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Mini Review

Nanotechnology in Cancer: an Overview on Importance of Patient's Screening in Nanomedicine Based Combinational Therapies

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Abstract

Targeting cancer using nanomedicine is not a new concept. Earlier focus was on targeted therapy and then concept came of combinational therapy. Along with the use of combinational therapies, Pre-selection screening of the patients using molecular approach is equally important to achieve the maximum benefit to the cancer patients.

Keywords: Nanotechnology; Nanomedicine; Cancer; Combinational Therapy; Biological Systems; Liposomal Formulations; Targeting Tumors; Cardiomyopathy; Solid Tumors; Meta-Analysis

Mini Review

Nanotechnology is the division of technology which deals with the design, production, characterization, and applications of the matter at nano scale in terms of size and shape ranging between 1 to 100nm [1]. Nanomaterials can be engineered either solid or hollow structure with different sizes, shapes along with different chemical compositions with the properties to deliver higher ratio of surface area over volume [2-4]. The applications of the nanotechnology are very diverse in the field of science ranging from Physics, chemistry to biological Science [5]. Nanotechnology is very useful in medical applications for the prevention, diagnosis as well as cure of diseases at molecular level, due to similarity in scale of biological molecules and nanomaterials, Applications of nanomaterials being designed for the biological systems include ability to cross the biological barriers for the transport of therapeutic or diagnostic materials so that efficient access to biological molecules, maximum molecular interaction and detection of molecular changes can take place in a high throughput manner [6-8]. To target cancer, several nanotechnology based drug delivery vehicles, nanomedicine, diagnostic devices, and contrast agents got approved from Food and Drug Administration (FDA) or are under clinical investigations [3,9,10]. Current overview describes the past, present and future prospects of nanomaterials in biological systems to target cancer.

Nanotechnology and Nanomedicine

The use of nanotechnology in medicine is not a new field and started back in 1990s when use first liposomal formulated nanomedicine was approved [11]. Despite showing improved therapeutic efficacy and reduced toxicity in nonclinical model systems, use of these liposomal formulations were limited due to lack of reproducibility in patients. Nanomedicine represents the contribution of physicists, chemists and biologists at a single platform and is highly intensive and creative area with wide range in concept and designs. Having a quick review over the years on nanomedicine research reveals that, despite early success rate with liposomal formulations of chemotherapies, nanomedicine research is mainly focused in academic departments, start ups, and in small industries and have limited investment of large pharmaceutical industries due to low success rate. Regardless of less success rate and due to several technical challenges over the years, new drug combinations and materials with improved therapeutic index have been designed and many of these newly formulations are in clinical trials [6-8].

Nanomedicine and Cancer

Targeting tumors and efficacy using nonmaterial as drug delivery vehicles is potential therapeutic approach in the field of

cancer therapy and is field of discussion especially in solid tumors [12]. Despite so much of research over the years, only few tumour-targeted nanomedicine formulations are succeeded till date in terms of potential drug products [13]. The major challenge is the uptake of drug in the solid tumors as recent meta-analysis study shows that in preclinical models, the only 0.7% uptake of injected dose (ID) the nanoparticle based drug formulation accumulates in tumors when administered intravenously [14]. Antibodies are also considered as nanomedicine being used for cancers and have similar scenario and tumor concentration ranges between 0.07 to 7% ID when compared to other nanomedicine or liposomes formulations, and not able to target tumors efficiently both in animal models and humans. In this context, patients benefit is the primary goal and efforts are going on in the direction. Administrations of nanomedicine like antibodies are able to increase uptake of targeted drugs at tumor site when compared to small molecules drugs given intravenously. To advance patients' benefit, more and more efforts are going on for the increased uptake of nanomedicine in tumor proximity, either alone or in combinations and with minimum loss to endangered healthy tissues of the body.

Nanomedicine and Cancer: Past, current and future prospects

In the past, several clinically successful tumor targeting nanomedicine have been designed and one of them is PEGylated liposomal doxorubicin (Doxil) [11]. Doxorubicin alone accumulates in the heart and causes cardiomyopathy but PEGylated liposomal formulation is better tolerated alone and/or in combinations and very effective in terms of improved tumor concentrations as well as attenuates drug accumulation in the heart and improve the quality of life of patient. Another effective drug is Abraxane with respect to patient benefit [15]. Abraxane ranges about 130nm in size and is made up of co-condensate of albumin and paclitaxel. Abraxane is very unstable in blood and less effective for solid tumors. Pharmacokinetically, Abraxane is similar to Taxol, another drug which is Cremophor EL-based formulation of paclitaxel and is routinely being used clinically. Abraxane have several advantages over Taxol and is clinically successful in terms of patient benefit as it have shorter infusion time, ability to increase drug dose and can be used in combination treatment. In our own study, we used Cremophor EL free alternative elastic liopsomal paclitaxel formulations for efficacy and toxicological studies in animal model and our formulation found to be very effective as reduced toxicity and enhanced anti-cancer activities were observed [16].

In the past and till date, the most of the cancer nanomedicine are on the basis of established drugs either its Paclitaxel or doxorubicin and selection of these drugs for preclinical trials is justified that a lot of information is available about these drugs including their efficacy, Pk/PD, clinical importance and side effects. Apart from established drugs, now a day's focus is on the new agents which appear to be highly potent but falling short in in-vivo studies due to undesired efficacy-to-toxicicological status and Pharmacokinatics properties. Nucleotide-based bioactive such as Tubulin-binding antimitotics mertansine and monomethyl auristatin E, carrier-based drug formulations are the best example of such chemotherapeutic drugs which are highly potent and at the same time are very toxic. To avoid their toxicity, efforts are in progress to prepare nano formulations of these drugs in conjugation with antibodies for accurate targeting so that concentration of these drugs can be enhanced in tumor proximity and drug toxicity can be avoided with the minimum loss to the normal critical organs. In this regard, conjugation of anti¬body–drug such as combination of Kadcyla (trastuzumab emtansine) and Adcetris (brentuximab vedotin) showed promising results in terms of improved patient heath and benefits. In recent times, most of the cancers are being treated in the combinational therapy and both Doxil and Abraxane are showing good clinical importance in combination regimens. Similar improved clinical importance was observed in combination therapies with other Onivyde (liposomal irinotecan) nanomedical drug. Recently, Vyxeos liposomes, a second-generation nanomedicine shown increased survival rate in severe acute myeloid leukaemic patients in phase III clinical trials when combination of cytarabine and daunorubicin co-loaded synergistically of 5:1 molar ratio. For the better future of nanomedicine in anticancer therapy, other efforts are going on to combine nano formu¬lations with other therapies such as immu¬notherapy and radiotherapy.

Before treatment, screening and selection of the patients is also an important aspect for the better treatment [17,18]. For example, before treatment with trastuzumab (Herceptin), human epidermal growth factor receptor (HER2) immune-histochemical staining biopsy is required in case of breast cancer patients [19]. With screening more than 50% patients responded to Herceptin treatment when compared to without biopsy-based pre-selection whose success rate is only 10-15%. Further more and more parallel diagnostic parameters are required for improved performance of nanomedicine formulations.

Another alternative pre-selection diagnostic companion is the use of nano-size based imaging tools, such as use of nano-probes in magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) [17,18]. Metastasis is the lethal form of cancer and till date imaging is the only tool to detect metastatic and very helpful in the exclusion of patients who are unlikely to respond due to no target site localization and only patients are being included with high accumulation of injected dose in tumors and metastasis and without it, it's unfeasible to assess the importance of anti-metastatic therapies. Enrolled clinical trials patients mostly suffer with metastasis phase and are severe form of cancer and accumulation of injected dose becomes important for nanomedicine therapies which suggest that imaging is important tool to fill the gap between nanomedicine and effective cancer therapy. In this direction, more dedicated efforts are required at academic and preclinical levels to make clinical evaluation more efficient to provide maximum benefit to the patients.

Conclusion

Despite lower percentage of tumor accumulation of injected dose, nanomedicine are effective alone and more effective in combinational therapies. Apart from just targeting and combinational therapies, to achieve rapid and efficient clinical translation and to provide maximum benefits to the patients, more and more efforts are required in the pre-selection screening of the patients, which is the overall aim to target cancer using nanomedicine.

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