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In Focus

# Nanomedicine for Combination Therapy of Cancer

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Despite the enormous progress in our understanding of cancer biology and significant investment in developing anticancer therapeutics, the mortality rates for many common cancers have not improved or have improved only slightly in the past two decades. Innovative approaches are needed to improve the efficacy and the therapeutic index of anticancer therapy. Nanomedicines based on nanometer-sized materials that carry therapeutic agents may hold the potential to improve tumor control and reduce treatment side effects by improving the pharmacokinetics and tumor deposition of the drug payloads (Davis et al., 2008). In animal models, monotherapy nanomedicines successfully take advantage of prolonged blood circulation times to efficiently deliver therapeutic agents to tumors via the enhanced permeability and retention (EPR) effect. Nanomedicines have been modified with active targeting ligand and/or endowed with controlled release properties to further enhance tumor selectivity and drug deposition in cancer cells which in turn enhances efficacy and reduces toxicity (Davis et al., 2008). Clinically, however, nanomedicine formulations have largely failed to meaningfully improve the efficacy of chemotherapeutic interventions, in spite of their reduced toxicity. The two FDA-approved liposomal doxorubicin formulations Doxil® (PEGylated liposomal doxorubicin) and Myocet® (non-PEGylated liposomal doxorubicin) reduce most side effects (i.e. cardiomyopathy, bone marrow depression, alopecia and nausea) while increasing a few (palmar-plantar erythrodysesthesia and dermatologic toxicity). However, the formulations do not enhance anti-tumor effects in metastatic breast cancer, multiple myeloma, or Kaposi's sarcoma. Myocet® reduced the incidence of cardiac events and congestive heart failure, but showed no improvements in response rate or progression-free survival when compared to free doxorubicin in a Phase III trial in metastatic breast cancer patients. CRLX101, a polymeric micelle carrying camptothecin, was highly efficacious in animal studies but did not provide overall survival benefit when compared to best supportive care in a Phase 2b trial enrolling previously treated non-small cell lung cancer (NSCLC) patients (NCT01380769). There are several other examples of monotherapy nanomedicines that fail to produce enhanced response rates over conventional chemotherapy in clinical trials despite promising preclinical efficacy results in animal models.

The reasons for the discrepancy between preclinical animal results and clinical human trial data are debated in the nanomedicine community, but we believe that the primary reasons are the less pronounced EPR effect in and the heterogeneity of human tumors as well as the intrinsic or acquired resistance to monotherapy. The less pronounced EPR effect in human tumors calls for nanomedicines with even superior pharmacokinetics and tumor deposition which are being actively pursued by researchers. Combination therapy can theoretically have an increased chance of addressing the issues of tumor heterogeneity and drug resistance. Cancers involve multiple pathways and often develop different successive mutations and intrinsic or acquired resistance as they progress (Gottesman, 2002). In conventional monochemotherapy, it was long established that patients became less sensitive over the treatment courses as their cancers acquired resistance to the drug. Administration of multiple chemotherapeutics in a combination therapy has become a standard practice in conventional chemotherapy in order to take advantage of distinct mechanisms of action to overcome cross-resistance and achieve synergistically enhanced therapeutic outcome without significantly increasing toxicities. It is thus no surprise that recent clinical trials of nanomedicines have focused on evaluating the therapeutic efficacy of combination therapies.

Several ongoing clinical trials are evaluating the feasibility of combining chemotherapeutic nanomedicines with radiotherapy or small molecule drugs (such as gemcitabine). Pegylated liposomal doxorubicin has shown improved therapeutic efficacy when combined with radiotherapy in several animal studies and clinical trials. A Phase I trial of poly(L-glutamic acid)-bound paclitaxel (Xyotax) and fractionated radiotherapy reported four complete and seven partial responses (with reductions in tumor volume of >50%) in 12 patients with advanced esophageal and gastric cancers (Dipetrillo et al., 2006). An ongoing Phase 1b/2 investigator-initiated trial of CRLX101 combines CRLX101, capecitabine, and radiotherapy for treating patients with non-metastatic rectal cancer (NCT02010567). NC-6004, a polymeric nanoformulation carrying cisplatin, showed reduced ototoxicity and neurotoxicity while appearing to maintain therapeutic efficacy in combination with gemcitabine in Phase II clinical trials of pancreatic cancer in the UK and Japan. In the clinical trial in Japan, 1 out of 19 patients had a partial response, and 10 had stable disease. The median overall survival and PFS were 8.2 months and 3.8 months, respectively, which was comparable to what is seen with the standard combination therapy of nab-paclitaxel (Abraxane®) and gemcitabine. This combination

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chemotherapy has entered Phase III clinical trials for the treatment of locally advanced and/or metastatic pancreatic cancer (NCT02043288) and Phases I & II clinical trials for the treatment of advanced solid tumors or NSCLC (NCT02240238) (Cabral and Kataoka, 2014).

To optimize combination therapy of cancers, next-generation nanomedicines are developed to co-deliver multiple drugs or accommodate multiple therapeutic modalities. Combining multiple therapeutic agents or modalities in a single platform offers the advantages of vehicle uniformity, ratiometric drug loading, and spatiotemporal drug release over single drug-containing particles. Langer and coworkers developed nanomaterials composed of polymers and cationic lipids for the co-delivery of cisplatin and siRNA or micro RNA mimics and siRNAs, which showed enhanced anticancer efficacy over monotherapies in mouse models of prostate cancer and lung cancer, respectively (Xue et al., 2014; Xu et al., 2013). We recently reported a versatile nanoparticle platform based on nanoscale coordination polymers (NCPs) that enables different combination therapies and has demonstrated dramatically enhanced anticancer efficacy compared to monotherapy nanoparticles in mouse models with different types of resistant cancers (Liu et al., 2014; He et al., 2015a, 2015b; Poon et al., 2015). We developed NCP-**1** carrying high payloads of cisplatin and the photosensitizer pyrolipid for combined chemotherapy and photodynamic therapy (PDT) (He et al., 2015a). NCP-**1** produced superior rates of tumor regression (83% reduction in tumor volume) to monotherapy nanoparticles containing equal dose of cisplatin or pyrolipid alone in a subcutaneous xenograft mouse model of radiotherapy and cisplatin-resistant head and neck cancer. We also reported a variant of the NCP particle (NCP-**2**) that carries oxaliplatin and gemcitabine monophosphate for the synergistic combination therapy of pancreatic cancer (Poon et al., 2015). To preemptively overcome drug resistance, we developed NCP-**3** carrying cisplatin and pooled siRNAs targeting drug-resistant genes P-glycoprotein, Bcl-2, and survivin. Intratumoral injection of NCP-**3** led to tumor regression (~60% reduction in tumor volume) in the cisplatin-resistant SKOV-3 ovarian cancer subcutaneous xenograft mouse model over nanoparticles of cisplatin or combination of free cisplatin and siRNAs (He et al., 2015b).

Recent clinical and preclinical data demonstrate the potential of nanomedicines in combination therapy of cancers using multiple therapeutic agents or modalities. In the next few years, significant effort should be invested in establishing novel and optimal combination regimens, such as the combination of chemotherapy with siRNA in order to achieve improved therapeutic outcomes. Combination nanomedicines can be further modified with antibody or other tumor-targeting molecules to increase tumor deposition. An ideal combination nanomedicine is anticipated to achieve synergistically enhanced therapeutic outcome but no additive toxicity and, equally importantly, to rely on simple, straightforward, and scalable manufacturing processes with minimal batch-to-batch variations. Next-generation combination nanomedicines are expected to reduce toxicity, enhance efficacy, and overcome drug resistance to elicit sustained treatment responses in cancer patients.

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