
Advances in Treatment of Acute Myeloid Leukemia

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Minderman *et al*, in a published article, demonstrate that multidrug resistance and genetic mutations of acute myeloid leukemia as well as patient relapse may constitute the main leading causes for the creation of innovative perspectives and the development of more specific medications for targeted genes [1]. Consequently, this serious disease becomes one of current emerging issues all over the world. Although cytarabine and anthracycline combination is still considered as a standard cure, clinical treatment outcomes of this conventional combination is poor and resulting in death of millions of patients annually [2].

Firstly, Liposomal daunorubicin and cytarabine nanoformation (CPX-351) had been formulated in 2015 by Dr. Lalit Raut, MD at Vancouver General Hospital at a 5:1 molar ratio and while the lipid composition of liposome nanocarrier is distearylphosphatidylcholine, distearylphosphatidylglycerol, and cholesterol at a 7:2:1 molar ratio. During 2018, Jeffrey Lancet *et al*, from H. Lee Moffitt Cancer Center in Florida stated that the total size of nanoformulation is 100 nm in pH 7.4 and daunorubicin and cytarabine half-lives in CPX-351 were 8.5 and 11.6 h, respectively during preclinical studies compared with 0.27 and 0.26 h, respectively, in the free state [3,4]. After performing comprehensive clinical trials, CPZ-351 showed favorable safety profile as well as definitely become a novel standard with high efficiency for patients treatment [5]. Furthermore, the US Food and Drug Administration (FDA) has approved CPX-351 so Vyxeos® was produced in 2017 by Jazz Pharmaceuticals company as intravenous infusion for the treatment of newly diagnosed adult patients [6].

Secondly, some researchers from Nanobiophotonics and Laser Microspectroscopy Center, Babes-Bolyai University, Romania have published a new formulation of FMS-like tyrosine kinase receptor-3 (FLT3) inhibitors for treatment namely, Gelatin-coated gold nanoparticles of FLT3 inhibitors. They reported that using gelatin as a unique polymer could protect the formulation from in vivo instability and also improve loading efficiency of drugs [7]. After measuring zeta potential and particle size to evaluate loading efficiency of different FLT3 inhibitors in the nanostructure, results have explicated a marked increase in zeta potential from $+22.5 \pm 0.4$ mV up to $+31.2 \pm 0.8$ mV and $+32.4 \pm 0.4$ mV for gelatin@GNPs-sorafenib and gelatin@GNPs-quizartinib, respectively. In addition, the increase in nanoparticle diameter from 99.5 ± 2.6 nm up to 225.28 ± 3.5 nm and 147.5 ± 1 nm for gelatin@GNPs-sorafenib and gelatin@GNPs-midostaurin, respectively has confirmed the ability of gelatin-GNPs surface to be able to load a huge amount of drug. Moreover, the measurement of plasmonic response of gelatin@GNPs stored in PBS solution for a one week has been performed in order to assess the stability of drug gelatin@GNPs in biological environments. The results have proved that there are no any aggregations after a one week of storage and subsequently FLT3 inhibitors nanostructures were formulated efficiently. Depending on the results of physicochemical characterization, dark field microscopy and MMT assay, quizartinib exhibits the highest biological activity compared with other FLT3 inhibitors [8,9].

Ultimately, TRIB2 is one of Tribbles pseudokinases that has major functions in cell signalling management and regulation of cancerous and normal stem cell production at human bone marrow. Thus, TRIB2 has become a prospective drug target for subdivisions of Acute Myeloid & Lymphocytic Leukemia which are still in critical necessity of therapeutically-targeted drugs for assisting to treat complicated, untargeted or highly-resistant patient cases [10]. The close correlation between TRIB2 and BCL2 overexpression has contributed to combine BCL2 inhibitor as a combined therapy with standard medicines in order to eradicate highly drug resistance. Thus, the US Food and Drug Administration (FDA) has approved ABT199 (Venclexta[®]) in 2016 as a new BCL2 inhibitor for chronic lymphocytic leukemia (CLL) treatment as well as has also granted the use of Venclexta with low dose of cytarabine in 2017 as a combination therapy for chemoresistant elderly patients [11].

Furthermore, FDA has approved afatinib (Gilotrif[®]), osimertinib (Tagrisso[®]) and neratinib (Nerlynz[®]) in order to treat non-small cell lung cancer (NSCLC) and HER2-rich early breast cancer. These approved drugs are EGFR inhibitor compounds identified by the study of Professor Patrick Eyers and colleagues in Department of Biochemistry, Institute of Integrative Biology, University of Liverpool that published in *Science Signaling*, as a potential curable agents lead for the development of TRIB2-targeted acute myeloid leukemia therapies [12]. Overall, the persistent evolution of TRIB2 targeted therapeutics for cancer treatment has presently taken an upward trend in particular to acute myeloid leukemia.

Different nanofabrications e.g., liposomal daunorubicin and cytarabine nanoformation, gelatin-coated gold nanoparticles of FLT3 inhibitors beside targeted therapeutics e.g., afatinib, osimertinib and neratinib are being overviewed for exhibiting novel trends that have fundamentally assisted in fulfilling optimal therapeutic outcomes with minimal side effects. The potential research revolution in management of acute myeloid leukemia is extending passing to CART-cell therapy (anti-CD33CAR-Tcells) and immune checkpoint inhibitor (PD1 inhibitors) which still require much more clinical evidences in the next future.

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