GAVIN PUBLISHERS

Journal of Vaccines, Immunology and Immunopathology

Li R , J Vaccines Immunol 2016: J106.

DOI: 10.29011/2575-789X.000006

Editorial

Targeting CD33 with Antibody-Drug Conjugates: Challenges and New Hopes

Ran Li*

Texas A&M University Health Science Center, USA

*Corresponding author: Ran Li, Texas A&M University Health Science Center, 445 Joe H,Reynolds Medical Sciences Building, 1114 TAMU, College Station, TX 77843, USA. Tel: 979-436-0740; E-mail: rli@medicine.tamhsc.edu

Citation: Li R (2017) Targeting CD33 with Antibody-Drug Conjugates: Challenges and New Hopes. J Vaccines Immunol 2017: J106. DOI: 10.29011/2575-789X.000006

Received Date: 31 January, 2017; **Accepted Date:** 08 February, 2017; **Published Date:** 15 February, 2017

Antibody-drug conjugates (ADCs) have emerged as one of the most fascinating cancer therapeutics in recent years, with two drugs (Adcetris and Kadcyla) approved for FDA and over 50 others under clinical development for different applications [1]. An ADC combines the specificity of antibody targeting with potent small molecular toxins, which promise to be more effective in eradicating cancer cells than the un-conjugated antibody. An important application of ADC in hematopoietic malignancies is treatment of acute myeloid leukemia (AML) with the expression of CD33, which is a myeloid differentiation antigen found in nearly all AML patients [2,3].

Gemtuzumab Ozogamicin (GO) is the first approved ADC, a CD33-targeting humanized IgG4 conjugated to the DNA damaging toxin calicheamicin-γ1 through an acid-labile linker, which releases the toxin in acidic lysosomes upon internalization of the antibody. Although showing improved survival in subsets of patients in several clinical trials, GO was withdrawn from the market in most countries in 2010 due to lack of efficacy and concerns for its toxicity. Importantly, although SGN-CD33A, a new generation of ADC improved with site-specific conjugation, more stable protease-cleavable linker and a potent DNA cross-linking cytotoxin, is highly active in a broad panel of preclinical AML models [4], several recent early-stage trials of SGN-CD33A have been halted due to the liver toxicity observed in patients.

The disappointing attempts of previously-developed ADCs including GO and recent issues of SGN-CD33A highlight the challenges of CD33-tageted therapies for treatment of AML. First, the cellular expression level of CD33 is low, with an average of 8000 molecules/cell [5]. Second, although CD33 undergoes internalization upon cross-linking of an antibody, the process is slower as compared to many other cell surface antigens [1]. The low level of surface expression together with relatively slow internalization limit the efficacy of CD33-directed ADCs which usually require to traffic to lysosomes to release the toxic payload. Third, the toxins of ADC are generally hydrophobic chemicals, which can be targets of cellular drug transporters, such as P-glycoprotein and MRP1 in the case of GO [6]. Moreover, in spite of a myeloid differentiation antigen, the expression of CD33 has also been reported on Kupffer cells or other cell populations in the liver such as hepatocytes [7,8], which might account for the liver toxicity of GO as well as SGN-CD33A. Last but not least, although SGN-CD33A and others are designed to release the toxin by lysosomal proteases, it is not fully known whether the linker may be subject to cleavage of certain serum proteases and release the toxin prior to reaching the target cells.

To overcome the challenge of low surface antigen level and slow internalization, it requires to increase the toxic payload per ADC molecule. One approach is to develop more potent toxins than the existing ones. The other approach is to increase the drug-antibody ratio (DAR). However, given the toxin's hydrophobic nature, it has been shown that hydrophobicity could significantly impair the persistence of an ADC and its therapeutic efficacy [9], which may also explain why an ADC with high DAR could behave poorly *in vivo*. Thus, reducing the hydrophobicity of an ADC while maintaining its high DAR status can be another way to increase its efficacy both *in vitro* and *in vivo*. Since cellular drug transporters could hamper the ADC's efficacy, combination therapies involving CD33-targeting ADCs and multi-drug transporter inhibitors to block the drug efflux could be more effective. Moreover, due to the genetic and epigenetic heterogenicity of AML, subsets of patents who may respond best to a specific CD33-targeted ADC need to be identified.

Although many questions and challenges still need to be addressed for CD33-directed ADCs in future studies, ADC remains

a fast-growing cancer therapy and many other agents being developed both preclinically and in clinic may offer new tools for the treatment of AML. Given the importance of immune system in cancer treatment, combination of ADCs with other approaches engaging cellular immune responses such as bispecific antibodies and chimeric antigen receptor (CAR) T cell therapies may even have better clinical efficacy than the single agent alone and will begin a new era of immunotherapy for cancer treatment.

References

1. de Goeij BE and Lambert JM (2016) New developments for antibody-drug conjugate-based therapeutic approaches. Curr Opin Immunol 40: 14-23.
2. Pollard JA, Alonzo TA, Loken M, Gerbing RB, Ho PA, et al. (2012) Correlation of CD33 expression level with disease characteristics and response to gemtuzumab ozogamicin containing chemotherapy in childhood AML. Blood 119: 3705-3711.
3. Krupka C, Kufer P, Kischel R, Zugmaier G, Bogeholz J, et al. (2014) CD33 target validation and sustained depletion of AML blasts in long-term cultures by the bispecific T-cell-engaging antibody AMG 330. Blood 123: 356-365.
4. Kung Sutherland MS, Walter RB, Jeffrey SC, Burke PJ, Yu C, et al. (2013) SGN-CD33A: a novel CD33-targeting antibody-drug conjugate using a pyrrolobenzodiazepine dimer is active in models of drug-resistant AML. Blood 122: 1455-1463.
5. Jilani I, Estey E, Huh Y, Joe Y, Manshouri T, et al. (2002) Differences in CD33 intensity between various myeloid neoplasms. Am J Clin Pathol 118: 560-566.
6. Cowan AJ, Laszlo GS, Estey EH, Walter RB (2013) Antibody-based therapy of acute myeloid leukemia with gemtuzumab ozogamicin. Front Biosci (Landmark Ed) 18: 1311-1334.
7. Rajvanshi P, Shulman HM, Sievers EL, McDonald GB (2002) Hepatic sinusoidal obstruction after gemtuzumab ozogamicin (Mylotarg) therapy. Blood 99: 2310-2314.
8. Maniecki MB, Hasle H, Bendix K, Moller HJ (2011) Is hepatotoxicity in patients treated with gemtuzumabozogamicin due to specific targeting of hepatocytes? Leuk Res 35: e84-e86.
9. Lyon RP, Bovee TD, Doronina SO, Burke PJ, Hunter JH, et al. (2015) Reducing hydrophobicity of homogeneous antibody-drug conjugates improves pharmacokinetics and therapeutic index. Nat Biotechnol 33: 733-735.