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Supramolecular nanomedicine targeted therapy for tumor treatment

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Abstract. In recent years, the incidence of multiple myeloma (MM) has been increasing significantly and showing a trend of younger age. With the advent of new therapies, the median overall survival of patients with MM has improved, but some still relapse early or even pass away. Meanwhile, chemotherapy drugs such as Bortezomib (BTZ) used in patients bring great pain to them because of its non-targeting. Based on this, this paper explores a supramolecular nanomedicine with targeted therapeutic effect on tumors and evaluates the potential of this drug to form new supramolecular nanomedicine. The drug is a combination of BTZ, the natural polyphenol Caffeic Acid (CA), and iron ion (Fe^{3+}), a supramolecular design that brings many advantages to cancer treatment systems, including efficient drug loading, excellent biodegradability and bio-compatibility. Studies have shown that this supramolecular nanomedicine can effectively reduce the killing effect of chemotherapy BTZ on normal cells. This kind of supramolecular nanomedicine provides a new idea for the construction of tumor targeting drugs and is also hopeful to be applied to more chemotherapy drugs.

Keywords: Multiple myeloma, Bortezomib, caffeic acid.

1. Introduction

MM is a plasma cell malignant tumor, mostly occurred in the middle-aged and elderly people. It is typified by the patient's bone marrow containing tumor-like plasma cells that proliferate, with the majority of them secreting monoclonal immunoglobulin, which ultimately leads to the damage of the patient's organs or tissues. The current common treatment for this disease is to treat patients with chemotherapy using BTZ. As a first-line anti-tumor drug, BTZ can induce tumor cell apoptosis, delay tumor growth and improve progression-free survival in patients with MM. However, because BTZ does not have the effect of targeted tumor therapy, it can also cause certain damage to normal cells, resulting in a series of related side effects such as weight loss and anemia in patients. Therefore, improving the non-targeting of BTZ will be conducive to better clinical treatment of MM.

Based on this situation, this article will introduce a new supramolecular nanomedicine, which combines BTZ with the natural polyphenols CA and Fe^{3+} to form a stable supramolecular nanomedicine with targeted tumor therapy properties. Among them, BTZ and natural polyphenols CA realized simple coupling through catechol-boric acid groups and further combined with cross-linking agent Fe^{3+} to increase the stability of the drug. By means of the acidic character of the malignancy environment and

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the endocytosis of cells, the catechol-boric acid group-coupled complex can produce dissociation, thereby releasing drugs targeted to the tumor site to produce drug effects. Therefore, the supramolecular nanocomplex composed of BTZ, CA and Fe^{3+} can target the tumor site, effectively deliver and release BTZ which can also weaken the non-targeted side effects of previous chemotherapy BTZ and significantly induce cancer cell apoptosis and inhibit tumor growth, providing new vitality for the treatment of patients with MM disease. This supramolecular nanocomplex therapy can also be further applied to other non-targeted drugs containing boric acid groups or non-hydrophilic drugs to treat more diseases.

2. Targeted therapeutic mechanism of supramolecular nanomedicines

Supramolecular nanomedicine refers to supramolecular preparations that are effective in the diagnosis and treatment of diseases at the nanoscale through non-covalent interactions or dynamic covalent bonds. Studies have shown that supramolecular nanomedicine has broad prospects in the identification, management, and avoidance of numerous illnesses, including cancer. Current design strategies typically involve reasonably designed layered assembly processes that result in a variety of thermodynamically or dynamically stable nanostructures with precisely controlled components of diagnosis and treatment as well as the features of the stimulus response to physiological markers.

Stimulus-activated nanomedicines can self-assemble, disassemble or functionally activate after exposure to endogenous/exogenous stimuli to improve their biosafety and diagnostic/therapeutic efficacy [1,2]. The borate bond of BTZ can be simply coupled with the catechol molecule of natural polyphenol and it is easy to form a dynamic drug diphiles and this binding is ph-dependent, and can produce dissociation under acidic conditions. Therefore, the acidic conditions in the surroundings of the tumor and inside cells of cancer cells able to used as an inducement to provide medication payloads, to free BTZ from natural polyphenols, and to ensure that the drug active sites of both components are free to exert their anticancer properties, and then treat the disease at the target tumor site [3].

3. Composition BTZ supramolecular nanomedicine

3.1. BTZ

BTZ is the first generation proteasome inhibitor. Currently, BTZ is commonly used in MM, T cell lymphoma and widely used in the chemotherapy of hematological malignancies. Although BTZ has effective anti-cancer activity, it cannot play the effect of targeted therapy. It can not only treat tumor cells but also cause damage to normal cells to a certain extent, leading to peripheral neuropathy. In addition, its drug resistance, poor stability and high toxicity are serious. Its long-term efficacy are also limited. In particular, BTZ-induced peripheral neuropathy (BIPN) is defined by paresthesia of deadness and pain, it continues to rank among the most disturbing hurtful events. The main mechanism of action of BTZ is to inhibit chymotrypsin-like sites in the 20S proteolytic core of the 26S proteasome, thereby inducing cell cycle arrest and apoptosis. However, in the last 5-10 years, various preclinical evidence has been generated. Although BTZ cannot penetrate the blood-brain barrier, which cousesthe central nervous system (CNS) to collect in the dorsal root ganglion (DRG) that results in neurotoxicity. Some pathologic Aspects including oxidative stress, transient receptor potential, and morphological alterations in the mitochondria and endoplasmic reticulum (ER) have all been noted ananchorin-1 (TRPA1) sensitization as well as inflammation in the brain. Through covalent binding, it reversibly preferentially inhibits the β5 subunit of the proteasome and the β5i subunit of the immune proteasome, thereby playing a wide range of roles, such as blocking NF-κB activation, blocking the cell cycle, inducing apoptosis, inhibiting DNA repair enzymes, MM and bone marrow stromal cell adhesion. BTZ is a reversible dipeptidyl boric acid proteasome inhibitor, which mainly targets the curd trypsin-like and Caspas-like active sites of proteasome and has minimal effect on trypsin-like activity. Through proteasomal inhibition, BTZ inhibits tumor survival pathways through multiple mechanisms, preventing tumor growth, tumor spread and angiogenesis [4,5].

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3.2. Natural polyphenols based on CA

Natural polyphenols represent a large class of plant-derived compounds with two or more phenolic units in their structure and include many bioactive molecules [6]. Strong supramolecular nanomedicines can be made using a tiny drug assembly method mediated by natural polyphenols, allowing for the efficient transport and regulated release of BTZ to specific tumor locations. This can also be used to various kinds of supramolecular therapies including boric acid that are intended to treat a variety of illnesses. With numerous phenolic hydroxyl groups that can form a variety of non-covalent interactions, natural polyphenols have exceptional structural and functional properties [7, 8]. Examples of such coordinating interactions include metal-organic and dynamic covalent bonds (particularly reversible catechol-boronic acid) allowing supramolecular structural alterations [9-11]. Because natural polyphenols are hydrophilic, it is also simple to add amphiphilic characteristics to supramolecular structures in order to facilitate additional hierarchical assembly. Regarding functional characterization, natural polyphenols are also a promising class of pluripotent chemopreventive and anticancer agents that, by significantly affecting the expression of protein signaling, cell cycle regulatory proteins, and several physiological pathways involved in cell growth, transformation, and metastasis, induce apoptosis and inhibit cancer cell growth. This is due to long-term selection and evolution. In conclusion, polyphenol building blocks are well suited to create a range of nanomedicines through targeted delivery of anticancer medications and bioimaging materials in therapy, as well as logical supramolecular design for cancer diagnostics.

Nanomedicines that are supramolecular and made of natural polyphenols CA, BTZ and Fe^{3+}combined through chemical bonding significantly caused apoptosis in cancer cells and, with few side effects, stopped the formation of tumors in models of subcutaneous and bone tumors. Its composite of novel supramolecular nanomedicines improves on the otherwise low targeting properties of BTZ. This stems from the ph-dependent nature of the presence of the complexes, allowing them to effectively target at acidic tumor sites and deliver and control the release of BTZ, significantly improving efficacy and elucidating their potential in cancer therapy (e.g., Figure 1).

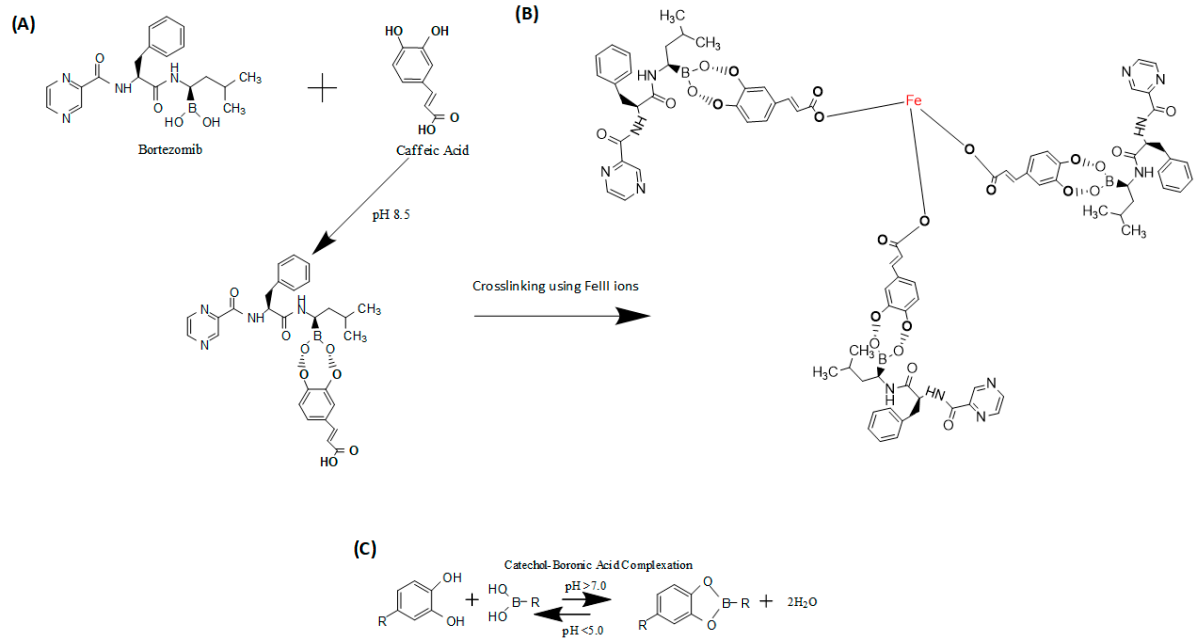

Figure 1. Chemistry Basis of the Synthesized Nanomedicine [3]. (a) Chemical schematic of the complexation of BTZ with CA to create the larger molecule. BTZ-CA. (b) Schematic representation of stabilize supramolecular prodrug nanodrugs by Fe^{3+} crosslinking. (c) Tow-sided complex separation of catechol-boric acid at different ph conditions.

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In addition, Fe^{3+} has been incorporated into supramolecular amphiphiles. This increases the stability of supramolecular nanomedicines by forming many coordination connections between the chains of Fe^{3+}-catecholic acid (e.g. Figure 2) [12]. Fe^{3+} acts as a stabilizer in the composition of this supramolecular nanodrug. Under alkaline conditions, the hydroxyl group (OH) of CA is protonated and forms a high affinity bond using the boronic acid functional group of BTZ. However, due to their polarity, stabilized nanoparticles with only this complexation cannot be fabricated. A stabilizer was required, and in this case the choice was made to use Fe^{3+} in FeCl3 dissolved in DW. Fe^{3+} covalently binds connects the BTZ-CA cross-links to the conjugated BTZ-CA macromolecule.

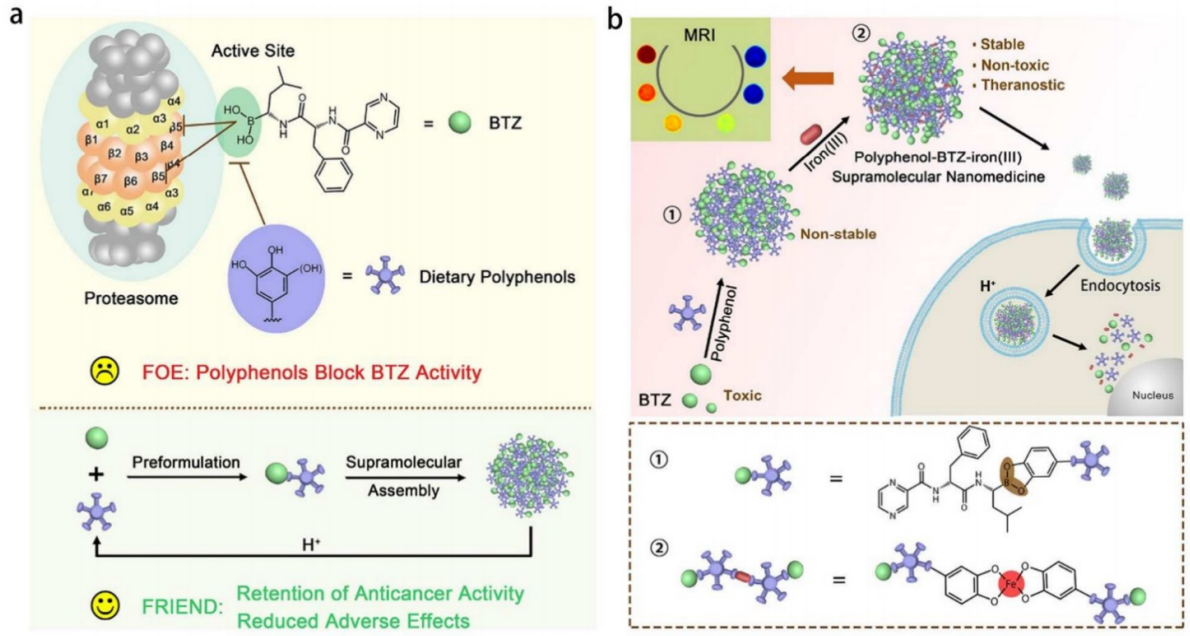

Figure 2. Diagram of the principle of Fe^{3+} as a stabilizer [2]. (a) Strategies for intracellular delivery of BTZ via natural polyphenols. (b) Supramolecular nanomedicines including natural polyphenols, BTZ and Fe^{3+} are used in cancer therapy. And two types of bonds involved in supramolecular nanomedicines: dynamic covalent bonds of catechol borate and interchain Fe^{3+}-catecholate coordination bonds.

Through the oxygen species that are reactive inducing and subsequent destructive properties of CA on harmful cells, the nanomedicines were shown to possess combinatorial anticancer properties, whereas the BTZ drugs inhibited the ability of cells to repair damaged intracellular proteins produced by the earlier. It is worth noting that previously, the therapeutic effect of BTZ was usually inhibited by dietary polyphenols due to its complexation with catechols. Whereas this BTZ-CA compound nicely converts the drug loss from polyphenolic substances into an advantage, this method of forming nanoparticles protects the active boric acid site of BTZ in the bloodstream and improves its pharmacokinetics [13].

In summary, this unique supramolecular design consisting of CA, BTZ and Fe^{3+}complexes offers many advantages for therapeutic systems, including highly great biodegradability and biocompatibility, straightforward manipulation and setup, exact control over drug loading, without requirement for pre-synthesis work and non-chromatographic purification.

4. Catechol-boronic acid bonding as the main constituent

Based on catechol-borate reversible bonding, an Arg-Gly-Asp (RGD) tripeptide targeting dendritic polymer coupled to catechol and polyethylene ethylene glycol moieties has been identified for targeted delivery of BTZ to metastatic bone tumors. BTZ is loaded onto dendritic polymers via borate-catechol linkages with ph-responsive properties that play a crucial role in controlling the loading and release of

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BTZ. The non-targeted BTZ at pH 7.4, nanomedicine demonstrated negligible cytotoxicity, but the anti-cancer action was significantly enhanced when the cyclical RGD molecules were anchored to the surface of the dendritic polymer. The ligand RGD allows the BTZ complex to be efficiently internalized by MDA-MB-231 breast cancer cells. This targeted nanomedicine effectively inhibited the development of metastatic bone cancers and markedly inhibited tumor-associated osteolysis in a model of bone tumors. This research sheds light on the development of nanomedicines for the treatment of metastatic bone tumors [14,15].

5. Conclusion

According to the analysis in this paper, the combination of BTZ with natural polyphenols leads to the formation of novel supramolecular nanodrugs. The drug is essentially an amphiphilic catechol-containing polymer coupled with the protease inhibitor BTZ, and the BTZ-loaded system responds to changes in ph via borate complexation between catechol and boric acid. Thus, the release of BTZ from the polymer micelles can be significantly accelerated under acidic conditions in cancer cells. The supramolecular design can be used as a novel delivery system for anticancer drugs, and this particular supramolecular design offers more advantages for cancer therapy systems, a high degree of carefully regulated drug loading, outstanding biodegradability and biocompatibility, and simplicity in handling and arrangement.

However, the current supramolecular nanomedicines are limited to the combination of BTZ with some natural polyphenolic substances. Future research could provide more insight into other mechanisms and advantages of supramolecular nanomedicine-targeted therapies and promote the study of diverse natural polyphenol supramolecular nanomedicines with a range of biological purposes and modifiable morphologies and dimensions, while thereafter the research could explore more about the combination of natural polyphenols with other boric acid-containing moieties or non-hydrophilic drugs, it might be used to develop further boric acid-containing supramolecular medicines for a variety of illnesses.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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