

Experimental therapies using nanoparticles: nanomaterials in triple-negative breast cancer (TNBC) treatment

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ABSTRACT

Triple-negative breast cancer (TNBC) accounts for approx. 10–20% of breast cancer diagnoses worldwide. Triple-negative breast cancer cells have no estrogen nor progesterone receptors and lack overexpression of human epidermal growth factor receptor. As no hormone therapy can be implemented, chemotherapy remains the main weapon. Nowadays, widely available

chemo regimens for TNBC treatment can consist of anthracyclines, taxanes, antimetabolites, or platinum, but all of the aforementioned are highly toxic to the bone marrow, liver, kidneys, and nervous system. Targeted treatment using nanotechnology seems to be a ray of hope in impeding this morbid disease.

Keywords: triple negative breast cancer; nanotechnology; nanoparticles; oncology.

INTRODUCTION

Triple-negative breast cancer (TNBC) accounts for approx. 10–20% of breast cancer diagnoses worldwide [1, 2]. Triple-negative breast cancer cells have no estrogen nor progesterone receptors and lack overexpression human epidermal growth factor receptor. For this reason, it remains a great challenge for clinicians to treat this cancer subtype successfully and its mortality rate is still unacceptably high [3]. As no hormone therapy can be implemented, chemotherapy still remains the main weapon. Nowadays, widely available chemo regimens for TNBC treatment can consist of anthracyclines, taxanes, antimetabolites, or platinum, but all of the aforementioned are highly toxic to bone marrow, the liver, the kidneys, and the nervous system [4]. As TNBC rapidly becomes chemo-resistant and can spread to distant organs, novel therapies are urgently needed to improve outcomes. Targeted treatment using nanotechnology seems to be a ray of hope in impeding this morbid disease, as nanocarriers can improve the bioavailability of the drug, minimizing toxicity at the same time. In this paper, the author would like to summarize some of the most interesting novel experimental therapies of TNBC based on nanoparticles (NPs).

SUPERIORITY OF NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS OVER TRADITIONAL METHODS

Traditional TNBC treatments, such as radiotherapy (RT) or conventionally delivered chemotherapy (intravenous or oral), lack site-specificity. For this reason, they are toxic not only to malignant cells but for the whole organism as well. The concentration

of chemotherapeutics is hard to control as water-solubility is mostly low, and drug resistance quickly develops [5]. With NPs, the pharmacological properties of chemotherapeutics may be enhanced – they become more stable and soluble, and their half-life expands. Nanocarriers can also overcome biological barriers due to their small size – remarkably smaller than cancer cells or their surrounding blood vessels. When encapsulated in a NP, a drug can also avoid being metabolized before reaching the target cell. Organic NPs, for example liposomes, are also biocompatible – this feature makes the treatment better tolerated by the patient as liposomes do not induce adverse immune reactions [6].

SELECTION OF CURRENT RESEARCH OF NANOPARTICLES IN TRIPLE-NEGATIVE BREAST CANCER

Liposomal edelfosine inhibits triple-negative breast cancer growth *in vitro* and *in vivo*

A study by Saraiva et al. focused on edelfosine, a synthetic alkyl-phospholipid in the form of nanoemulsion as a potential treatment for TNBC [7]. Edelfosine itself showed promising effects in phase I and phase II trials in acute leukemia, osteosarcoma, or brain tumor treatment, but its gastrointestinal toxicity and immunosuppressive effect when administered via the traditional route is high [8]. Saraiva et al. created an ethanol-dissolved mixture of Miglyol 812, phosphatidylcholine, and edelfosine and injected it into ultrapure water while magnetically stirring to obtain nanoemulsified edelfosine (ET-NEs). The particles were then studied *in vitro* and *in vivo*. *In vitro*, ET-NEs showed higher toxicity to TNBC cells than free

ET. Furthermore, the study performed *in vivo* on zebrafish embryos containing a xenograft TNBC tumor showed significant regression in tumor size when treated with ET-NEs [7]. Thus, liposomal edelfosine arises as a promising treatment option for TNBC, though further studies are certainly needed.

Overcoming hypoxia-induced doxorubicin resistance using nanoparticles

Hypoxia in the cancer cells is one of the underlying causes of developing chemotherapy resistance. It is most common in rapidly growing neoplasms, as their ability to develop proper vasculature is inadequately low for the expanding tumor size. Thus, chemotherapeutics cannot be distributed into the cancer cells as well as expected [9]. Interesting original research by Cheng et al. revealed that calcium peroxide-modified magnetic nanoparticles (CaO₂-MNPs) can improve the effects of doxorubicin treatment of TNBC due to their ability to generate oxygen, thus altering the hypoxic tumor environment [10]. The study was conducted on a mouse model. First, the authors stated that overexpression of hypoxia-inducible factor 1- α (HIF-1 α) occurs in tissues that lack oxygen. Hypoxia-inducible factor 1- α significantly amplified doxorubicin resistance in tumor cells and inhibited their apoptosis after doxorubicin exposure. In the study, CaO₂-MNPs succeeded to stimulate the degradation of HIF-1 α and promote apoptosis of TNBC cells as an effect. Researchers concluded that overcoming hypoxia via oxygen-releasing NPs can be a powerful additional weapon to standard medications.

Boosting radiotherapy effects in triple-negative breast cancer using gold nanoparticles (AuNPs)

Radiotherapy is typically included in the TNBC treatment regimens, as it works via direct DNA damage and can enhance the cytotoxic effects. Unfortunately, like conventionally delivered chemotherapeutics, RT does not distinguish between healthy and cancerous cells and can result in major side effects, including fibrosis, skin burns, or lymphoedema. Thus, NPs can act as localized sensitizers that improve the absorption of radio waves in cancerous tissues, sparing the neighboring ones. The idea of NP-driven RT is based on the high absorption coefficient of metals with high Z (atomic) numbers, such as gold, gadolinium, or hafnium [11, 12]. Janic et al. focused on gold nanoparticles (AuNPs) as vectors to raise the effectiveness of standard RT in TNBC [13]. They grew TNBC on nude mice, then injected 100 μ g of 4–14 nm AuNPs into the tumors and irradiated them with a 15 Gy dose of X-ray. The size of each tumor was evaluated every 4 days, and after 36 days of the experiment, they were excised and underwent immunohistochemical analysis. Injecting the NPs directly into the tumor allowed greater bioavailability, as there was no uptake by the liver or filtration by the kidneys. In the study, the use of both sizes of AuNPs resulted in a delay in tumor growth even before the RT was induced. Mice that underwent RT and had 14 nm AuNPs injected, also had better results of irradiation. The authors concluded that smaller-size NPs may not have significantly influenced results

when combined with RT due to their more uneven distribution in the tumor, as they tend to aggregate in the cytosol. Interestingly, the injection of AuNPs itself, no matter the size, resulted in increased levels of serum cell death biomarkers, such as calreticulin – a protein considered to be pre-apoptotic.

Exosomes, endogenous nanoparticles as drug delivery systems in triple-negative breast cancer

Exosomes are small vesicles of endogenous origin that can measure up to 150 nm in diameter. They develop from the cell membrane and can naturally act as carriers of a whole spectrum of substances such as nucleic acids, lipids, proteins, etc. Exosomes have numerous other functions – not only cell-to-cell substance transport but also immunomodulation or tissue repair [14, 15]. There is a field of growing research on using exosomes as drug-delivering Trojan horses in TNBC. In a study by Yu et al., researchers encapsulated erastin, a ferroptosis-inducing chemotherapeutic, into folic-acid (FA) enriched exosomes using ultrasound. Erastin acts via inducing reactive oxygen species production and depleting cells' glutathione supplies, which results in cell death. Placing erastin into an exosome helped to increase its water-solubility and make it less toxic to the kidneys [16]. Folic acid was used as a “road-sign” here, as FA receptors are being overexpressed in TNBC cells, thus erastin could be delivered in a more targeted way to the cancerous tissues. The study showed greater efficacy in inducing ferroptosis by FA-enriched erastin exosomes (erastin@FAexo) than erastin exosomes (erastin@exo) or erastin itself.

CONCLUSION

Nanomedicine is a relatively new field that requires the cooperation of numerous specialists, not only clinicians, to improve patient outcomes and quality of life. With rapidly evolving knowledge, there are many promising therapeutic targets in pre-clinical trials for the most morbid type of breast cancer – TNBC. According to clinicaltrials.gov, there are currently over a dozen recruiting studies, regarding the use of NPs in this specific type of neoplasm. In these studies, regimens include mostly albumin-bound paclitaxel in combination with other previously known or newly developed drugs. Having said this, it is a necessity to point out that there is still a whole broad spectrum of NPs to investigate. They can be used not only as superior drug-carriers but can also be of great value in malignancy detection and monitoring the therapeutic response. The author of this summary believes NPs are powerful and innovative weapons.

REFERENCES

1. Howard FM, Olopade OI. Epidemiology of triple-negative breast cancer: a review. *Cancer J* 2021;27(1):8-16. doi: 10.1097/PPO.0000000000000500.

2. Boyle P. Triple-negative breast cancer: epidemiological considerations and recommendations. *Ann Oncol* 2012;23 Suppl 6:vi7-12. doi: 10.1093/annonc/mds187.
3. Cho B, Han Y, Lian M, Colditz GA, Weber JD, Ma C, et al. Evaluation of racial/ethnic differences in treatment and mortality among women with triple-negative breast cancer. *JAMA Oncol* 2021;7(7):1016-23. doi: 10.1001/jamaoncol.2021.1254.
4. Gupta GK, Collier AL, Lee D, Hoefler RA, Zheleva V, Siewertsz van Reesema LL, et al. Perspectives on triple-negative breast cancer: current treatment strategies, unmet needs, and potential targets for future therapies. *Cancers (Basel)* 2020;12(9):2392. doi: 10.3390/cancers12092392.
5. Kumari P, Ghosh B, Biswas S. Nanocarriers for cancer-targeted drug delivery. *J Drug Target* 2016;24(3):179-91. doi: 10.3109/1061186X.2015.1051049.
6. Lungu II, Grumezescu AM, Volceanov A, Andronescu E. Nanobiomaterials used in cancer therapy: an up-to-date overview. *Molecules* 2019;24(19):3547. doi: 10.3390/molecules24193547.
7. Saraiva SM, Gutiérrez-Lovera C, Martínez-Val J, Lores S, Bouzo BL, Díez-Vilares S, et al. Edelfosine nanoemulsions inhibit tumor growth of triple negative breast cancer in zebrafish xenograft model. *Sci Rep* 2021;11(1):9873. doi: 10.1038/s41598-021-87968-4.
8. Lasa-Saracíbar B, Aznar MÁ, Lana H, Aizpún I, Gil AG, Blanco-Prieto MJ. Lipid nanoparticles protect from edelfosine toxicity *in vivo*. *Int J Pharm* 2014;474(1-2):1-5. doi: 10.1016/j.ijpharm.2014.07.053.
9. Luo W, Wang Y. Hypoxia mediates tumor malignancy and therapy resistance. *Adv Exp Med Biol* 2019;1136:1-18. doi: 10.1007/978-3-030-12734-3_1.
10. Cheng FY, Chan CH, Wang BJ, Yeh YL, Wang YJ, Chiu HW. The oxygen-generating calcium peroxide-modified magnetic nanoparticles attenuate hypoxia-induced chemoresistance in triple-negative breast cancer. *Cancers (Basel)* 2021;13(4):606. doi: 10.3390/cancers13040606.
11. Verry C, Porcel E, Chargari C, Rodriguez-Lafrasse C, Balosso J. Utilisation de nanoparticules comme agent radiosensibilisant en radiothérapie: où en est-on? *Cancer Radiother* 2019;23(8):917-21. doi: 10.1016/j.canrad.2019.07.134.
12. Her S, Jaffray DA, Allen C. Gold nanoparticles for applications in cancer radiotherapy: Mechanisms and recent advancements. *Adv Drug Deliv Rev* 2017;109:84-101. doi: 10.1016/j.addr.2015.12.012.
13. Janic B, Brown SL, Neff R, Liu F, Mao G, Chen Y, et al. Therapeutic enhancement of radiation and immunomodulation by gold nanoparticles in triple negative breast cancer. *Cancer Biol Ther* 2021;22(2):124-35. doi: 10.1080/15384047.2020.1861923.
14. Simons M, Raposo G. Exosomes – vesicular carriers for intercellular communication. *Curr Opin Cell Biol* 2009;21(4):575-81. doi:10.1016/j.ceb.2009.03.007.
15. Zhou X, Xie F, Wang L, Zhang L, Zhang S, Fang M, et al. The function and clinical application of extracellular vesicles in innate immune regulation. *Cell Mol Immunol* 2020;17(4):323-34. doi: 10.1038/s41423-020-0391-1.
16. Yu M, Gai C, Li Z, Ding D, Zheng J, Zhang W, et al. Targeted exosome-encapsulated erastin induced ferroptosis in triple negative breast cancer cells. *Cancer Sci* 2019;110(10):3173-82. doi: 10.1111/cas.14181.