Advanced Drug Delivery Reviews 98 (2016) 35–40

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Opportunities and challenges in combination gene cancer therapy☆

Kent L. Nastiuk [b], John J. Krolewski [a,b,*]

[a] Roswell Park Cancer Institute, Center for Personalized Medicine, United States
[b] Department of Cancer Genetics, Elm & Carlton Streets, Buffalo, NY 14263, United States

ARTICLE INFO

Article history:
Received 19 October 2015
Received in revised form 28 November 2015
Accepted 2 December 2015
Available online 23 December 2015

Keywords:
Cancer
Therapeutics
Chemotherapy
Hormonal therapy
Targeted therapy
Gene therapy
Death receptors
c-FLIP

ABSTRACT

Treatment for solid tumor malignancies, which constitute the majority of human cancers, is still dominated by surgery and radiotherapies. This is especially true for many localized solid tumors, which are often curable with these treatments. However, metastatic cancers are beyond the reach of these therapies, and many localized cancers that are initially treated with surgery and radiation will recur and metastasize. Thus, for over 60 years there has been a concerted effort to develop effective drug treatments for metastatic cancers. Combination therapies are an increasingly important part of the anti-cancer drug armamentarium. In the case of cytotoxic chemotherapy, multi-drug regimens rapidly became the norm, as the earliest single agents were relatively ineffective. In contrast to chemotherapy, where combination therapies were required in order to achieve treatment efficacy, for both hormonal and targeted therapies the impetus to move toward the use of combination therapies is to prevent or reverse the development of treatment resistance. In addition, emerging evidence suggests that combination therapy may also improve cancer treatment by neutralizing an emerging treatment side effect termed therapy-induced metastasis, which accompanies some effective single agent therapies. Finally, although gene therapy is still far from use in the clinic, we propose that combination therapies may enhance its effectiveness.

Contents

1. Purpose

The purpose of this set of reviews is to describe advances in the development and deployment of multi-modal therapies. Most of the reviews focus on exciting new technologies that can deliver two or more drugs to patients, including those with cancer. This review will complement those discussions of advanced drug delivery technologies by describing some of the biological, clinical and practical arguments that favor the use of combination cancer therapy and suggest that such combination therapies will be superior to the still widely-employed cancer treatment paradigm of serial application of single therapeutic modalities. While the accompanying reviews discuss many of the technical impediments and opportunities in the development of multi-modal drug delivery, here we will review the other challenges in effectively implementing combination cancer therapies. Specifically, we will identify drug therapy combinations that make

☆ This review is part of the Advanced Drug Delivery Reviews theme issue on "Therapeutics for Synergistic Therapy".

* Corresponding author at: Department of Cancer Genetics, Elm & Carlton Streets, Buffalo, NY 14263, United States. Tel.: +1 716 845 1300x6968.
E-mail address: john.krolewski@roswellpark.org (J.J. Krolewski).

http://dx.doi.org/10.1016/j.addr.2015.12.005
0169-409X/

good biological sense as well as when and where novel multimodal therapy delivery is required for effective combination treatment, rather than simply delivering two drugs simultaneously by established oral or intravenous routes. Therapeutic modalities for cancer can be divided into seven types: surgery, radiotherapy, chemotherapy, hormone therapy, the recently developed class of targeted therapy, the emerging category of cellular (immune) therapy, and finally the still more or less exclusively experimental category of gene therapy. There are other possible categories (such as drug-based immunotherapy) and there is definitely overlap among these categories, but this classification facilitates our discussion of the biological basis for advanced multimodal delivery technology.

Three of these seven treatment modalities – surgery, radiotherapy and cellular therapy – are not relevant in the context of the advanced delivery technologies discussed in this issue, and therefore this review will focus on the remaining four categories of drug-based therapies. However, it is useful to mention that surgery, and to a somewhat lesser extent, radiotherapy have historically been frequently used in combination with drug therapies in the treatment of cancer. Specifically, drug therapy given soon after excisional surgery of the main tumor mass is referred to as adjuvant cancer therapy, which is widely employed to eliminate residual disease, typically micro-metastatic cancer. Cellular immune therapy might serve a similar adjuvant role although this application is still in its infancy [1]. Similarly, neo-adjuvant drug therapy is applied prior to surgical excision, often to reduce the bulk primary tumor mass prior to surgery. Radiation is one of the most common types of neo-adjuvant therapy. Finally, radiation has been used in combination with drug therapies to sensitize tumors to the effects of local radiation, allowing lower regional radiation dosing and thereby preserving normal tissue surrounding the site of radiation [2].

2. An abbreviated history of combination cancer drug therapies

2.1. Chemotherapy

As detailed in Mukherjee's comprehensive and illuminating history of cancer [3], beginning as far back as medieval times, treatment focused on improving the efficacy of surgery and to a lesser extent (and much later) on radiotherapy, with the occasional application of cell therapy to stimulate anti-tumor immunity (e.g., Coley's toxins [4,5]). Following WWII a number of single agent chemotherapeutic drugs were developed. These were either metabolic or DNA replication poisons sometimes referred to as 'cytotoxic' chemotherapies. These early drugs demonstrated only limited value in human clinical trials as single agents, but by the 1960s successful treatments were devised using combinations of these drugs [6]. A key scientific breakthrough was the realization that efficacy (mainly assessed in rapidly proliferating cancers) was dependent on highly efficient tumor cell killing, which was best achieved employing multiple agents simultaneously (or in rapid cycles) [6]. It was also critical that the different component agents constituting the combination therapy 'cocktails' act by distinctly different cytotoxic mechanisms [7]. Thus, similar to the use of multiple antimicrobial agents in stubborn infectious diseases such as TB (and later HIV), multi-modal chemotherapy for cancer became widely employed in many human cancers [7].

2.2. Hormone therapy

In contrast to chemotherapy, many of hormonal and targeted anticancer drugs have been successfully employed as single agent therapies. However, it has become increasingly clear that while these single agent therapies extend patient survival, resistance eventually develops. Therefore, these classes of therapy are increasingly being combined with other drug therapies in order to prevent the development of resistance. Hormonal therapies typically interfere with the binding of the steroid ligands to the family of nuclear hormone receptors, most notably the androgen and estrogen receptors, in prostate and breast cancers, respectively. As an example, we describe the evolution of hormonal therapeutic strategy in prostate cancer, the leading cause of cancer in US men [8]. Huggins and Hodges demonstrated in 1939 that androgen deprivation therapy (ADT) by castration was effective in the treatment of metastatic prostate cancer [9]. Subsequently, 'chemical castration', employing gonadotropin releasing hormone agonists such as leuprorelin that lead to reduced androgen levels via feedback inhibition, has largely replaced castration surgery. While ADT is initially effective in the treatment of metastatic prostate cancer, there is near universal recurrence as a form of prostate cancer referred to as castration resistant prostate cancer (CRPC), which is usually fatal within two years [10–13]. Since 2004, multiple agents have been approved for CRPC, including docetaxel chemotherapy [14], the anti-androgen enzalutamide [15–17] and the androgen biosynthesis inhibitor abiraterone [18,19]. These have been employed as single agents, and are often used serially, but all ultimately induce resistance [20–23], re-activating tumor growth. Within the past year, the combination of chemotherapy (docetaxel) plus ADT has significantly increased overall survival [24,25], likely marking the beginning of routine combination drug treatments for CRPC. Moreover, an ongoing trial will determine the value of using a combination of the anti-androgen enzalutamide and the androgen biosynthesis inhibitor abiraterone in the same patient population (https://clinicaltrials.gov/ct2/show/NCT01949337).

While resistance is a frequent reason for the failure of single agent hormonal therapy, it may not be the only cause. Single agent hormonal therapies such as leuprorelin and enzalutamide appear to induce resistance via multiple mechanisms, including i) mutation in the androgen receptor (AR) ligand binding domain, creating variant AR proteins that can recognize an anti-androgen (antagonist) as an agonist [22,23,26]; ii) epigenetic mechanisms that increase the relative expression of AR splice variants, such as those encoding ligand-independent versions [27] and iii) the up-regulation of WNT pathway signaling genes which are known to drive proliferation in other cancers [28]. However, these same hormonal treatments of advanced prostate cancers may result in the development of a type of treatment failure that has been described as 'treatment-induced metastasis' (TIM) by Ebos [29]. For example, castration and enzalutamide increase metastasis in both mouse and cell culture models of human prostate cancer, via the induction of the chemoattractant protein CCL2, which promotes migration of tumor cells and infiltration tumor-associated macrophages [30–34]. The observation of TIM in model systems is supported by some initial patient studies [32,35,36], indicating that combination therapies that include either anti-CCL2 monoclonal antibodies [37–40] or anti-CCR2 inhibitor [41] represent an additional opportunity to increase the efficacy of leuprorelin or enzalutamide in CRPC. Radiation therapy of prostate cancers increases expression of the AR, and reduces patient survival, suggesting that another single agent treatment for prostate cancer produces TIM and its effect might be reversed by additional combination therapies, such as the use of enzalutamide immediately following radiotherapy [36], and might also account for improved survival for patients receiving extended ADT following radiotherapy.

2.3. Targeted therapy

This category [42] is predicated on the concept of oncogene addiction, first postulated by Weinstein [43]. He reasoned that inhibition of a single mutant driver oncogene is sufficient to induce cancer cell death in those cancers in which sustained proliferation is 'addicted' to constitutive activation of the corresponding signaling pathway. The grand-daddy of targeted therapy is imatinib (Gleevec), a tyrosine kinase inhibitor (TKI) that has been remarkable effective in controlling the growth of chronic myelogenous leukemia (CML) caused by the bcr–abl fusion oncogene produced by the so-called Philadelphia chromosome [44]. Examples of successful similar kinase targeted cancer