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Opinion Article

Enhancing Boron Neutron Capture Therapy with Light-Triggered Polymer-Drug Conjugates

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DESCRIPTION

In Boron Neutron Capture Therapy (BNCT), the effectiveness of boron-based drugs depends on achieving high concentrations of boron in the tumor while ensuring rapid clearance from the blood and healthy tissues. However, accomplishing both high tumor accumulation and fast systemic clearance simultaneously remains a challenge. To address this, we developed a polymer-drug conjugate capable of controlling the clearance of boron drugs from the bloodstream in a temporal manner. This conjugate is based on a biocompatible polymer that passively accumulates in tumors. The polymer's side chains are linked to low-molecular-weight boron compounds, which are rapidly excreted by the kidneys, using photo labile linkers. In a murine subcutaneous tumor model, the conjugate showed significant tumor accumulation, with a Tumor-to-Normal tissue boron concentration ratio (T/N ratio) of approximately 10 after intravenous administration. However, an important portion of the conjugate remained in the bloodstream. When exposed to light, the photo labile linkers in the blood vessels were cleaved, releasing the boron drugs, which were then quickly eliminated via renal excretion. This light-triggered clearance of the boron drug from the bloodstream allowed for the maintenance of high boron concentrations in the tumor, enhancing the efficacy of BNCT. Given that BNCT relies on the dose of thermal neutrons delivered to solid tumors without exceeding radiation limits in normal tissues, this approach can potentially increase the therapeutic radiation dose to tumors, improving treatment outcomes.

BNCT works by targeting cancer cells with α particles and lithium recoil nuclei generated when boron (10B) atoms absorb thermal neutrons. These high-energy particles travel only short distances (around 10 μm, which is the size of a cell), allowing selective destruction of cells that take up sufficient boron. For effective therapy, it is important that boron is selectively delivered to tumor cells, as thermal neutrons are scattered throughout the body, irradiating both tumors and healthy tissues. Currently, for BNCT to be effective, the boron concentration within tumors needs to be ≥ 25 ppm and the Tumor-to-Blood (T/B) and T/N ratio ratios should be ≥ 2.5. These ratios dictate the maximum tolerable radiation dose, so improving the T/B and T/N ratios is critical for enhancing the therapeutic efficacy of BNCT.

Upon photo irradiation of blood vessels, the photo labile linker was cleaved, causing rapid renal clearance of the released boron drug from the bloodstream, while the boron concentration in the tumor remained high. As a result, the T/B ratio was significantly increased in a light dose-dependent manner, exceeding the clinical threshold. This strategy not only enhanced the boron concentration within the tumor but also improved the therapeutic effects of BNCT in challenging conditions representing clinical situations. The concept of light-controlled pharmacokinetics holds great promise for advancing Drug Delivery Systems (DDSs), offering a new approach to optimize drug delivery and enhance therapeutic outcomes.

In cancer drug delivery, particularly with alkylating agents and kinase inhibitors, ensuring sustained drug exposure to the tumor is crucial. Strategies that improve tumor accumulation and extend blood circulation are key to enhancing therapeutic outcomes. For practical boron neutron capture therapy (BNCT), designing drug delivery systems (DDSs) requires a fundamental shift in how pharmacokinetics are managed. This study presents a novel approach by demonstrating the enhancement of BNCT efficacy through active pharmacokinetic control using light. This innovative strategy optimizes the timing of thermal neutron irradiation, ensuring that the drug is effectively present in the tumor at the right moment for maximum therapeutic benefit. This is the first study to showcase how light can be used to control pharmacokinetics and improve BNCT outcomes, offering a new direction for developing more effective cancer treatments.

CONCLUSION

By utilizing light-controlled pharmacokinetics, this system effectively increases the T/B ratio, a critical factor for optimizing therapeutic efficacy in BNCT. The conjugate demonstrated sustained tumor accumulation with high boron concentrations while enabling rapid clearance from the bloodstream upon light irradiation. This approach not only meets the clinical

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requirements for BNCT but also enhances treatment outcomes by maximizing tumor radiation dose while minimizing damage to normal tissues. Light-triggered pharmacokinetics offers an exciting strategy for improving drug delivery in cancer therapy.