Nanomedicine on the move: from monotherapeutic regimens to combination therapies

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Twan Lammers

Department of Experimental Molecular Imaging, RWTH Aachen University, Aachen, Germany and
Department of Targeted Therapeutics, University of Twente, Enschede, The Netherlands and
Department of Pharmaceutics, Utrecht University, Utrecht, The Netherlands
Tel.: +49 241 808 0254
tlammers@ukaachen.de

“...besides reducing drug-related side effects (in monotherapeutic regimens), nanomedicine formulations also hold significant potential for improving the efficacy of systemic anticancer therapy (when integrated in rationally designed combination regimens).”

Significant progress has been made over the years in better understanding the molecular and pathophysiological principles of malignant transformation and tumorigenesis. These improved insights into the etiology of cancer have led to the identification of several novel and highly promising classes of anticancer therapeutics, such as growth factor receptor inhibitors, proteasome inhibitors and anti-angiogenic agents. Given their ability to specifically interfere with certain hallmarks of cancer [1], these so-called molecularly targeted therapeutics, such as Herceptin® (Genentech), Erbitux® (ImClone LLC), Iressa® (AstraZeneca), Tarceva® (Astellas Pharma US, Inc.), Zolanza® (Merck & Co., Inc.), Avastin® (Genentech), Nexavar® (Onyx Pharmaceuticals) and Sutent® (Pfizer), are expected to hold significant potential for improving the balance between the efficacy and toxicity of systemically administered anticancer therapy.

An important drawback that these second-generation anticancer agents share with their first-generation DNA-damaging counterparts, however, relates to their poor pharmacokinetic and biodistributional profile upon intravenous administration. Consequently, as is the case with standard chemotherapeutic drugs, they tend to be degraded and/or excreted relatively

quickly, and they fail to efficiently localize to tumors over time. This, together with the fact that intravenously administered anticancer agents localize to and cause toxicity towards several different healthy tissues, limits their efficacy and their widespread use, and explains why only modest improvements have been made thus far in improving the therapeutic index of systemic anticancer therapy.

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To overcome these shortcomings, at least to some extent, a large number of drug-delivery systems have been designed and evaluated over the years [2,3]. These formulations are currently routinely referred to as nanomedicines, and they include, for example, passively and actively targeted liposomes, polymers, micelles, proteins, dendrimers, nanotubes, nanospheres and nanoshells. As outlined in an article in this issue, these formulations primarily aim to assist anticancer agents in overcoming some of the anatomical, physiological, chemical and clinical barriers that drug molecules are confronted with upon

intravenous administration [4]. Examples of such barriers include low molecular weight, low stability, low solubility, large volume of distribution, renal excretion, hepatic degradation, cellular and nuclear membranes, the blood–brain barrier, drug efflux pumps, low cost–effectiveness and low time–effectiveness [5]. By assisting drug molecules in overcoming some of these barriers, and thereby improving their pharmacokinetics, their biodistribution and their target site accumulation, nanomedicine formulations aim to improve the balance between the efficacy and the toxicity of systemic anticancer therapy.

In animal models, nanomedicines generally work very well: by means of their prolonged circulation kinetics and their ability to efficiently deliver drug molecules to tumors over time (via the enhanced permeability and retention effect [6]), they are generally able to improve both the efficacy and the tolerability of systemic drug therapy. In patients, on the other hand, nanomedicines are often only able to attenuate the toxicity of the intervention and they generally fail to improve the efficacy of the drug. This can be exemplified by taking into account that Doxil® (Janssen Products, LP) – PEGylated liposomal doxorubicin, arguably the most well-known nanodrug – significantly reduces doxorubicin-related side effects (such as cardiomyopathy, bone marrow depression, alopecia and nausea), but in the majority of cases does not increase patient survival. Doxil only significantly improves therapeutic outcome in patients suffering from cisplatin-responsive ovarian carcinoma; in all other tumor types for which it is approved, such as in metastatic breast cancer, multiple myeloma and Kaposi sarcoma, it only reduces the toxicity of intervention [2,3,5]. Analogously, Myocet® (Cephalon), which is non-PEGylated liposomal doxorubicin, also only affects the toxicity of systemic drug therapy: in a large Phase III trial in patients suffering from metastatic breast cancer, it reduced the incidence of cardiac events by more than half and the incidence of congestive heart failure by a factor of four, but its response rates and its progression-free survival times were comparable to those obtained for free doxorubicin. Similar observations have essentially been made for all other nanomedicine formulations evaluated in patients thus far, and polymers, proteins and micelles also generally do not improve the therapeutic index of systemic anticancer therapy by improving its efficacy, but by reducing its toxicity [2,3,5].

Based on these considerations, it seems tempting to argue that the formulations developed to date are simply not good enough. However, the picture is (much) more complicated, especially in the case of cancer, since many aspects of tumor biology and pathophysiology are still not yet properly understood, while certain others have been over- or mis-interpreted [3,7,8]. Examples of the latter include: the enhanced permeability and retention effect (the main driving force for passive drug targeting, which in patients turns out to be less prominent and less homogenous than in animal models); the poor tumor penetration of nanomedicines (especially for formulations larger than ~10 nm); and the realization that active targeting to tumor cells does not lead to increases in tumor accumulation (and therefore is only advantageous in very specific cases, such as in the case of siRNA, which needs to be delivered into cells). Another important misconception relates to the clinical use of nanomedicine formulations. Especially in early-stage clinical

trials, nanomedicines are routinely used alone and are not embedded in combination therapies. This is despite the widely accepted notion that malignancies need to be treated with more than one therapeutic modality in order to be effective and/or curative.

Based on this reasoning, in the last few years, significant efforts have been invested into the development of treatment regimens in which nanomedicine formulations are used to improve the efficacy of combined-modality anticancer therapy [5,8–11]. These include studies in which they are combined with clinically relevant fractionated radiotherapy, and in which they are used to simultaneously deliver multiple (chemo-)therapeutic drugs to tumors.

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Regarding radiotherapy, considering that the temporal and spatial interaction between intravenously administered (bi- or tri-) weekly chemotherapy and clinically relevant daily radiotherapy is suboptimal, and that long-circulating and passively tumor-targeted drug-delivery systems are able to improve the temporal and spatial parameters of this interaction, we and others have convincingly demonstrated that nanomedicine formulations hold significant potential for improving the efficacy of radiochemotherapy. Initial proof-of-principle for this tumor-targeted combination regimen has been provided by Harrington and colleagues, who showed that animals treated with PEGylated liposomal doxorubicin (i.e., Doxil) in combination with both single-dose (4.5 and 9 Gy) and fractionated (3×3 Gy) radiotherapy survived significantly longer than animals treated with free doxorubicin plus single-dose and fractionated radiotherapy [12]. Similar findings were reported in the same study for PEGylated liposomal cisplatin [12]. Davies and coworkers confirmed this notion, showing not only that Doxil is more effective than free doxorubicin when combined with single-dose (8 Gy) and with fractionated (3×3.6 Gy) radiotherapy, but also that radiotherapy improves the tumor accumulation and the intratumoral distribution of Doxil [13]. Li and colleagues reported similar findings for poly(glutamic acid)-bound paclitaxel (i.e., Opaxio™; Cell Therapeutics Inc.) [14], and also several of our own studies focusing on poly(N-[2-hydroxypropyl]-methacrylamide)-bound doxorubicin and gemcitabine convincingly showed that radiotherapy and carrier-based chemotherapy interact synergistically, with radiotherapy improving the tumor accumulation of nanomedicine formulations, and with nanomedicine formulations improving both the efficacy and the toxicity of clinically relevant regimens of radiochemotherapy [15–18]. For Xyotax, early-stage clinical trials have convincingly confirmed the potential of ‘carrier-based radiochemotherapy’, resulting in four complete and seven partial responses (with reductions in tumor volume of >50%) in 12 patients suffering from advanced esophageal and gastric cancer [19]. Similar studies with other polymer–drug conjugates, as well as with liposomal, micellar and protein-based nanomedicines, are eagerly awaited.

Nanomedicine formulations have also been shown to be highly useful for improving the efficacy of chemotherapy combinations, in particular for delivering multiple (chemo-) therapeutic drugs to tumors simultaneously. Pioneering efforts in this regard have been reported by Mayer and coworkers, who co-loaded doxorubicin and vincristine, irinotecan and floxuridine, and daunorubicin and cytarabine into liposomes, and who optimized the ratios of the encapsulated agents, in order to achieve synergistic therapeutic responses [10]. Similarly promising results have been provided for polymer therapeutics by Vicent and colleagues and by us, co-conjugating doxorubicin and aminoglutethimide, and doxorubicin and gemcitabine to the same polymeric backbone, respectively, and showing that 'polymer-based multidrug targeting' can lower the apoptosis threshold [20,21]. Analogously, Sengupta and coworkers prepared 'temporally targeted' nanoparticles termed 'NanoCells' (consisting of a doxorubicin-containing poly[lactic-co-glycolic acid]-based core and a combrestatin-containing phospholipid-poly[ethylene glycol]-based coating), and showed that the initial release of the antiangiogenic agent from the shell, followed by the subsequent release of the chemotherapeutic agent from the core, resulted in synergistically improved anti-tumor responses [22]. Clinical proof-of-principle for using nanomedicine formulations for improving the efficacy of chemotherapy combinations has also already been provided by the people who pioneered this particular area of research (that is, by Mayer and colleagues) [10]. In two recent trials, they showed that liposomes co-loaded with daunorubicin and with cytarabine are able to achieve complete disease remission in approximately 25% of refractory leukemia patients, and that liposomes co-loaded with irinotecan and with floxuridine resulted in disease control in 11 out of 15 patients suffering from colorectal cancer [23,24]. These promising findings, together with the encouraging results obtained preclinically with the above and with a number of other

two-drug-containing nanomedicine formulations, indicate that nanomedicines are highly suitable systems for improving the efficacy of chemotherapy combinations.

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Taken together, these insights convincingly demonstrate that besides reducing drug-related side effects (in monotherapeutic regimens), nanomedicine formulations also hold significant potential for improving the efficacy of systemic anticancer therapy (when integrated in rationally designed combination regimens). This notion is in line with the results obtained for the majority of molecularly targeted therapeutics, such as for Erbitux and Avastin, which are also only able to improve therapeutic outcome when combined with radio- and/or chemo-therapy. Consequently, in addition to making more (and ever more advanced) nanomedicines, future studies should also focus on the development of novel and rational combination regimens, in order to fully exploit the biocompatibility and the beneficial biodistribution of nanomedicine formulations.

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