May 7, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript No.10447-Edited.doc).

Title: Adjuvant Chemotherapy: To Use or Not To Use, The Anthracyclines

Author: Jennifer A. Crozier, Abhisek Swaika and Alvaro Moreno-Aspitia.

Name of Journal: *World Journal of Clinical Oncology*

ESPS Manuscript NO: 10447

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated

2. Typesetting was corrected

3. Revision has been made according to the suggestions of the reviewer

Reviewer 2444925

1. "It is shown that anthracyclin sensitivity is related to HER2 overexpression. The main target of anthracyclines is topoisomerase IIa (TOP2A) gene, which locates on the same amplicon as the HER2 gene on 17q21. Therefore, anthracyclines appear to be most effective in patients whose tumors have amplification of TOP2A gene, usually associated with HER2 amplification. But the relationship between anthracyclin sensitivity and TOP2A amplification is controversial in the adjuvant setting. From the aspect of TOP2A gene amplification, the authors should describe the role of anthracyclines in detail in adjuvant chemotherapy."
   This area of the manuscript has been expanded to include TOP2A amplification and the role of anthracyclines.
2. Many kinds of spectrums of molecular targeted drugs is about to be evaluated for use in early breast cancer. Therefore, the authors should describe the possibility of anthracyclines in combination with them in the adjuvant setting.
   A paragraph addressing the future clinical trials of targeted therapies has been added.

Reviewer 02903608

1. The molecular subtype plays pivotal role in determining the necessity for patients requiring (neo)adjuvant chemotherapy as well as the pathological staging. It affects the sensitivity to different chemotherapy regimens and need more delineation in total paper.

   Unfortunately due to space limitations a thorough review of the different molecular subtypes of breast cancer and their response to anthracyclines and non-anthracycline-based regimens is not possible and is beyond the scope of this review.

2. "Sentences "With no single standard regimen as the gold standard of care for adjuvant treatment of breast cancer; the treatment must be individualized but overall chemotherapy should try to include an anthracycline and/or a taxane if the patient is a candidate for this therapy." have no sense in its paragraph."

   This sentence has been removed.

3. "No single regimen has been defined as the absolute gold standard treatment but based on well conducted prospective trials and meta-analyses conducted by the EBCTCG, anthracycline-based regimens have been recommended for more than 2 decades." These points need more explanation and please note the references.

   The references have been added.

4. In the chapters "Anthracycline vs. Non-Anthracycline Adjuvant Regimens" there is no comparison between FEC and TC.

   To our knowledge no trial comparing FEC and TC has been conducted.

5. "It has been hypothesized that a specific population of patients who may benefit from the use of anthracycline is that of patients with HER2 positive tumors." Please cite the references.

   An appropriate reference has been added.

6. "Anthracyclines plus taxanes are important components of what is called today "third generation regiments". Please cite the references. I am not sure whether it is correct or not.

   Regimens containing anthracyclines plus taxanes are commonly referred to as "third generation regimens". These are regimens usually used for node-positive or high risk node-negative breast cancer and can lead to a 40-50% relative risk reduction of cancer relapse in the adjuvant setting. This terminology was coined by the authors of the Adjuvant Online software and an appropriate reference has been added.

Thank you again for publishing our manuscript in the *World Journal of Clinical Oncology*.

Sincerely yours,

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