New paradigms in oncological therapeutics: redefining combination chemotherapy

Definitions

As oncological therapeutics evolve from cytotoxic-focused treatment to more mechanism-based interventions, it is time to redefine the terminology to more precisely reflect the tools being employed. Nuance counts; the widely used term for systemic cancer treatment with drugs, ‘chemotherapy’, carries with it well deserved negative connotations to the lay public. Among professionals, ‘chemotherapy’ implies treatment with cytotoxic agents, but can lead to confusion and miscommunication among healthcare team members, and from professionals to patients and their families.

Systemic cancer treatments include hormonal, immunological stimulatory, cytotoxic and molecular-targeted approaches. The efficacy, toxicities and mechanisms of action of these various modalities differ substantially. Lumping all of these treatments under the term ‘chemotherapy’, or even ‘multi-agent chemotherapy’, does the profession and the public a disservice, by not recognizing the profound differences in mechanism of action, therapeutic index and treatment outcome from these different types of treatment. Eliminating the term ‘chemotherapy’ in favor of more accurate terminology will probably improve the public and professional view of oncology, enhance recruitment to clinical trials, and permit more selective and beneficial treatment for cancer patients.

Future role of combined cytotoxic therapeutics

The fundamental concepts of combining cytotoxic therapeutics were conceived over four decades ago, after the realization that single agents were largely ineffective in the treatment of cancer. Cytotoxic agents were combined on the basis of their perceived cytotoxic mechanism of action, which, more often than not, was found to be nuclear DNA-based. While the attention paid to DNA-based mechanisms was scientifically fruitful, the methodologies employed to discover these mechanisms usually relied on DNA preparations in vitro. Intracellular trafficking, metabolism, organelle binding or cellular membrane protein receptor binding mechanisms have not been carefully investigated. Thus, insight into multiple mechanisms of cytotoxic agent activity has been limited. For example, cytotoxic agents have been found to induce apoptosis in many transformed cells, a mechanism attributed primarily to p53 activation associated with drug-induced DNA damage [1, 2]. However, cytotoxic agents have effects on multiple, redundant signal transduction pathways. Many of these pathways ultimately impact Bax translocation into the mitochondria membrane, a common trigger pathway for apoptosis initiation [3]. Resistance to apoptosis induced by individual cytotoxic agents may be a key target for future therapeutics or combined systemic anticancer interventions [3]. Selected cytotoxic agents may inhibit angiogenesis in transformed cells at doses much lower than those used for known cytotoxic effects [4]. Mechanisms of antiangiogenesis are not well understood, but will provide future opportunities for novel therapeutic combinations and rethinking the concept of antineoplastic therapeutic index and targets.

Broad-mechanism non-specific combination ‘chemotherapies’ with cytotoxins may have a place in future therapeutics, perhaps in preliminary tumor mass cytodestruction or, more interestingly, as specific targeting agents at lower less toxic doses. More might not be better; more might be detrimental to efficacy, due to enhanced toxicity and loss of antiangiogenic effects at the lower doses—a Gaussian rather than sigmoidal dose–response curve. Re-evaluating and rethinking cytotoxic mechanisms of action in the context of new mechanism-based therapeutics may lead to innovative combinations at doses that one might not consider if toxicity is used as the dosing end point.

Targeted therapeutics

Therapeutic agents targeting specific signal transduction pathways are rapidly moving towards the clinic. Clinical proof of this principle has emerged with the successful treatment of chronic myelocytic leukemia (CML) with imatinib mesylate (STI-571, Gleevec) [5, 6] and with the success of trastuzumab (Herceptin), a humanized mouse monoclonal antibody binding to HER-2/neu [7]. The therapeutic success of imatinib mesylate with CML can be attributed to the 95% incidence of Bcr-Abl translocation in these tumor cells unmasking constitutively activated tyrosine kinase. All transforming functions of the Bcr-Abl protein are dependent on this translocation-induced tyrosine kinase activity [8]. Based on these data, one might predict that selective inhibition of a disease-related tyrosine kinase that is not transforming in heterogeneous solid tumor masses should have minimal impact on tumor cell proliferative and apoptotic control. Imatinib’s efficacy in reducing tumor cell mass and inducing clinical remissions in patients with gastrointestinal stromal tumors is therefore all the more surprising [9]. Yet not all intestinal stromal tumors with mutated c-kit respond to imatinib mesylate. The mechan-
isms by which these unresponsive tumors subvert inhibition of the c-kit tyrosine kinase are of major importance. Studies of unresponsive or resistant tumors will teach us whether redundant pathways may also be targeted and ultimately therapeutically exploited or whether heterogenous mutations in the c-kit tyrosine kinase proteins produce stoichiometric changes in the protein that no longer permit binding of imatinib mesylate to the target [10, 11]. Future therapeutic decisions might employ cost-effective high throughput proteomic or genomic tools to provide molecular profiles for identifying whether the targeted protein or related genetic mutations are present in a tumor. Such a paradigm would allow for individualized therapies for tumors.

New concepts in combination oncological therapeutics

Will a single agent, chosen on the basis of molecular profiling, be sufficient to remove the selective advantage enjoyed by cancer cells? Not according to current thinking. Combined oncological therapeutics will be defined using many interventions. Potentially, combination non-specific cytotoxic agents might initially cytoreduce large bulk tumor masses. Clinical and preclinical synergy of classical DNA-directed non-specific cytotoxic agents with targeted therapies [12, 13] suggests that classical cytotoxic agents modulate important cellular signaling pathways so, when combined with targeted agents, they will lead to enhanced clinical efficacy. Concepts of dose-response should be considered and exploited to reduce exposure to toxic agents. Careful phase I biomarker-targeted trials could confirm unique mechanisms of classical cytotoxic agent action discovered in vitro that may lead to innovative and unexpected combination therapies.

Combination cancer therapeutics might require identification of mutated upstream signal transduction genes using high throughput genomic profiles, and identification of downstream signals with high throughput proteomic profiles with therapeutic targets individually selected. New epidermal growth factor receptor tyrosine kinase inhibitors (e.g., ZD1839/Iressa, cetuximab) will expand the repertoire of signal transduction inhibitors in cancer therapy. Many angiogenesis inhibitors that variously target vascular endothelial growth factor receptor tyrosine kinase, fibroblast growth factor receptor tyrosine kinase and the αvβ3 integrin may be useful antineoplastic agents. The challenge of understanding or predicting efficacy with these agents will be to reproducibly quantify whether drug-induced phosphorylation of other downstream signal transduction intermediates is translated into the clinical setting. Moreover, we are now challenged with redefining the concept of clinical efficacy—is lack of tumor proliferation and metastatic spread without ablation sufficient to define efficacy?

Will all of this come to pass? Only innovative well-designed translational investigations will reveal the answer. But the future today is far brighter than it was 10 years ago. And ‘combination chemotherapy’ will take on a totally different nuance and meaning than it has today.

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References