[*]**Corresponding author:** Mehmet Varol, Department of Molecular Biology and Genetics, Faculty of Science, Kotekli Campus, Mugla Sitki Kocman University, Mugla TR48000, Turkey, Tel:0090-252-2113132; Fax: +90-252-2119280, E-mail: mehmetvarol@mu.edu.tr

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Introduction

As the conventional treatment strategies, systemic cancer chemotherapies have been still recommended to treat wide variety of cancer diseases [1]. To ensure the maximum clinical benefits by destruction of the greatest possible number of cancer cells, the clinicians prescribe the maximum tolerated dose of chemotherapy [2-4]. However, this treatment method leads to some side effects for patients such as systemic toxicity, drug resistance and potential long-term side effects [5-7]. The attention and efforts of scientists had been, therefore, drawn to develop new chemotherapy treatment strategies to improve clinical benefits and reduce the side effects by taking into consideration the impact of dose intensity, dose density, and treatment duration [3].

Metronomic therapy had been proposed as the one of the alternative treatment modalities to reduce side effects and apply greater cumulative doses of chemotherapeutic agents [8]. This alternative strategy has been performed by using low dose conventional chemotherapeutic agents with no prolonged drug-free breaks to kill maximum tumor cells [8]. However, the oncologists generally have faced the developing drug resistant cancer cell populations as the most important and major problem of classical, metronomic or molecularly targeted chemotherapy [9].

Some rational hypothesis for the evolving chemo-resistant cancer cell populations have been proposed by dividing into two major categories as the developing resistance due to the intrinsic factors including phenotypic drug resistance (increased DNA repair and expression of p-glycoprotein etc.), tumor cytokinetics (undergoing mitosis despite the anti-mitotic therapeutics) and evaluation (Darwinian selection of resistant population against chemotherapeutics), and the developing chemo-resistant populations by extrinsic factors including poor perfusion, increased intratumoral interstitial pressure, hypoxia, extracellular acidosis and protective effects of the tumor-associated mesenchymal cells [9]. On the other hand, it had been also established that environmentally or phenotypically mediated resistant cancer cells are present before the chemotherapeutic treatment, and the applied chemotherapy might lead to a Darwinian selection for the chemo-resistant cell populations due to the genetically unstable and heterogeneous features of cancer cell populations [10-13]. By consideration the Darwinian principles, different types of populations and cells compete with each other for space and substrate within the heterogeneous structure of a tumor. Thus, the chemo-resistant cells or populations come forward and excessively proliferate due to the more space and adequate substrate when the applied chemotherapeutics kill the chemo-sensitive cells and populations [10,14,15].

Similarly, the occurrence of chemo-sensitive cancer cells in the micro-environment limit to the proliferation and expansion of chemo-resistant cell population due to the high metabolic cost of the chemo-resistant phenotype which needs synthesis, maintenance, and operation of membrane extrusion pumps [10]. This Darwinian thought about the dynamics of tumor microenvironment have created the eco-evaluation-based cancer treatment strategy (adaptive therapy) to block the evolving of chemo-resistant populations and to maximize time to progression rather than reduction in tumor size [13,16-19].

Enriquez-Navas and colleagues have recently published a paper which provides significant evidences that showed the advantages of adaptive therapy (low dose, frequent chemotherapy) as a better alternative to conventional high dose chemotherapy [10]. Their study provide that optimized adaptive cancer therapy either limit to the tumor size and the proliferation of drug resistant population. So the therapeutics could preserve the effectiveness on the cancer cell population and indicate less damage the surrounding tissues. Additionally, the tumor size may be reduced with the approaches of combinational chemotherapy applications by using anti-angiogenic drugs and immune system modulators [20], and the natural compounds which are cancer selective but low cytotoxic might be gain more importance with this Darwinian touch to conventional chemotherapeutic strategies. Consequently, the new strategies seems to be completely less aggressive despite the offensive manner of the past treatment modalities, and the side effects are not acceptable anymore for the clinicians and patients.

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