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Review

Applications of nanoparticles in treatment and diagnosis of leukemia

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ABSTRACT

The conventional chemotherapy for leukemia involves frequent dosing, severe side effects and lack of specificity of such anticancer drugs. The treatment with most of the anti-leukemic drugs would be improved if they were delivered to their biological targets through appropriate application of nanotechnology by manipulating at the molecular level. Nanoparticles in the recent years have shown tremendous application with respect to diagnosis and treatment of leukemia. The review specifically focuses on the use of nanoparticles for sustaining the release of anti-leukemic drugs and intracellular delivery of such nanoparticles. The review also highlights the application of nanoparticles in reversal of multidrug resistance.

Contents

1. Introduction

Leukemia, the cancer of the blood, is characterized by the widespread uncontrolled proliferation of large number of abnormal white blood cells, which invade the bone marrow and often spill out into the blood stream. The conventional therapy of leukemia causes severe side effects which are mainly caused by the lack of specificity of the anticancer drugs, that is, the anticancer drugs not only kill cancer cells but also inhibit normal cell growth and eventually lead to necrosis of normal cells. Moreover, the conventional drugs are not effective in penetrating into the spinal cord or brain. Leukemia cells flourish into these central nervous system hideouts, eventually causing fatal complications. Directing the drug to its target site is one of the best ways to increase its efficacy, reduce its toxicity and maintain its concentration at the target site for a sufficient period of time. The chemotherapy by most of the anti-leukemic drugs would be improved if they were delivered to their biological targets through appropriate application of nanotechnology by manipulating at the molecular level to develop drug delivery systems with novel properties [1].

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Nanotechnology applied to medicine will bring significant advances in the diagnosis and treatment of cancer [2]. Nanoparticles have demonstrated enormous potential as cellular drug delivery vehicles which improve the drug's stability as well as its availability and retention at the target intracellular site of action. Nanoparticles offer certain advantages such as penetrating into tissues through fine capillaries and crossing the epithelial lining of the cancer cells. Nanoparticles selectivity targets the cancer cells, thereby reducing the drug's toxicity towards normal cells. They can be endocytosed/phagocytosed by cells, with resulting cell internalization of the encapsulated drug. Nanoparticles enhance the intracellular concentration of drugs. Due to the enhanced permeability and retention effect, the drug accumulation in the required site is even higher than that observed in plasma and other tissues [3].

Various nano-particulate carriers such as polymeric nanoparticles, polymer conjugates, polymeric micelles, solid lipid nanoparticles and liposomes are utilized for selectively delivering various anti-cancer agents at the tumor site. Nanoparticles have recently gained attention for targeting and sustaining the release of the anti-leukemic drugs. Nanoparticles can encapsulate both hydrophilic and hydrophobic drugs. Moreover, the rate of drug release can be controlled by modification of the polymer side chain, development of novel polymers or synthesis of copolymers. The release of encapsulated drugs occurs at a controlled rate in a time or environment dependent manner [4].Nanoparticles may consist of either a polymeric matrix (nanospheres) or of a reservoir system in which an oily or aqueous core is surrounded by a thin polymeric wall (nanocapsules). Most of the polymeric nanoparticles are biodegradable and biocompatible in nature and hence are suitable for the entrapment of wide range of anti-cancer agents. Nanoparticles of biodegradable polymers can provide controlled and targeted delivery of the drug with better efficacy and fewer side-effects. Some of the commonly used polymers are polylactic acid, poly(lactic-co-glycolic acid) copolymer, poly(alkylcyanoacrylate), poly(methylmethacrylate), and poly(butyl)cyanoacrylate. Natural macromolecules such as proteins and polysaccharides and inorganic materials such as metal oxides and silica have been also used for preparation of nanoparticles [5]. The drawbacks associated with the conventional nanoparticles, such as uptake by the mononuclear phagocyte system (MPS) and inability to cross the blood–brain barrier (BBB), can be overcome by surface modification of the polymers. Polymers exhibit potential for surface modification to alter or improve their biodistribution properties. Poly(ethylene glycol) (PEG) has been widely used for adsorbing or covalently linking onto the surface of nanoparticles which makes them long circulating in blood [6,7]. Surface modified nanoparticles are able to penetrate the BBB. The mechanism involved is endocytosis of the nanoparticles via the low density lipoprotein receptor of the endothelial cells of the brain followed by the release of the drug inside the brain [8].

This review describes the sustained delivery, cellular uptake, cytotoxicity, diagnosis, and reversal of multidrug resistance aspects of nanoparticles in the therapy of leukemia.

2. Basics of leukemia

Leukemia is a cancer that starts in blood stem cells in the bone marrow. Bone marrow is the soft, spongy material that fills the center of most bones (Fig. 1A). Blood cells are made in the bone marrow. Blood stem cells develop into either myeloid stem cells or lymphoid stem cells. Blood has three types of cells: red blood cells that helps to carry oxygen, white blood cells that fight infection and platelets that help blood to clot. Every day, hundreds of billions of new blood cells are produced in the bone marrow. Normally the red blood cells are the ones produced more and hence are more in number (Fig. 1B). But this situation changes in people suffering with leukemia. In leukemia the body starts producing more white cells than it needs. In leukemia there is an abnormal rise in the number of white blood cells (Fig. 1C). These increased white blood cells in leukemia crowd over the other blood cell elements such as red blood cells (erythrocytes) and platelets.

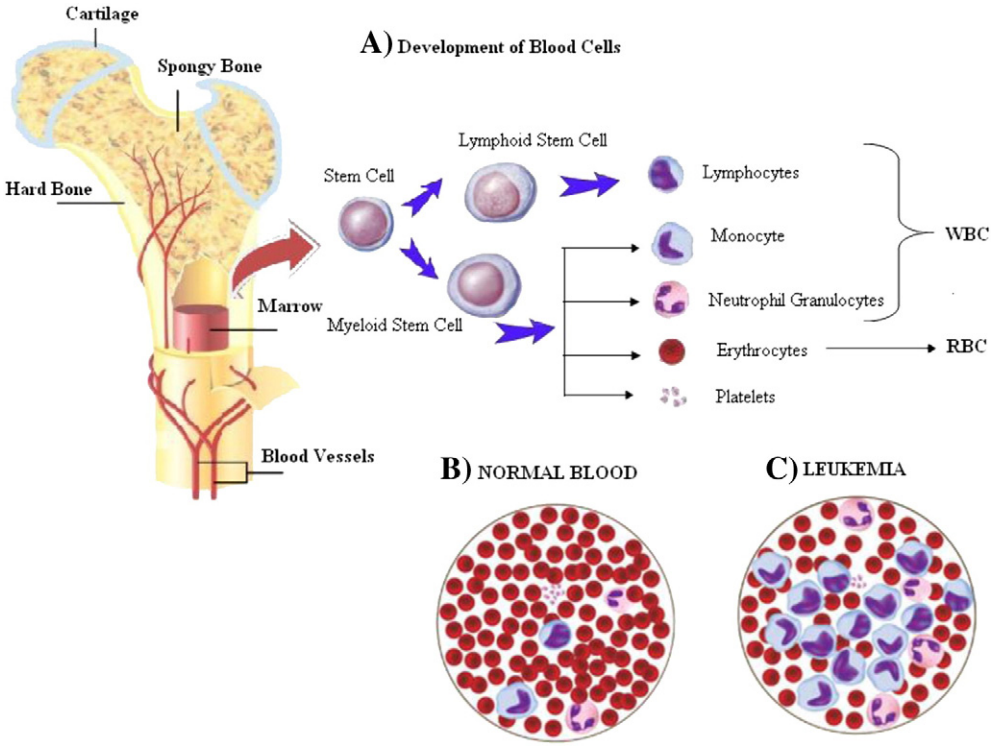

Fig. 1. A. Development of blood cells from bone marrow, B. normal blood, C. blood during leukemia.