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Perspectives

Nanomedicine formulations for combination therapies

Nanomedicine formulations are nanometer-sized carrier materials designed for improving the biodistribution of systemically applied (chemo-) therapeutic drugs. Clinically relevant examples of nanomedicine formulations are liposomes, polymers and micelles. By delivering pharmacologically active agents more selectively to pathological sites (site-specific drug delivery) and/or by guiding them away from potentially endangered healthy tissues (site-avoidance drug delivery), nanomedicine formulations aim to improve the balance between the efficacy and the toxicity of therapeutic interventions (1).

For obvious reasons, the majority of efforts in the nanomedicine field have focused on cancer, and a significant amount of preclinical evidence has been obtained showing that both passively and actively targeted carrier materials are able to improve the tumor-directed delivery of low molecular weight chemotherapeutic drugs. As a result of this, the antitumor efficacy of the conjugated or entrapped chemotherapeutic drug can often be substantially improved, while its toxicity can be attenuated.

Clinically, however – i.e. in patients instead of in animal models – nanomedicine formulations have thus far largely failed to improve the efficacy of chemotherapeutic interventions, in spite of clear evidence for prolonged circulation times and increased tumor concentrations. The primary justification for approving the well-known liposomal doxorubicin formulations Doxil and Myocet (i.e. PEGylated and unPEGylated liposomal doxorubicin, respectively), for instance, has been their ability to attenuate drug-related toxicity (i.e. cardiomyopathy, bone marrow depression, alopecia and nausea) rather than to enhance antitumor efficacy. This can be exemplified by taking the results of a phase III head-to-head comparison of free doxorubicin versus Myocet in patients with metastatic breast cancer into account, in which similar response rates (26%) and progression-free survival times (4 months) were found but in which the incidence of cardiac events (29 vs. 13%) and of congestive heart failure (8 vs. 2%) was significantly lower for the liposomal agent (1, and references therein).

Also for Doxil, significant reductions in cardiomyopathy were observed as compared to the free drug, while its response rates, its progression-free survival times and its overall survival times were comparable. Only in certain specific cases, e.g. in patients suffering from AIDS-related Kaposi Sarcomas, which are characterized by a dense and highly permeable vasculature, Doxil turned out to be able to improve both the efficacy and the toxicity of the intervention: as compared to the formerly standard combination regimen ABV (i.e. adriamycin [doxorubicin], bleomycin, and vincristine), which produced a partial response in 31 out of 125 patients (RR = 25%), Doxil achieved 1 complete response and 60 partial responses (RR = 46%) (1, and references therein).

Similar findings have been reported for polymer therapeutics. PK1, for instance – i.e. poly[N-(2-hydroxypropyl)methacrylamide]-GlyPheLeuGly-doxorubicin; the first tumor-targeted polymeric prodrug to enter clinical trials – was also found to be equally effective and less toxic than free doxorubicin. As was the case for Myocet and for Doxil, as opposed to highly promising results observed in animal models, in patients, PK1 was only found to be able to improve the therapeutic index of doxorubicin by attenuating its toxicity. This can be exemplified by taking into account that the maximum tolerated dose determined for PK1 was more than five times higher than that of free doxorubicin (320 vs. 60 mg/m^2, respectively), but that clear responses were only observed in 4 out of 36 patients (i.e. two partial and two minor responses; in patients with non-small cell lung cancer, colorectal cancer, and doxorubicin-resistant breast cancer) (1, and references therein).

To overcome this shortcoming and to broaden the clinical applicability of tumor-targeted nanomedicines, we (and others) have in the past 5 years developed several concepts for using nanomedicine formulations to improve the efficacy of combined modality anticancer therapy (2). Convincing and clinically highly relevant evidence has for instance been obtained showing that nanomedicine formulations are highly useful for improving the efficacy of radiochemotherapy and of chemotherapy combinations.

Regarding the former (i.e. radiochemotherapy), we have for instance been able to show that local external beam radiotherapy and polymeric nanomedicines interact synergistically, with radiotherapy improving the tumor accumulation of HPMA copolymers, and with the copolymers improving both the efficacy and the

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tolerability of radiochemotherapy. Using magnetic resonance imaging and γ-scintigraphy, we demonstrated in three different tumor models that pretreating tumors with radiotherapy increases their tumor accumulation by 25%–100%, depending on polymer size and on the tumor model used (3). These findings were explained by taking into account that radiotherapy increases the production of the permeability-enhancing growth factors VEGF (vascular endothelial growth factor) and FGF (fibroblast growth factor), that it induces endothelial cell apoptosis, that it reduces the cell density in tumors, and that it lowers the interstitial fluid pressure. In addition to this, reasoning that (I) the temporal and spatial interaction between i.v. applied weekly chemotherapy and clinically relevant daily radiotherapy is suboptimal, and that (II) long-circulating and passively tumor-targeted nanomedicines are able to improve the temporal and spatial parameters of this interaction (Fig. 1A, B), we have shown that HPMA copolymers are able to improve both the efficacy and the toxicity of clinically relevant regimens of radiochemotherapy (4). Both doxorubicin- and gemcitabine-containing copolymers were used for this purpose, and growth inhibition was achieved in an aggressively growing and radio- and chemo-resistant tumor model. These findings are in line with preclinical studies in which Doxil was combined with radiotherapy (5), as well as with the results of a phase I trial in which 12 patients with localized esophageal and gastric cancer were treated with the combination of poly(l-glutamic acid)-bound paclitaxel (Xyotax) and fractionated radiotherapy, and in which four complete responses and an additional seven partial responses (with reductions in tumor size of more than 50%) were achieved (6). Together, these insights convincingly show that 'carrier-based radiotherapy' holds significant potential for improving the treatment of advanced solid malignancies.

Regarding the latter (i.e. chemotherapy combinations), following up on the pioneering efforts by Vicent and colleagues (7), we have recently for the first time provided in vivo evidence showing that passively tumor-targeted polymeric drug carriers can be used to deliver two different drugs to tumors simultaneously. Both doxorubicin and gemcitabine were hereto co-conjugated to the same HPMA copolymer, and it was shown that this formulation – which we termed P-Gem-Dox – circulated for prolonged periods of time, that it localized to tumors both effectively and selectively, and that it increased the efficacy of the combination of doxorubicin plus gemcitabine without increasing its toxicity (8). In addition to this and in line with the proposed concept (Fig. 1C, D), it was found that P-Gem-Dox more effectively induced apoptosis and reduced angiogenesis than did all relevant control regimens. These findings are in line with the results recently reported by Segal and colleagues, who co-conjugated the antiangiogenic agents aminobisphosphonate alendronate and TNP-470 to a single HPMA copolymer (9), as well as with those published by Mayer and coworkers, who co-encapsulated optimal (ratiometric) ratios of doxorubicin and vincristine, of irinotecan and floxuridine, and of daunorubicin and cytarabine

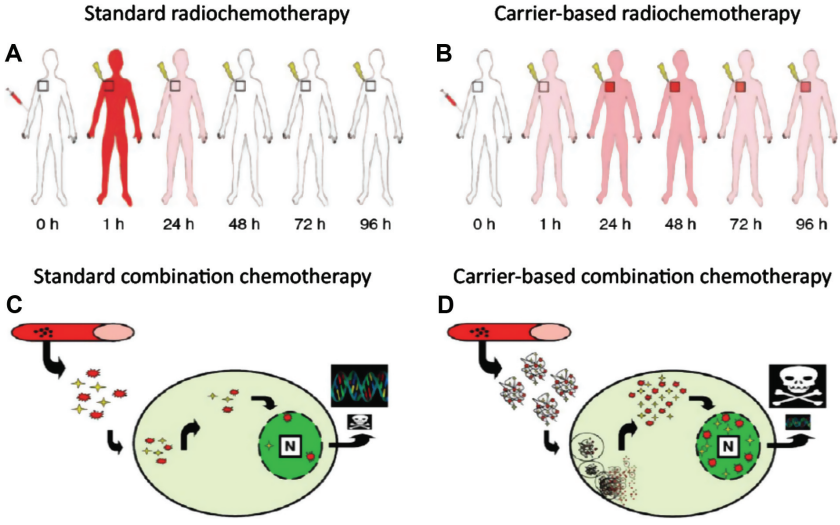

Fig. 1. Nanomedicine formulations hold significant potential for improving the efficacy of combined modality anticancer therapy. A–B: By improving the temporal and spatial interaction between i.v. applied weekly chemotherapy (red needle) and clinically relevant daily radiotherapy (yellow arrow), long-circulating and passively tumor-targeted nanomedicines increase the therapeutic index of radiochemotherapy. C–D: By simultaneously and more selectively delivering multiple chemotherapeutic agents to and into tumor cells, nanomedicine formulations lower the apoptosis threshold and thereby improve the efficacy of chemotherapy combinations.

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into liposomes and who are currently evaluating the potential of the latter two formulations in clinical trials (10).

Collectively, the above insights and advances convincingly demonstrate that nanometer-sized carrier materials hold significant potential for improving the efficacy of combined modality anticancer therapy. Consequently, they strongly suggest that along with developing novel and ever more advanced nanomedicine formulations, significant efforts should also be invested in establishing novel and more optimal combination regimens, in order to more optimally exploit the beneficial biodistribution and the advantageous efficacy-to-toxicity ratio of tumor-targeted nanomedicines.

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References

1. Lammers T, Hennink WE, Storm G. Tumour-targeted nanomedicines: principles and practice. Br J Cancer 2008; 99: 392–7.
2. Lammers T, Subr V, Ulbrich K, Hennink WE, Storm G, Kiessling F. Polymeric nanomedicines for image-guided drug delivery and tumor-targeted combination therapy. Nano Today 2010; 5: 197–212.
3. Lammers T, Peschke P, Kühnlein R, Subr V, Ulbrich K, Debus J, et al. Effect of radiotherapy and hyperthermia on the tumor accumulation of HPMA copolymer-based drug delivery systems. J Control Release 2007; 117: 333–41.
4. Lammers T, Subr V, Peschke P, Kühnlein R, Hennink WE, Ulbrich K, et al. Image-guided and passively tumour-targeted polymeric nanomedicines for radiochemotherapy. Brit J Cancer 2008; 99: 900–10.
5. Davies C, Lundstrom LM, Frengen J, Eikenes L, Bruland SOS, Kaalhus O, et al. Radiation improves the distribution and uptake of liposomal doxorubicin (Caelyx) in human osteosarcoma xenografts. Cancer Res 2004; 64: 547–53.
6. Dipetrillo T, Milas L, Evans D, Akerman P, Ng T, Miner T, et al. Paclitaxel poliglumex (PPX-Xyotax) and concurrent radiation for esophageal and gastric cancer: a phase I study. Am J Clin Oncol 2006; 29: 376–9.
7. Vicent MJ, Greco F, Nicholson RI, Paul A, Griffiths PC, Duncan R. Polymer therapeutics designed for a combination therapy of hormone-dependent cancer. Angew Chem Int Ed Engl 2005; 44: 4061–6.
8. Lammers T, Subr V, Ulbrich K, Peschke P, Huber PE, Hennink WE, et al. Simultaneous delivery of doxorubicin and gemcitabine to tumors in vivo using prototypic polymeric drug carriers. Biomaterials 2009; 30: 3466–75.
9. Segal E, Pan H, Ofek P, Udagawa T, Kopeckova P, Kopecek J, et al. Targeting angiogenesis-dependent calcified neoplasms using combined polymer therapeutics. PLoS One 2009; 4: e5233.
10. Mayer LD, Janoff AS. Optimizing combination chemotherapy by controlling drug ratios. Mol Interv 2007; 7: 216–23.