Opinion
Volume 7:7, 2022

Journal of Cancer Clinical Trials

ISSN: 2577-0535 Open Access

Safety and Efficacy Profile of Trastuzumab Deruxtecan in Solid Cancer: Pooled Reanalysis Based on Clinical Trials

Matthew Witek*

Department of Clinical Pharmacology, University of Wisconsin, USA

Introduction

Human epidermal growth factor receptor 2 (HER2) is one of the epidermal growth factor transmembrane receptor family. The amplification, mutation and overexpression of HER2 can promote the proliferation, adhesion, migration, differentiation and apoptosis of tumor cells and is associated with aggressive diseases. Targeting HER2 is a burgeoning method for treating several kinds of HER2-positive tumors, including breast cancer, gastric cancer, and non-small cell lung cancer. About 15-20% of breast cancer, 6 to 30% of advanced gastric or gastro-esophageal junction cancers, and 7 to 9% NSCLCs are HER2-positive. Combination of anti-HER2 humanized monoclonal antibody and chemotherapy is the first line therapy recommended to patients with metastatic HER2-positive breast cancer, and the antibody-drug conjugate (ADC) trastuzumab emtansine is the standard second-line therapy. According to the phase 3 ToGA trial, trastuzumab is the first approved drug for anti-HER2 therapy in HER2-overexpressing gastric cancer. However, breast cancer is still the disease that responds best to these drugs, which may account for the higher expression of HER2 in breast cancer [1].

Description

ADC commonly has three components, an antibody, a linker and a payload cytotoxic agent. The antibody is used to against the target antigen, the cytotoxic agents have standby effect, and the linker connects these two components. Trastuzumab deruxtecan (DS-8201a) is a kind of ADCs and composed of a humanized anti-HER2 antibody, a potent topoisomerase I inhibitor (an exatecan derivative, DXd) and a tetrapeptide linker, which is stable in plasma and can be cleaved by cathepsin in tumor cells. The anti-HER2 antibody in DS-8201a is a human monoclonal IgG1 and its amino acid sequence is the same as trastuzumab. The drug-to-antibody ratio of DS-8201a is seven to eight, which is higher than that of trastuzumab emtansine (about four). Previous studies used trastuzumab, pertuzumab or trastuzumab emtansine to treat HER2-positive cancers, while some of them did not prolong overall survival of patients and some achieved high objective response rate (ORR) with severe drug resistance problem [2]. As both the basic information and clinical results indicate DS-8201a as a potent effective drug for HER2-positive cancers, we found it necessary to summarized existing results. Hence, to explore the potency of DS-8201a in treating solid cancers, this study reviewed and pooled the results of all completed clinical studies.

For curing patients with HER2-positive carcinoma, especially breast and gastric cancer, DS-8201a is a newly developed ADC, having combination of the HER2-targeted antibody and a topoisomerase I inhibitor, with great potency. As patients with HER2-positive cancer still suffer from disease progression after using medicines according to guidelines, new drugs are in urgent demand. This is the first study that explored the efficiency and safety of DS-8201a in treating HER2-positive cancer. The most common adverse event of DS-8201a is associated with gastrointestinal system and blood system. The ORR is higher and the time of PFS is longer in patients with breast and gastric cancer. According to the pooled results, treated by DS-8201a resulted in an acceptable safety profile. The most common AEs mainly related to gastrointestinal and hematological system. In all grades, nausea, decreased appetite, vomiting, fatigue, anemia, decreased neutrophil count, alopecia and diarrhea had rates larger than 30%. In grade 3 or more, only decreased neutrophil count, anemia and decreased white blood cell count happened with relatively high rate. Compared with other anti-HER2 drugs like trastuzumab, pertuzumab and trastuzumab emtansine, which can lead to cardiac dysfunction and pulmonary toxicity, the AEs of DS-8201a are different and in high grades AEs are mainly related to hematological system. In addition, drug-related interstitial lung disease and pneumonia are life-threatening AEs despite their low incidence. For patients suspected to have these AEs, treatment with DS-8201a should be interrupted pending further evaluations, like pulmonologist consultation, blood culture, high-resolution computerized tomography, et al. With early detection of symptoms, discontinuation, or reduction of DS-8201a use, and timely systemic corticosteroids, these life-threatening AEs may be effectively reduced. The relative safety of DS-8201a may due to its stabilization in plasma, as the cleavage of its linker needs lysosomal enzymes, which are sufficient in tumor cells and lack in plasma [3].

DS-8201a has high potency for HER2-positive cancers. The effect of DS-8201a for patients with HER2-positive breast and gastric carcinoma had been proved in included studies, in which a large proportion of patients had objective response to DS-8201a (ORR 37-79.9%). Compared with previous HER2-targeted agents, including margetuximab, neratinib, trastuzumab emtansine and lapatinib, the efficiency of DS-8201a was higher. For example, studies like SOPHIA, NALA, TH3RESA, EMILIA for breast cancer and GATSBY and TyTAN for gastric cancer used other HER2-targeted agents and gained ORR ranged from 16 to 32.8%. For HER2-positive breast cancer, the recommended first-line neoadjuvant treatment is trastuzumab plus pertuzumab and a taxane, and the second-line therapy is ADC trastuzumab emtansine. In comparison to previous study that used these neoadjuvant therapies for breast cancer, having ORR ranged from 40 to 60%, the ORR of DS-8201a was comparative. In comparison with other recent therapies for HER2-positive breast cancer, the PFS of DS-8201a for breast cancer was longer (< 10 vs. 9.9-22.1 months). These results indicated that DS-8201a had durable antitumor activity to HER2-positive cancer, especially breast cancer [4].

Though the ORR and PFS of patients with other kinds of solid tumor was relatively lower (17.5-65.5%, 4.1-11.9 months), conclusions could not be drawn due to the insufficient sample size. Larger studies are warranted to determine the potency of DS-8201a for HER2-amplified cancers. The variation of efficiency among different HER2-positive cancers may be due to different HER2 expression level in these cancers since many studies have proven the negative correlation between HER2 expression and cancer prognosis. The potency of DS-8201a to other HER2-mutated cancers may be mainly due to its high drug-to-antibody ratio and cytotoxic bystander effect. In addition to higher ORR, PFS and OS, DS-8201a also offers more treatment options for patients who are resistant to previous anti-HER2 drugs. The resistance rate of using trastuzumab alone ranged from 66 to 88% and that of combination therapy was 20 to 50%. Even in patients with response, the one-year disease

***Address for Correspondence:** Matthew Witek, Department of Clinical Pharmacology, University of Wisconsin, USA, E-mail: witekmatthew1985@gmail.com*

Date of Submission: 06 July, 2022; Manuscript No. jcct-22-73619; **Editor Assigned:** 08 July, 2022, PreQC No. P-73619; **Reviewed:** 11 July, 2022, QC No. Q-73619; **Revised:** 22 July, 2022, Manuscript No. R-73619; **Published:** 25 July, 2022, DOI: 10.37421/2577-0535.2022.7.172.

progression rate was high. Many hypothesis reasons had been denounced, like the decrease, heterogeneous expression, or mutation of the out-membrane HER2, alternation of the proteinsides related to drug efflux and resistance to the intro-cellular drug payload. In included studies DS-8201a was still effective to patients previously treated by trastuzumab, pertuzumab or trastuzumab emtansine, and this may due to different pharmaceutical properties, including the potency of topoisomerase I inhibitor, the higher membrane permeability, bystander killing effect and larger drug-to-antibody ratio (7-8) of DS-8201a [5].

Conclusion

There still are some limitations in this study and leaded to the high heterogeneity. Firstly, the dose of DS-8201a is 5.4 or 6.4 mg per kilogram of body weight, and for insufficient data subgroup analysis was not available. Secondly, patients included were heterogeneous with different kinds of HER2-positive tumors and differently prior treatments, which required more available research to address. Meanwhile, we included more than 50 kinds of symptoms reported in different research and it also contributed to the high heterogeneity. Lastly, no internal comparison was made to explore the efficiency of DS-8201a more directly. Thus, larger random control studies are required to assess the potency of DS-8201a.

Conflict of Interest

None.

References

1. Wieduwilt, M.J and M.M. Moasser. "The epidermal growth factor receptor family: biology driving targeted therapeutics." *Cell Mol Life Sci 65* (2008): 1566-1584.
2. Verma, Sunil, David Miles, Luca Gianni and Ian E. Krop et al. "Trastuzumab emtansine for HER2-positive advanced breast cancer." *N Engl J Med 367* (2012): 1783-1791.
3. Bang, Yung-Jue, Eric Van Cutsem, Andrea Feyereislova and Hyun C. Chung et al. "Trastuzumab in combination with chemotherapy *vs.* chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial." *Lancet* 376 (2010): 687-697.
4. Mazieres, J., F. Barlesi, T. Filleron and B. Besse, et al. "Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: results from the European EUHER2 cohort." *Ann Oncol 27* (2016): 281-286.
5. Carey, Lisa A., Charles M. Perou, Chad A. Livasy and Lynn G. Dressler, et al. "Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study." *JAMA* 295 (2006): 2492-2502.

How to cite this article: Witek, Matthew. "Safety and Efficacy Profile of Trastuzumab Deruxtecan in Solid Cancer: Pooled Reanalysis Based on Clinical Trials." J Cancer Clin Trials 7 (2022): 172.