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Targeted Approaches Through Nanocarriers In Leukemia: A Review

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Abstract: Leukemia is a global concern as it is affecting the global population. Many anticancer drugs have used in the disease, although toxicities can not ignored. The important targets for the disease are B cell receptor pathway that is spleen tyrosine kinase, mammalian target of rapamycin (mTOR), phosphoinositide 3'-kinase (PI3K), Bruton's tyrosine kinase (BTK) which potentially the disease and can be used as the target for targeted delivery of anticancer drugs in disease. The need of the hour is to develop the formulation, should be specific and have minimum toxicities. The nanoformulations have proved their efficacy in disease targeting and minimization of toxicities. In this review paper, we have performed a systematic review of more than 250 papers and selected those one related to our research work. The findings suggest that nanoparticles can be a game changer in the lane of disease management as they can be targeted delivery and minimization of toxicities too.

Keywords: Leukemia, B cell receptor pathway, anticancer, nano formulations, targeted deliver

Introduction

Leukemia is a complex disease that is increasing day by day. Globally the surge of disease is not only affectes the patients but their social life too. The disease etiology suggests that the B cell receptor pathway plays a critical role in the survival, and proliferation of chronic lymphocytic leukemia cells. Nanocarriers have shown therapeutic efficacy and minimization of toxicities of these anti-cancer drugs. Nanotechnology is an emerging field for development of new drug formulation it provides great applicability in disease management.

Role of B cell receptor

The B cell receptor plays an important role in chronic lymphocytic leukemia disease [1]. The Activation of BCR results in the generation of spleen tyrosine kinase (SYK) and the SRC kinase LYN which causes phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) of the accomplice proteins of the BCR complex i.e. CD79a and CD79b. Phosphorylation of these complexes generates adaptor proteins and other kinases, such as Bruton's tyrosine kinase or phosphatidylinositol 3-kinase (PI3K). The signaling of these molecules causes downstream activation of AKT/mTOR, NF-κB, and ERK. Reported work on CLL cells confirmed that BCR signaling associated with the role of the ζ-associated protein of 70 kD (ZAP-70) [2, 3,4] that expressed in nearly half of all chronic lymphocytic leukemia diseases. The role of ZAP-70 in B-cell receptor signaling in chronic lymphocytic leukemia not depends on kinase activity only, but somewhat on other kinases like SYK, to the B-cell receptor complex.

The Stimulation of disease through activation of B-cell receptor signaling can aggravate CLL cell appearance by important chemokines CCL3 and CCL4 [5]. The activated CLL cells secrete chemokines which exert a pull on leukemia cells that is regulatory T cells [6, 7]. Some reports suggest that Activated chronic lymphocytic leukemia cells have high levels of CLL3 and CCL4 when isolated from lymph nodes [8], explaining that B- Cell Receptor has a prominent role in creating a favorable environment which helps in CLL cell expansion and endurance.

Some reported data suggest that CD38 is an indicator of adverse prognosis and a sign of activation and proliferation of CLL cells [9, 10, and 11]. Another work reported by some researchers explains that CD31A is a ligand for CD38 expressed by nurselike cells and other accessory cells in the leukemia microenvironment [12]. The CD38 Ligation on CLL cells can activate ZAP-70 and ERK1/2 signaling pathways to enhance CLL cell proliferation and chemotaxis [13, 14]; interaction between CD38 and ZAP-70 may enhance BCR signaling. Recent research data suggest that macromolecular complexes of CD38, CD49d, CD44, and matrix metalloproteinase on the CLL cells express ZAP-70 [15, 16].

Hyaluronic acid also plays role as it acts on the CD44 receptor found in endothelial venules of lymphoid tissue in the leukemia microenvironment. The migration and invasion of CLL cells depend on interactions between CD38 and CD44, MMP-9, and CD49d, that in turn enhance the signaling leading to the growth or survival of CLL cells through CD38, CD44, MMP-9, CD49d, and ZAP-70 complexes which may be responsible for the progression of the disease through ZAP-70 and CD38 [17].

Some researchers reported that CXCR4 chemokine receptor CD184 is highly expressed in CLL cells when isolated from blood [18] other reported data suggests that proliferation of Ki-67+ CLL cells found in the bone marrow and in lymphatic tissues articulate significantly decreases levels of CXCR4 and CXCR5, possibly reflecting chemokine-induced surface receptor downmodulation of these chemokine receptors [19].

TLRs

These receptors are present on the cell surface and essenial for the innate immune system through binding to structural microbial antigens that triggers innate immune responses. Some researchers reported that many TLRs are expressed and functional in CLL; stimulation of these TLRs could induce surface expression of activation markers such as CD25 and CD80 [20].

From the above discussion, it is clear that the B cell receptor pathway plays crucial role in the endurance, proliferation, and trafficking of chronic lymphocytic leukemia (CLL) cells.

The drugs which can inhibit kinases in this pathway that is spleen tyrosine kinase (SYK), mammalian target of rapamycin (mTOR), phosphoinositide 3’-kinase (PI3K), and Bruton's tyrosine kinase (BTK), can be utilized for treatment more ever various pre-clinical models established to decrease CLL cell viability both directly and indirectly through modulation of the microenvironment. Oral drugs targeting these kinases have implicated through phase-1 studies of clinical trials in patients with CLL. BCR pathway adversaries appear as highly active in degenerated refractory CLL, independent of high-risk disease makers such as Del (17p). These agents have a unique pattern of suggesting early transient lymphocytosis that typically is linked with a nodal response.

Nano particles and nano carriers

Today nanomedicine is proving their efficacy in many chronic diseases. These are new but showing their efficacy in the treatment of diseases. The applicability of nanoscale range is utilized to deliver therapeutic agents to specific targeted sites in a controlled manner. Today nanomedicine is proving its efficacy in many chronic diseases. These are new but show their applicability in the treatment of diseases. The nanoscale range is for delivering the therapeutic agents to specifically targeted sites in a controlled manner. Nanotechnology offers multiple benefits in treating chronic human diseases by site-specific and target-oriented delivery of precise medicines that can also reduce the adverse effects common amongst anticancer drugs.

Nanomedicine is a promising field employing the use of knowledge through techniques of nanoscience in disease prevention and treatments. The utilization of nanoscience is increasing day by day nanorobots, and nanosensors in diagnostic kits. The applicability of nanoparticle-based methods reported by authors suggests that combined approach in treatment and imaging modalities of cancer diagnosis [21].

Material and methods:

In this review paper we have performed systematic review on work already reported through nanocarrirers in leukemia and targeted sites.

Table: 1 Anticancer Nanocarriers and their targets in Leukemia

S.No	Name of Nano-carriers	Targeted	Reference no.
1.	Iron Oxide Nanoparticles Combined with Cytosine Arabinoside	Regulating Reactive Oxygen Species	[22]
2.	ferumoxytol iron oxide nanoparticle	Regulating Reactive Oxygen Species	[23]
3.	anti-CD20 nanoparticles containing hydroxychloroquine and chlorambucil		[24]
4.	Anti-CD123 antibody-modified niosomes of daunorubicin	DNR-CD123-PEG-NS	[25]
5.	PPI-G4-M3 dendrimers	NFκB pathway	[26]
6.	Sphingomyelin/cholesterol liposome loaded with vincristine	Diffuse large B cell lymphoma (DLBCL)	[27]
7.	liposome co-loaded with daunorubicin and cytarabine	Anthracycline topoisomerase inhibitor, Nucleoside metabolic inhibitor	[28]
8.	BAT1-liposome	Prevent the binding of the chemokine CXCL12 to CXCR4 in CLL	[29]
9.	Chlorambucil Iron Oxide Nanoparticles		[30]
10.	Carboxymethyl Chitosan Nanoparticles Containing Covalently Entrapped 6-Mercaptopurine	Folate Receptor and GSH stimulation	[31]
11.	P-glycoprotein carbon nanotubes loaded with doxorubicin	K562R cells	[32]
12.	Cationic drug-derived nanoparticles of mitoxantrone	Tumor cells	[33]
13.	Epigallocatechin-3-gallate encapsulated realgar nanoparticles	HL-60 cells	[34]
14.	AP9-cd loaded solid lipid nanoparticles	Molt-4 cells	[35]
15.	Glycodendrimer Nanoparticles	brain Tumour and internal organs	[36]
16.	Phosphatidylinositol 3-Kinase inhibitor umbralisib gold Nanoparticles	non-Hodgkin's lymphoma	[37]
17.	Maltotriose-modified poly(propylene imine) Glycodendrimers	Tumour	[38]
18.	Glycodendrimer PPI	Apoptosis	[39]

Conclusion

The review work strongly suggests that the nanocarriers of anti-cancer drugs that have an inhibitory action on spleen tyrosine kinase, mammalian target of rapamycin, phosphoinositide 3’-

kinase, and Bruton's tyrosine kinase can be an appropriate therapeutic option for the treatment of leukemia. These nanocarriers of anti-cancer drugs can also reduce the well-known toxicities of anti-cancer drugs. Much clinical research is also going on that can provide the direction for future treatment of disease. We have reviewed the targets and applicability of nanocarriers in leukemia. In our future work, we will emphasize the development of anticancer-based nanocarrier formulation that can target the kinase pathway.

References

1. Woyach JA, Johnson AJ, Byrd JC. The B cell receptor signaling pathway as a therapeutic target in CLL. *Blood.* 2012; 120:1175–1184.
2. Chen L, Apgar J, Huynh L, Dicker F, Giago-McGahan T, et al. ZAP-70 directly enhances IgM signaling in chronic lymphocytic leukemia. *Blood.* 2005; 105:2036–2041.
3. Chen L, Huynh L, Apgar J, Tang L, Rassenti L, et al. ZAP-70 enhances IgM signaling independent of its kinase activity in chronic lymphocytic leukemia. *Blood.* 2008; 111:2685–2692.
4. Pandey R, Upadhyay P, Shukla SS. Plants having Anti-arthritic and Immunomodulator Potentials: An Review. Research Journal of Pharmacy and Technology 2017;10(4):1252-1256.
5. Burger JA, Quiroga MP, Hartmann E, Burkle A, Wierda WG, et al. High-level expression of the T cell chemokines CCL3 and CCL4 by chronic lymphocytic leukemia B cells in nurselike cell cocultures and after BCR stimulation. *Blood.* 2009; 113:3050–3058.
6. Patten PE, Buggins AG, Richards J, Wotherspoon A, Salisbury J, et al. CD38 expression in chronic lymphocytic leukemia is regulated by the tumor microenvironment. *Blood.* 2008; 111:5173–5181.
7. Ghia P, Strola G, Granziero L, Geuna M, Guida G, et al. Chronic lymphocytic leukemia B cells are endowed with the capacity to attract $CD4^+$, $CD40L^+$ T cells by producing CCL22. *Eur. J. Immunol.* 2002; 32:1403–1413.
8. Herishanu Y, Pérez-Galán P, Liu D, Biancotto A, Pittaluga S, et al. The lymph node microen-vironment promotes B cell receptor signaling, NF-κB activation, and tumor proliferation in chronic lymphocytic leukemia. *Blood.* 2011; 117:563–574.
9. Ibrahim S, Keating M, Do KA, O'Brien S, Huh YO, et al. CD38 expression as an important prognostic factor in B cell chronic lymphocytic leukemia. *Blood.* 2001; 98:181–186.
10. Damle RN, Temburni S, Calissano C, Yancopoulos S, Banapour T, et al. CD38 expression labels an activated subset within chronic lymphocytic leukemia clones enriched in proliferating B cells. *Blood.* 2007; 110:3352–3359.
11. Deaglio S, Aydin S, Grand MM, Vaisitti T, Bergui L, et al. CD38/CD31 interactions activate genetic pathways leading to proliferation and migration in chronic lymphocytic leukemia cells. *Mol. Med.* 2010; 16:87–91.
12. Deaglio S, Vaisitti T, Bergui L, Bonello L, Horenstein AL, et al. CD38 and CD100 lead a network of surface receptors relaying positive signals for B-CLL growth and survival. *Blood.* 2005; 105:3042–3050.

13. Burger JA, Ghia P, Rosenwald A, Caligaris-Cappio F. The microenvironment in mature B cell malignancies: a target for new treatment strategies. *Blood.* 2009; 114:3367–3375.
14. Malavasi F, Deaglio S, Damle R, Cutrona G, Ferrarini M, Chiorazzi N. CD38 and chronic lymphocytic leukemia: a decade later. *Blood.* 2011; 118:3470–3478.
15. Buggins AG, Levi A, Gohil S, Fishlock K, Patten PE, et al. Evidence for a macromolecular complex in poor prognosis CLL that contains CD38, CD49d, CD44 and MMP-9. *Br. J. Haematol.* 2011; 154:216–222.
16. Zhang S, Wu CCN, Fecteau J-F, Cui B, Chen L, et al. Targeting chronic lymphocytic leukemia cells with a humanized monoclonal antibody specific for CD44. *Proc. Natl. Acad. Sci. USA.* 2013; 110:6127–6132.
17. Zhang S, Kipps TJ. The pathogenesis of chronic lymphocytic leukemia. Annu Rev Pathol. 2014; 9:103-18. doi: 10.1146/annurev-pathol-020712-163955. Epub 2013 Aug 26. PMID: 23987584; PMCID: PMC4144790.
18. Burger JA, Burger M, Kipps TJ. Chronic lymphocytic leukemia B cells express functional CXCR4 chemokine receptors that mediate spontaneous migration beneath bone marrow stromal cells. *Blood.* 1999; 94:3658–3667.
19. Bennett F, Rawstron A, Plummer M, de Tute R, Moreton P, et al. B cell chronic lymphocytic leukaemia cells show specific changes in membrane protein expression during different stages of cell cycle. *Br. J. Haematol.* 2007; 139:600–604.
20. Chu CC, Catera R, Hatzi K, Yan XJ, Zhang L, et al. Chronic lymphocytic leukemia antibodies with a common stereotypic rearrangement recognizes nonmuscle myosin heavy chain IIA. *Blood.* 2008; 112:5122–5129.
21. Calissano C, Damle RN, Hayes G, Murphy EJ, Hellerstein MK, et al. In vivo intraclonal and interclonal kinetic heterogeneity in B cell chronic lymphocytic leukemia. *Blood.* 2009; 114:4832–4842.
22. Haba Y, Kojima C, Harada A, Ura T, Horinaka H, Kono K. Preparation of poly (ethylene glycol)-modified poly (amido amine) dendrimers encapsulating gold nanoparticles and their heat-generating ability. Langmuir. 2007; 23:5243–6.
23. Dou J, Li L, Guo M, Mei F, Zheng D, Xu H, Xue R, Bao X, Zhao F, Zhang Y. Iron Oxide Nanoparticles Combined with Cytosine Arabinoside Show Anti-Leukemia Stem Cell Effects on Acute Myeloid Leukemia by Regulating Reactive Oxygen Species. Int J Nanomedicine. 2021 Feb 17; 16:1231-1244. Doi: 10.2147/IJN.S278885.
24. Trujillo-Alonso V, Pratt EC, Zong H, et al. FDA-approved ferumoxytol displays anti-leukaemia efficacy against cells with low ferroportin levels. *Nat Nanotechnol*. 2019; 14(6):616-622. doi:10.1038/s41565-019-0406-1
25. Capolla S, Mezzaroba N, Zorzet S, et al. A new approach for the treatment of CLL using Chlorambucil/hydroxychloroquine-loaded anti-CD20 nanoparticles. *Nano Res*. 2016;9(2):537–548. doi:10.1007/s12274-015-0935-3
26. Fu-rong Liu, Hui Jin, Yin Wang, Chen Chen, Ming Li, Sheng-jun Mao, Qiantao Wang & Hui Li (2017) Anti-CD123 antibody-modified niosomes for targeted delivery of

daunorubicin against acute myeloid leukemia, Drug Delivery, 24:1, 882-890, DOI: 10.1080/10717544.2017.1333170

27. Ida Franiak-Pietryga, Kinga Ostrowska, Henryk Maciejewski, Barbara Ziemba, Dietmar Appelhans, Brigitte Voit, Magdalena Jander, Jacek Treliński, Maria Bryszewska, Maciej Borowiec, Affecting NF-κB cell signaling pathway in chronic lymphocytic leukemia by dendrimers-based nanoparticles, Toxicology and Applied Pharmacology, Volume 357, 2018, Pages 33-38,ISSN 0041-008X, https://doi.org/10.1016/j.taap.2018.08.007.
28. Larry Boehlke & Jane N Winter (2006) Sphingomyelin/cholesterol liposomal vincristine: a new formulation for an old drug, Expert Opinion on Biological Therapy, 6:4, 409-415, DOI: 10.1517/14712598.6.4.409
29. Blair, H.A. Daunorubicin/Cytarabine Liposome: A Review in Acute Myeloid Leukaemia. *Drugs* **78**, 1903–1910 (2018). https://doi.org/10.1007/s40265-018-1022-3
30. Catriona McCallion, Anna D. Peters, Andrew Booth, Karen Rees-Unwin, Julie Adams, Raisa Rahi, Alain Pluen, Claire V. Hutchinson, Simon J. Webb, John Burthem, Dual-action CXCR4-targeting liposomes in leukemia: function blocking and drug delivery, Blood Advances, Volume 3, Issue 14, 2019, Pages 2069-2081, ISSN 2473-9529,https://doi.org/10.1182/bloodadvances.2019000098.
31. Hussein-Al-Ali SH, Hussein MZ, Bullo S, Arulselvan P. Chlorambucil-Iron Oxide Nanoparticles as a Drug Delivery System for Leukemia Cancer Cells. Int J Nanomedicine. 2021 Sep 8; 16:6205-6216. Doi: 10.2147/IJN.S312752.
32. Wei X, Liao J, Davoudi Z, et al. Folate Receptor-Targeted and GSH-Responsive Carboxymethyl Chitosan Nanoparticles Containing Covalently Entrapped 6-Mercaptopurine for Enhanced Intracellular Drug Delivery in Leukemia. *Mar Drugs*. 2018;16(11):439. Published 2018 Nov 8. Doi: 10.3390/md16110439.
33. Li R, Wu R, Zhao L, Wu M, Yang L, Zou H. P-glycoprotein antibody functionalized carbon nanotube overcomes the multidrug resistance of human leukemia cells. *ACS Nano*. 2010; 4(3):1399-1408. Doi: 10.1021/nn9011225.
34. Chang RS, Suh MS, Kim S, et al. Cationic drug-derived nanoparticles for multifunctional delivery of anticancer siRNA. *Biomaterials*. 2011; 32(36):9785-9795. doi:10.1016/j.biomaterials.2011.09.017.
35. Fang W, Peng ZL, Dai YJ, Wang DL, Huang P, Huang HP. (-)-Epigallocatechin-3-gallate encapsulated realgar nanoparticles exhibit enhanced anticancer therapeutic efficacy against acute promyelocytic leukemia. *Drug Deliv*. 2019; 26(1):1058-1067. doi:10.1080/10717544.2019.1672830.
36. Bhushan S, Kakkar V, Pal HC, Mondhe DM, Kaur IP. The augmented anticancer potential of AP9-cd loaded solid lipid nanoparticles in human leukemia Molt-4 cells and experimental tumor. *Chem Biol Interact*. 2016; 244:84-93. doi:10.1016/j.cbi.2015.11.022.
37. Ziemba B, Sikorska H, Jander M, et al. Anti-Tumour Activity of Glycodendrimer Nanoparticles in a Subcutaneous MEC-1 Xenograft Model of Human Chronic

Lymphocytic Leukemia. *Anticancer Agents Med Chem*. 2020; 20(3):325-334. doi:10.2174/1871520619666191019093558

38. Ali AM, Makki AA, Ibraheem W, et al. Design of Novel Phosphatidylinositol 3-Kinase Inhibitors for Non-Hodgkin's Lymphoma: Molecular Docking, Molecular Dynamics, and Density Functional Theory Studies on Gold Nanoparticles. *Molecules*. 2023; 28(5):2289. Published 2023 Mar 1. Doi: 10.3390/molecules28052289.
39. Franiak-Pietryga I, Ziemba B, Sikorska H, et al. Maltotriose-modified poly (propylene imine) Glycodendrimers as a potential novel platform in the treatment of chronic lymphocytic Leukemia. A proof-of-concept pilot study in the animal model of CLL. *Toxicol Appl Pharmacol*. 2020; 403:115139. doi:10.1016/j.taap.2020.115139.
40. Franiak-Pietryga I, Ziółkowska E, Ziemba B, et al. Glycodendrimer PPI as a Potential Drug in Chronic Lymphocytic Leukaemia. The Influence of Glycodendrimer on Apoptosis in In Vitro B-CLL Cells Defined by Microarrays. *Anticancer Agents Med Chem*. 2017; 17(1):102-114.