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PRE-TARGETING BISPECIFIC ANTIBODY (BSAB) AND PEGYLATED LIPOSOMAL DRUG NANOCARRIER AS MANAGEMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN PEDIATRICS

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is a neoplastic condition commonly found in pediatric patients especially that involve B cell (B-ALL). Current treatments revolve around immunotherapy approaches such as Chimeric-Antigen Receptor T-cell (CAR-T) and tyrosine kinase inhibitor (TKI). However, flaws in both methods such as low pharmacokinetics, technical limitations, inability to recognize more than one antigen and other side effects remain a predicament to be solved. "immunotherapy", "pediatry", "b-all", "bispesific antibody" and "PEGylated liposomal" were the keywords applied to scientific online databases, such as ScienceDirect, PubMed, dan Researchgate. A total of 25 journals were screened, reviewed and utilized with utmost precision to construct a literature review. Preparation of targeting bispesific antibody (BsAb) is constructed through the formation of chemical bond between the anti-mPEG scFV and CD20, whereas PEGylated liposomal drug nanocarriers is prepared through a covalent bonding chemical reaction. PEGylated drug nanocarriers has nontoxic, immunogenicity, antigenicity, and long half-life properties that increases both the pharmacokinetics and pharmacodynamics of anticancer drugs like chemotherapy through increased distribution, accumulation and decrease elimination of the drugs. BsAb will specifically target cancer-specific antigens, such as CD20 in cancer cells to initiate adaptive immune responses. Additionally, the antibody dependent endocytosis properties are a vital part in cancer therapy to increase cellular uptake of the liposome. All in all, the combination of bispesific antibody (BsAb) PEGylated liposomal drug nanocarriers towards B-ALL shows great promise towards the management of B-ALL in pediatric patients.

KEYWORDS *bispecific antibody, PEGylated liposom, immunotherapy, leukemia, pediatric*

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INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) or acute lymphoblastic leukemia is a neoplastic condition with primary characteristics in the form of an abnormal increase in the production of immature lymphocytes in the bone marrow (Coccaro et al., 2019; Hunger & Mullighan, 2015; Paul et al., 2016). These conditions can cause normal hematopoiesis pathway suppression and malignancy infiltration of the extremular area, especially the liver and spleen (Alshibani et al., 2018; Liu et al., 2016; Terwilliger & Abdul-Hay, 2017).

A total of 5,690 cases of ALL occurred in the United States with a total of 1,580 deaths in 2019. In addition, 80% of worldwide ALL cases occur in children and generally cause a poor prognosis when it appears or relapses in adulthood. Of all childhood cancers, ALL has a prevalence of 25% in children under 15 years of age. The incidence rate of ALL in Indonesia also reaches 2.4 to 4.0 cases per 100,000 children or 2,000 to 3,200 cases per year (Pehlivan et al., 2018; Perdana et al., 2020).

Despite the progress of ALL therapy development, survival in B-ALL patients for 5 years only reached 38.0 ± 10.6%. Various therapies used today, especially in the blood cancer class, focus on Chimeric-Antigen Receptor T-cell (CAR-T)-like immunotherapy approaches that have high clinical potential. Unfortunately, CAR-T has a variety of low pharmacokinetic-like limitations and is only able to target one type of antigen in cancer cells, allowing for the risk of antigen-less cancer clones and leading to a high incidence of relapse in patients (Alhallak et al., 2021; Z. Wang et al., 2017). What's more, CAR-T therapy also has technical limitations involving a long manufacturing process that takes a long time, starting from extraction to ex vivo purification before being injected into patients.

Another similar approach using tyrosine kinase inhibitor (TKI) immunotherapy is also being developed in conjunction with CAR-T. TKIs are effective in inhibiting the proliferation of cancer cells as well as eradicating minimal residual disease (MRD) so that there will be no relapse in ALL patients (X. Li & Chen, 2019; Xu et al., 2019). However, therapy with TKI still shows side effects such as thrombocytopenia, neutropenia, and severe anemia20 as well as high toxicity to the cardiovascular system.

Bispecific Antibody (BsAb) is an antibody molecule that combines the specificity of two antibodies simultaneously so that it can detect two different types of antigens or epitopes (Maude et al., 2018). This allows the establishment of therapeutic modalities with a broader and more diverse range of specific targets. The antibody modification is also able to enhance the therapeutic effect of a drug through the mechanism of bridging cells, regulation (inhibition or activation) of receptors, mimetic cofactors, and piggyback transport modalities (chemically linked BsAb to B cell receptors in induction of internalized toxicity).[23-25] The use of BsAb has developed in myeloid and lymphoid strain cancers with high clinical potential (Aldoss & Stein, 2018). Unfortunately, a literature review on the use of BsAb in ALL has not been further developed.

Polyethylene glycol (PEG)ylated Liposomal is a drug carrier that encapsulates drugs using a phospholipid membrane in the form of a lipid bilayer29 layer which can increase the therapeutic effect of drugs and reduce side effects through various mechanisms involving the immune system (Foà et al., 2020; King et al., 2019). Nanoparticle preparations in the use of PEGylated Liposomes or

called PEGylated Liposomal nanocarriers can improve the specificity and sensitivity of conjugation to specific ligands as well as prolong systemic circulation time and provide a low toxicity profile in normal body tissues.

In addition, the use of BsAb modalities with two antigen-binding domains,22 namely anti-PEG that will bind to PEGylated liposomal nanocarriers and anti-cancer specific antigens is known to be able to radicalize cancer tissue through antibody dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) and increase the internalization of chemotherapy preparations through antibody-dependent endocytosis (ADE). Moreover, this mechanism is able to provide a wide range of therapeutic options, especially in the management of ALL strains that are resistant to various chemotherapy agents through the ability to substitute in the antigen target binding domain on antibodies and the type of chemotherapy or anticancer drugs loaded on liposomal nanocarriers (Cornelison et al., 2012; L. Li & Wang, 2020; Q. Wang et al., 2019). Therefore, the authors are interested in further studying the potential of the combination of BsAb and PEGylated Liposomal Nanocarriers in the management of ALL, especially B-cell lymphocyte strains that are commonly found in pediatrics.

RESEARCH METHOD

The literature search was carried out from March 7, 2021 to March 17, 2021 through three online-based scientific journal databases, namely ScienceDirect, PubMed, and Researchgate. The keywords used in the search were "immunotherapy", "pediatry", "b-all", "bispesific antibody", and "PEGylated liposomal" with the use of similar boolean operators "AND" and "OR". The inclusion criteria used in this literature review are (1) publications in the last 10 years; (2) studies using United Kingdom or Indonesian. The exclusion criteria are (1) not explaining the use of BsAb orylated liposomal PEG ;(2) not focusing on B-ALL disease After a literature study, then a study screening was carried out so that 25 suitable journals were obtained as the main reference and have been reviewed in terms of validity, importance, and applicability.

RESULT AND DISCUSSION

Patogenesis ALL

Lymphocytes are part of the adaptive immune system derived from hematopoietic cells that begin to be produced in the sac and hepatic yolk during the fetal phase and end up in the bone marrow in adulthood. ALL is a hematologic malignancy that encompasses the entire line of B/T lymphoid cells that arise from genetic damage and cause abnormal cell proliferation and function. Chromosomal aberrations, including hyperdiploidy (>50 chromosomes), hypoploidy (<44 chromosomes), t-translocation {[12; 21], [1; 19], [9; 22], [4; 11]} are most commonly markers of ALL in children. These genetic disorders affect lymphoid development, tumor suppression, cytokine and kinase receptors, and other signaling pathways. Several molecular pathways and gene expression associated with ALL, including mechanisms or disruptions involving TEL-AML1/ETV6-RUNX135,41,42, BCR-ABL43, PAX545, RAS46, and PKT/Akt-mTOR/Bcl-247,48, as well as involving the expression of CD1042.44, CD1942, CD3442, CD3842.44, c-MYC49.50, RTKs, and GTPase46 in lymphocyte cells.

Bispecific Antibody (BsAb)

Bispecific Antibody (BsAb) is a second-generation antibody molecule in immunotherapy51 that combines the specificity of two antibodies that simultaneously provide novel adaptability in simultaneously targeting two antigens or epitopes in cells. BsAbs are classified into 2 types: IgG-like molecule and non-IgG-like molecule and are rapidly being developed in cancer therapy. BsAb will work by targeting CD19/CD20 and other CD receptors depending on the reconstruction of BsAb in a 100 kDa single-chain Fv-Fc format. BsAb will target the CDx subunit of cancer lymphoid cells and induce the occurrence of ADCC, CDC, and ADE.

PEGylation

PEGylation is a chemical modification technique that involves the conjugation of active polyethylene glycol (PEG) on therapeutic proteins or peptides. In addition, this technique can also be applied to drug delivery such as liposomes and nanoparticles. PEGylation is also defined as the covalent or non-covalent binding of PEG to different molecules so that it can improve the pharmacokinetics and pharmacodynamics of a drug. Increased hydrophilicity of size, molecular weight, conformational changes, as well as steric barrier will enhance the therapeutic effects of PEGylation drugs related to optimization of half-life, immunogenicity, antigenicity, and low toxic profile of the drug itself.

Liposomal drug nanocarrier

Liposomes are one of the drug delivery nanocarriers with an aqueous nucleus wrapped in a lipid bilayer. PEGylated Liposomal or PEGylated Liposomal nanocarriers can improve the specificity of conjugation with special ligands as well as long circulation times and provide a low toxicity profile to the drug. Reduced toxic profile and increased pharmacokinetic parameters are due to distribution, increased circulation time, controlled release, increased intracellular concentration, and increased solubility and stability of the drug.

Construction mechanism

Bispecific Antibody (BsAb) Pre-Targeting preparation

BsAb molecules are made by the formation of C-terminus between the anti-mPEG scFv and the antibody Anti-CD20 via flexible peptide $(GGGGS)_3$ to form CD20 Ab-mPEG scFv antibodies. Furthermore, the VL-Ck and VH-CH1-CH2-CH3 domains on ScFv were removed to form the pLNCX-CD20 Ab-mPEG scFv plasmid using Hind III and Cla I endorestrictive enzymes (Brinkmann & Kontermann, 2017). The plasmid preparation will be amplified in culture E. coli TOP10 using media Luria broth. Incubation of bacterial cultures was carried out at 8% CO2 and 37oC for 5 days (Brinkmann & Kontermann, 2017; Q. Wang et al., 2019). Antibody protein molecules from the culture results were carried out using centrifugation at a speed of 1500 rpm for 5 minutes. supernatant further purification will be carried out using direct incubation and molecular weight measurements using sodium dodecyl sulphate polyacryl amide gel electro phoresis (SDS-PAGE) (Brinkmann & Kontermann, 2017; L. Li & Wang, 2020; Q. Wang et al., 2019).

Preparation of PEGylated Liposomal Drug Nanocarriers

The CH3-PEG2K-succinimidyl propionic acid molecule is dissolved in DMSO 2mg/mL which is then mixed with β-glucuronidase 10 mg/mL to form PEGylated β-glucuronidase which will be further purified using the ion exchange method. Furthermore, PEGylated liposomal nanocarriers preparations are made by preparing liposomes with a diameter of 50 nm (nanoparticles) containing chemotherapy agent preparations using the conventional drug loading step method. The liposome preparations are further conjugated with PEGylated β-glucuronidase through the formation of covalent bonds of the reaction between the PEG domain with the terminal azide domain and the hydrophobic alkyne-ended anchor built on the phospholipid layer of the liposome.

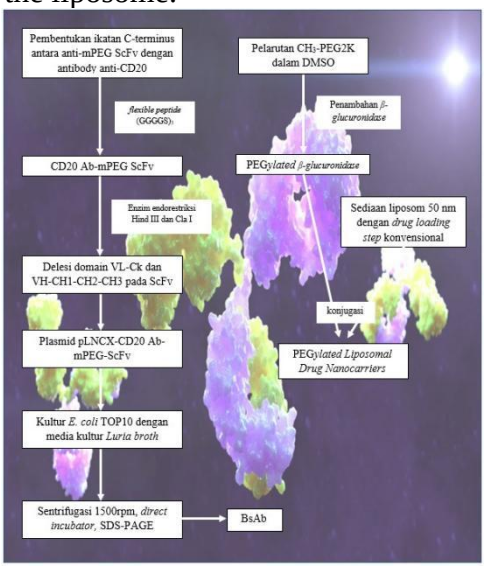

Figure 1. Construction Mechanism Scheme of BsAb and PEGylated Liposomal Drug Nanocarriers

Pharmacokinetics

PEGylated drug nanocarriers are an efficient method of delivering anticancer drugs such as blinatumumab, denintuzumab, and doxorubicin. PEGylated delivery applications provide nontoxicity, low immunogenicity, antigenicity, and longer half-lives that can improve the pharmacokinetics of a drug. PEG nanocarriers also provide a shelf life of up to 7 days at ±80% without reducing their effectiveness excessively (Appendix 1).

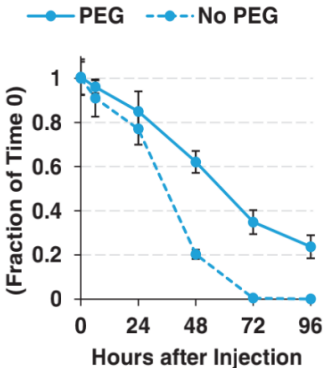

Figure 2. Schematic of PEG fraction and No PEG drug in post-injection blood67

An increase in half-life also occurred in PEGylated drug nanocarriers for 96 hours compared to non-PEGylated drugs for 48 at fractions of 0.2 so that dosing could be minimized (Figure 2). Research by Susanne et al., in mice, demonstrated the effectiveness of PEGylated drug nanocarriers in improving drug distribution and elimination as well as rapid accumulation of tumor cells in tissues compared to low molecule weight drugs (Figure 3).

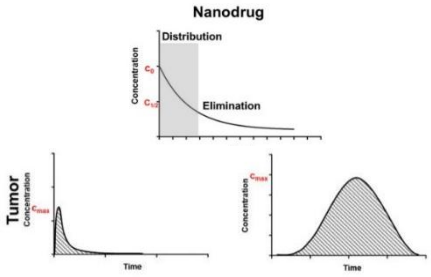

Figure 3. Graph of distribution and elimination of PEGylated nanodrugs.

PEGylated drug nanocarriers cause a 48-hour delay in drug release at a drug release rate of ±30% which has a good impact on the prevention of leakage in the drug delivery process (Figure 4).

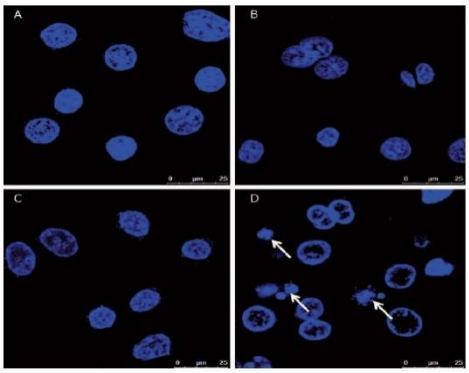

Figure 4. Morphologic changes of PEG-liposomes on MDA-MB-231. Morophologic changes of PEG-liposomes on MDA-MB-231. (A), free irinotecan (B), PEG-coated irinotecan liposomes (C) and PEG-coated irinotecan cationic liposomes (D), viewed again. Arrows: fragmented nuclei.

The accumulation of PEGylated biodistribution is centered in the liver as the main metabolic site and is followed by excretion in urine, plasma, and bile.

Pharmacodynamics

Previous CD20-focused BsAb research has shown that CD20 Ab-mPEG scFv action will target CD20 expressing cells to trigger ADCC and CDC. These drug molecules will also recognize PEGylated nanodrugs to induce internalization in enhancing drug pharmacokinetics (Appendix 2).

In addition, PEGylated drug nanocarriers also provide an important antibody-dependent endocystosis (ADE) effect in cancer therapy in increasing cellular uptake of liposomes through the anti-mPEG scFv part of BsAB. Previous studies using HER2 x mPEG BsAb with the same drug mechanism showed a 2.2-fold more effective efficacy than HER2 x DNS BsAb. This shows that the action of PEGylated drug nanocarriers and BsAb significantly inhibits the development and inhibits the growth of cancerous lymphoid cells.

The mechanism of first attack begins with the binding of BsAb to the CD-x receptor which triggers ADCC and CDC on the target cell. BsAb will mediate effector cells through binding of Fcγ receptors to effector cells. This binding activates C1q which will trigger the activation of the complement pathway to the Fc region of the target cell-bound antibody which will then activate the membrane attack complex (MAC) of a series of complement proteins and mediate the lysis of the target cell. In addition, the ADCC mechanism can also be activated by changes in the conformational of the Fc region of the antibody that increase the affinity of the Fc receptor in the effector cell that occurs after BsAb binds to the CD-x receptor of the target cell. FcγRIIIA-specific antibodies in NK cells will immediately recognize BsAb-coated target cells and induce the occurrence of ADCC.

The second attack mechanism will be initiated as soon as PEGylated liposomal is injected. BsAb will recognize liposomal PEGylated and initiate liposomal PEGylated internalization as well as cytotoxicity against cancerous lymphoid cells. Internalization of the ADE properties of PEGylated liposomal BsAb will increase by 56% in 24 hours compared to other non-PEGylated nanodrugs. The properties of BsAb in minimal residual disease (MRD) eradication provided efficacy of 59% complete remission from 98 samples with an explosion of ≥ 5%. This is supported by the effectiveness of BsAb second attack in studies using mice which showed that the pretarget experiment of PEG-BsAb Fab-IgG1 was 25 times higher in cells with HER2+SKBR3 compared to other antibody modalities in mean fluorescence intensity (MFI) images. The same was shown with green fluorescent protein (GFP), cell binding to HER2+SKBR3 was 20 times higher in PEG-BsAb Fab-IgG1 than in other modalities (Appendix 3).

Effects PEGylated Liposomal Drug Nanocarriers terhadap B-ALL

Research by Ho, et al. through in vivo studies showed that doxorubicin preparations in PEGylated liposomal drug nanocarriers or PEGylated liposomal doxorubicin (PLD) were able to increase the internalization process by 36.6% to 83.6% after 24 hours of intravenous administration. In addition, administration of the same dosage in vitro also increased the cellular cytotoxicity of doxorubicin in cancer cells by 11 times compared to conventional doxorubicin preparations alone . Research by Hong, et al. also showed a decrease in the toxicity level of paclitaxel to somatic cells and an increase in the rate of hemolysis of cancer cells in the form of PEGylated liposomal paclitaxel (PLP) compared to conventional preparations.

Zhang, et al. also showed linear results in the form of a significant increase in the efficacy of irinotecan chemotherapy ($p<0.001$) using PEGylated liposomal irinotecan preparations in MDAMB231 strain chemotherapy-resistant breast cancer cells in vitro. In the same study, it was known that the survival rate in vivo after injection of 5 μM PEGylated liposomal irinotecan was 23.77 ± 1.43% compared to free irinotecan of 5.57 ± 1.14%.

Effects of Bispecific Antibody (BsAb) on B-ALL

The use of BsAb in leukemia therapy, especially B-ALL, aims to facilitate and improve the performance of PEGylated liposomal nanocarrier preparations. The increase in internalization of chemotherapy preparations is known to show a linear relationship with the level of chemotherapy efficacy in cancer cells. Other studies showed that the use of CD-19-targeted BsAb internalizable immunoliposomes was able to significantly improve therapeutic outcomes and extend the lifespan of Namalwa cell-bearing mice ($p<0.001$). Research by Chuang, et al. designed liposomes with nonendocytic receptors through the cutting of NPXY endocytosis signals so that they are unable to bind to the anti-PEG domain on antibodies. After administration of the preparation, B-cell leukemia cancer strains with endocytosizable liposomes were completely suppressed on day 63 in vivo.

These results show that the role of BsAb in inducing liposomal endocytosis is very significant. In addition, BsAb also chains specific immune responses to cancer cells, especially in lymphoid cell pathways that are highly sensitive to systemic antibody-like immunotherapy modalities.

Effect of Bispecific Antibody (BsAb) Combination PEGylated Liposomal Drug Nanocarriers on B-ALL

Cong wu, et al. found a significant increase in survival rate ($p<0.05$) in B-cell leukemia-induced mice in vivo through the administration of PEGylated liposomal adriamycin (ADR) and Fab fragments from rituximab as well as CD20 and PEG liposome-targeted BsAb. Sun, et al. also reported an increase in cellular update of 1.8 times and cytotoxicity of 1.53 times against acute leukemia in vitro using leaforubicin and CD123/CD33 targeted BsAb preparations and PEG liposomes using similar methods.

Research by Strop et al. used microbial transglutaminase to conjugate amine-containing drugs to antibodies instead of using PEGylated liposomal.[80] Unfortunately, the conjugation causes liposome heterogeneity in functional group domains (amino, carboxyl, thiol) thus leading to clinical limitations in targeting liposomes by antibodies (Appendix 7).

The use of the BsAb modality in conjunction with chemotherapy agents in the form of liposomes also plays an important role as a strategy in the management of chemotherapy-resistant B-cell leukemia. Previous research has shown that cancer B cells are able to develop resistance to rituximab and stop the expression of CD20 on the membrane surface. The study using the CTL019 CAR-T in these cases only showed an increase in survival rate that was not clinically significant. On the other hand, this problem has been proven to be overcome through recent research using a CD19 target approach and blinatumumab chemotherapy. In addition, B-cell leukemia is also known to be able to form resistance, especially doxorubicin through MDR1 and MRP1 which act as drug efflux pumps so that drug preparations can be removed from the cell. Recent studies have shown that specific antibodies can initiate an increase in intake up to 7.64 times with inhibition of drug efflux pump by 45.6% (CI 30.2-67.6%, $p<0.001$) in vitro.

CONCLUSION

Bispecific Antibody (BsAb) is an antibody molecule that can detect two different types of antigens or epitopes . On the other hand, PEGylated Liposomes or called PEGylated Liposomal nanocarriers can improve the specificity and sensitivity of conjugation to specific ligands as well as prolong systemic circulation time and provide a low toxicity profile in normal body tissues. The effect of Bispecific Antibody (BsAb) PEGylated Liposomal Drug Nanocarriers on B-ALL can be an effective management modality against B-ALL, especially in the pediatric group.

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