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EDITORIAL NOTE

Recent Advances in Sorafenib based Nanoformulation for Enhanced Cancer Therapy

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Sorafenib, a multi-kinase inhibitor has gained significant attention in cancer therapy. However, the clinical use of sorafenib is limited by poor aqueous solubility, low bioavailability, unfavorable pharmacokinetic properties, and undesirable side effects including anorexia, gastrointestinal bleeding, and severe skin toxicity. To overcome these drawbacks, the encapsulation of sorafenib into nanocarriers is an effective strategy. With advancements in nanotechnology, sorafenib-based nanoformulation has been developed to enhance their targetability and bioavailability. Various strategies, such as ligand-mediated targeting and stimuli-responsive systems, enable selective drug delivery to cancer cells while overcoming multidrug resistance. This editorial highlights the recent advances in sorafenib-based nanoformulation (liposomal, polymer, metallic) for improved cancer therapy.

Sorafenib marketed as Nexavar® by Bayer, is a drug approved for the treatment of advanced renal cell carcinoma, hepatocellular carcinoma, and radioactive iodine-resistant advanced differentiated thyroid carcinoma. The anti-tumor mechanism involves cell growth, proliferation, metastasis, angiogenesis inhibition, and downregulation of apoptosis pathways. The clinical use of this drug caused severe side effects like liver problems, heart problems, bleeding, high blood pressure, and severe skin reactions. The targetability and bioavailability have been improved by encapsulating sorafenib in biomacromolecules, synthetic polymers, and silver and gold nanoparticles.

Nanoformulations have been under research to specifically target tumor tissues with various targeting strategies, including ligand-mediated targeting, stimuli-responsive systems, and passive targeting through the enhanced permeability and retention effect. By incorporating ligands or antibodies onto the surface of nanocarriers, sorafenib has been selectively delivered to cancer cells. Furthermore, stimuli-responsive systems, such as pH or enzyme-responsive nanoparticles, enable site-specific drug release in the tumor microenvironment, further enhancing the tumor-targeting capabilities of sorafenib-based nanoformulation.

Sorafenib caused resistance through various mechanisms such as JAK-STAT pathways,

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PI3K/Akt pathway, hypoxia-inducible pathways activation, and epithelial-mesenchymal transition among others. Strategies such as the co-delivery of sorafenib with MDR inhibitors, modulation of drug efflux mechanisms, and nanoparticle-mediated drug penetration have been explored. Multidrug resistance (MDR) remained a significant challenge in cancer treatment. Nanoformulation has shown promise in overcoming MDR by improving the intracellular accumulation of sorafenib and circumventing efflux pumps. These approaches have demonstrated the ability to sensitize MDR cancer cells to sorafenib, restoring its efficacy and improving patient outcomes.

Liposomal sorafenib delivery offered the advantages like enhanced drug solubility, improved stability, enhanced pharmacokinetics, targeted delivery, biodegradability, and controlled release. We have reported the use of folate-ornamented sorafenib-loaded liposomes for safe intravenous administration, their anticancer effect, biodistribution, and bioavailability in mice with ultrasound application. Our study has provided valuable insights into the potential of these liposomes as theranostic agents with dual properties of therapeutics and imaging, as demonstrated through ultrasound and optical imaging.

Polymeric nanoparticles, often made from polymers such as poly (lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), or chitosan, micelles, polymer-drug conjugates, and dendrimers have been utilized to encapsulate sorafenib. Metallic nanoparticles like gold nanoparticles (AuNPs), iron oxide nanoparticles, silver, and platinum-based nanoparticles have been explored as carriers for sorafenib delivery due to their unique antimicrobial and anticancer properties and potential synergistic effects for cancer therapy.

Ultrasound-mediated sorafenib delivery holds promise as a non-invasive and targeted approach for enhanced therapeutic effects. We have reported the development of folate-ornamented sorafenib-loaded liposomes for the treatment of liver cancer. The liposomes improved drug solubility and safe intravenous administration, while ultrasound application enhanced drug penetration and release at the tumor site. Our results suggested that these theranostic liposomes, with both therapeutic and imaging capabilities, overcome oral delivery limitations and improved drug biodistribution within tumor tissues. Targeted delivery combined Sorafenib-loaded nanoformulation with imaging agents, such as fluorescent dyes or contrast agents (Fluorescein, Indocyanine Green, quantum dots, and MRI) to enable real-time drug delivery visualization and monitoring. This integration of imaging modalities allows for the assessment of drug distribution, accumulation, and therapeutic response, helping to guide targeted delivery strategies.

In conclusion, sorafenib-based nanoformulation offered enhanced drug delivery, improved therapeutic outcomes, and reduced side effects. Targeting strategies, imaging agents, and ultrasound-mediated delivery techniques further enhanced the potential of these nanoformulations for cancer therapy. Further research and development are needed to optimize these approaches and translate them into clinical practice.