Sci Eng Ethics (2018) 24:1809–1811
https://doi.org/10.1007/s11948-017-9966-3

LETTER

Conflict of Interest and the CREATE-X Trial in the New England Journal of Medicine

Akihiko Ozaki[1,2]

Received: 14 August 2017 / Accepted: 28 August 2017 / Published online: 15 September 2017

Abstract There is an increasing emphasis on clear disclosure of conflict of interest in medical communities, following repeated scientific frauds in clinical trials. However, incomplete COI statements continue to be prevalent in the medical community, as appears to have occurred in the Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) trial, which was recently published in the New England Journal of Medicine. The authors of the article did not clearly report the roles of the Japan Breast Cancer Research Group, a sponsor and funder of the study, although a majority of the Japanese authors served in important positions in the organization. Furthermore, the conflict of interest related to Chugai Pharmaceutical Company, a Japanese distributor of capecitabine, was not correctly disclosed. More transparent statements of conflict of interest and clarification of sponsors and funders' roles, as well as rigorous review by academic journals are required to fairly interpret the findings of clinical trials, including and beyond the single case of the CREATE-X trial.

Keywords Conflict of interest · Capecitabine · Breast cancer · Clinical trial · New England Journal of Medicine

Despite growing attention to the importance of appropriate disclosure of potential conflict of interests (COIs), incompletely reported COIs are still prevalent in the medical community. In June 2017, the results of Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) trial were published in the New England Journal of Medicine (NEJM); the study assessed the effect of additional capecitabine on

✉ Akihiko Ozaki
ozakiakihiko@gmail.com

[1] Department of Surgery, Minamisoma Municipal General Hospital, 2-54-6 Takamicho, Haramachi, Minamisoma, Fukushima 975-0033, Japan

[2] Teikyo University Graduate School of Public Health, 2-11-1 Kaga, Itabashi-ku, Tokyo, Japan

disease-free survival (DFS), the primary end point, and overall survival (OS), one of the secondary end points, among female breast cancer patients with human epidermal growth factor receptor 2 (HER2)-negative residual invasive diseases following standard neoadjuvant chemotherapy (Masuda et al. 2017).

The authors report that the Japan Breast Cancer Research Group (JBCRG), a sponsor and funder of the study, did not make any contributions to the trial design, data collection, analysis, or the interpretation of results in the main article. Nonetheless, in the study protocol published as supplementary material, the JBCRG was described as the one and only research organization to conduct the trial, and the corresponding and senior author was named as the representative physician of the JBCRG. Further, nine of the twelve Japanese authors serve in important positions of the JBCRG (Japan Breast Cancer Research Group 2017), which was not mentioned in the article.

Further questions arise when looking at the donations from the Chugai Pharmaceutical Company (CRC), a Japanese distributor of capecitabine, to the JBCRG. The CRC disclosed a donation of 100,000,000 yen (approximately 0.92 million USD) to the JBCRG from 2012 to 2014, and 236,000,000 yen (approximately 2.2 million USD) to the Advanced Clinical Research Organization (ACRO), the other funder of the study, from 2012 to 2015 (Chugai Pharmaceutical Company 2017). Nonetheless, only four Japanese authors disclosed a COI related to CRC. Given that CRC has donated a large amount of money to the JBCRG and the ACRO, and that these two organizations are the funders and supporters of the trial, incomplete disclosure of COIs related to CRC may be a significant violation of the internationally accepted consensus for COI statement.

The CREATE-X trial is groundbreaking in that it clearly showed a significantly prolonged DFS and OS with the addition of capecitabine among breast cancer patients with an incomplete response to the standard neoadjuvant chemotherapy. Given that it is generally accepted that combinations including taxanes or anthracyclines are the standard regimens in breast cancer preoperative or adjuvant settings (National Comprehensive Cancer Network 2017), it is surprising that the addition of capecitabine achieved positive results not only in DFS but also in OS, with median follow-up of only 3.6 years. Yet, given that this study applied an open-label design, a series of incomplete disclosures of COIs and contradictory descriptions in the article and the study protocol may undermine the credibility of these observed findings.

Accordingly, I indicated my concerns to the editorial office of the NEJM, and they decided to make a correction to the COI statement. In a correspondence piece related to the CREATE-X trial, published in August 2017, the authors of the study nonchalantly reported being members of the board of the JBCRG and the existence of the previously undisclosed COI with CPC (Toi et al. 2017). However, interpretation of the study results could differ depending on whether the incomplete COI occurred by honest error or intentional concealment, a distinction which remains unclear. Now is the right time to discuss the ideal relationships between medical researchers and pharmaceutical companies once again in the global medical community.

Compliance with Ethical Standards

Conflict of interest The author declares that there is no conflict of interest.

References

Chugai Pharmaceutical Company. (2017). *Funding to medical institutions and individuals (in Japanese)*. Available at: https://contact.chugai-pharm.co.jp/gl/medical/jp/summary.php. Accessed 22 August 2017.

Japan Breast Cancer Research Group. (2017). *Home page of Japan Breast Cancer Research Group*. Available at: http://www.jbcrg.jp/en/about/. Accessed 22 August 2017.

Masuda, N., Lee, S. J., Ohtani, S., Im, Y. H., Lee, E. S., Kuroi, K., et al. (2017). Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *New England Journal of Medicine, 376*(22), 2147–2159.

National Comprehensive Cancer Network. (2017). *NCCN clinical practice guidelines on oncology (NCCN guidelines) breast cancer version 2.2017*—April 6, 2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 22 August 2017.

Toi, M., Masuda, N., & Ohashi, Y. (2017). Adjuvant capecitabine for breast cancer. *New England Journal of Medicine, 377*(8), 791–792.