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Participation in International ABC and ATLAS Trials of Adjuvant Treatment for Breast Cancer: An Inspiring Clinical Research Experience

Peiman Haddad*[a]

[a] *Radiation Oncology Research Center, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran*

Iranian cancer specialists generally have a great interest in clinical research carried out in international settings, but participation in large multicenter clinical trials that include other countries is often difficult to arrange. In this regard, two of the most successful endeavors in Iran are the Adjuvant Breast Cancer (ABC) and Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trials.

In late 1992, Prof. John Yarnold and his team in the United Kingdom (UK) Institute of Cancer Research (ICR) initiated the (ABC) trial to assess overall survival and other long-term outcomes of combined modality therapy for women with early breast cancer. The chemotherapy side of the ABC Trial tested the addition of chemotherapy to prolonged tamoxifen (with or without elective ovarian ablation or suppression), and the ovarian ablation or suppression side of the trial assessed the addition of ovarian ablation or suppression to prolonged tamoxifen (with or without elective chemotherapy).

From the very beginning, Prof. Yarnold sought collaboration with many countries, and received a positive response from Iran through the efforts of Prof. Kamaleddin Dehshiri and Prof. Jahangir Rafat (Cancer Institute, Tehran University of Medical Sciences) and also Professor Seyed-Hossein Mortazavi, (Jorjani Hospital, Shahid Beheshti University of Medical Sciences).

Subsequently, *i.e.* after the start of the trial in Iran in 1993 and under the leadership of these esteemed professors, other colleagues - including the author of this editorial - joined the trial (ABC Trial collaborators from Iran, as listed in ABC Trial reports published, were K. Dehshiri, P. Haddad, F. Amouzgar-Hashemi, S.H. Mortazavi, B. Shahrad, M. Shahidi).[3,4]

Cancer researchers and clinicians from 10 countries took part in the ABC Trial. Between January 1993 and September 2000, 2144 patients from 106 UK and 16 non-UK centers were recruited.

We entered 184 patients from Iran (100 from Cancer Institute and 84 from Jorjani hospital) into the trial.

Results of the ABC Trial were presented in major international oncology meetings in 2004 and published in the Journal of the National Cancer Institute (JNCI) in 2007.[1-4] The ABC Trial added new information to the limited data available at that time on the effects of combined long-term tamoxifen, chemotherapy, and ovarian ablation or suppression.[4] It also established a collaborative network for breast cancer trials in the UK and globally.[3]

The subject of long-term effects of hormonal therapy was a focus of the ABC Trial, and considering the importance of this area other researchers started to investigate this issue. The ATLAS Trial began recruiting in 1996 as an international trial of continuation of adjuvant tamoxifen for an extra 5 years after the initial treatment. This trial was run from the University of Oxford under the leadership of Dr. Christina Davies and Prof. Sir Richard Peto. In Iran the ATLAS Trial started again with the supervision of professors Dehshiri, Rafat, and Mortazavi. University approval for participation in the trial was received by Cancer Institute in December 1998. Recruitment was done in Cancer Institute and Jorjani, Shohada and Mehrad hospitals. Younger colleagues joined the trial (ATLAS Trial collaborators from Iran, as listed in

Address for correspondence:
Peiman Haddad, M.D.
Address: Department of Radiation Oncology, Cancer Institute, P.O. Box 13145-158, Tehran, Iran
Tel: +98 21 61192585
Fax: +98 21 66948672
Email: haddad@tums.ac.ir

the ATLAS Trial reports, were P. Haddad, K. Dehshiri, F. Amouzgar-Hashemi, H. Madani, S.H. Mortazavi, M.A. Mousavizadeh, J. Raafat, B. Sadrolhefazi, M. Tabatabaeefar.), and the author of this letter worked as the national coordinator.[5]

ATLAS recruited patients from 36 countries during the time period from 1996 to 2005. Patients were offered information leaflets in local languages (Persian in Iran). After patients provided signed consents, baseline characteristics were recorded and patients were entered into the study by faxing the relevant information to the Oxford Clinical Trial Service Unit (CTSU). Free tamoxifen was provided from the UK if needed. The trial was simple in design; other than duration of tamoxifen treatment, patient management was at the responsible clinician's discretion. Patients were not required to make any extra visits, and no extra investigations were required.[5]

In total, 15,244 women entered the ATLAS Trial all over the world. For budget-related reasons, in the UK this work was done by its counterpart, adjuvant Tamoxifen-To offer more? (aTTom) Trial, which recruited 6,953 women from 176 UK centers.[5] Together, the ATLAS and aTTom trials make the largest clinical trials of adjuvant treatment of breast cancer ever performed.

We entered 247 patients from Iran into the ATLAS Trial. Free tamoxifen shipped from the UK was provided to the patients allocated to longer duration of treatment, and this was received and distributed by Cancer Institute. We took part in the steering meetings of the trial in Oxford, UK and through this experience we got access to some of the meetings of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which was remarkably interesting.

The findings of the ATLAS Trial were presented at the December 2012 San Antonio Breast Cancer Symposium and published simultaneously in The Lancet. With a mean 7.6 years of further follow-up after 5 years of tamoxifen, results showed that 10 years of effective endocrine therapy can approximately halve breast cancer mortality within 10–14 years after diagnosis of ER-positive breast cancer.[5]

These findings were immediately met with great enthusiasm by international breast cancer clinicians and researchers and described as "practice-changing". Since then, the ATLAS Trial has been reviewed in various publications, cited 173 times as reported by Scopus in February 2015, and labeled as one of the "three remarkable advances" in the relevant oncology literature in 2013.[6,7] It has made a considerable impact on breast cancer treatment guidelines all over the world.

Our 20-year journey through time with these two international trials was not easy. A great deal of effort was put into it and the circumstances were sometimes frustrating, especially with the difficulties of following up patients in Iran (though the results of the ATLAS Trial have already been published, we are still filling out follow-up forms for an update). But this journey was very educative and inspiring too, and gave us the strength to believe in ourselves as significant members of the world's oncology research community, for which we are very thankful.

References

1. Yarnold J, Bliss J, Earl H, George D, Lawrence D, Mortazavi S, *et al.* Ovarian ablation (OA) in pre-menopausal women with early breast cancer prescribed 5 years tamoxifen (T) or T plus chemotherapy (CT)-results from the UK NCRI Adjuvant Breast Cancer (ABC) international trial of 2,144 patients. ASCO Annual Meeting Proceedings; 2004; 2004. p. 535.
2. Barrett-Lee P, Bliss J, Brunt A, Dehshiri K, Harnett A, Johnson L, *et al.* Polychemotherapy (CT) in pre-and post-menopausal women with early breast cancer prescribed 5 years tamoxifen (T)-results from the UK NCRI Adjuvant Breast Cancer (ABC) international trial in 1991 patients. ASCO Annual Meeting Proceedings; 2004; 2004. p. 656.
3. The Adjuvant Breast Cancer Trials Collaborative Group. Polychemotherapy for early breast cancer: results from the international adjuvant breast cancer chemotherapy randomized trial. J Natl Cancer Inst 2007; 99(7): 506-15.
4. The Adjuvant Breast Cancer Trials Collaborative Group. Ovarian ablation or suppression in premenopausal early breast cancer: results from the international adjuvant breast cancer ovarian ablation or suppression randomized trial. J Natl Cancer Inst 2007; 99(7): 516-25.
5. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, *et al.* Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013; 381(9869): 805-16.
6. Smith GL. The Long and Short of Tamoxifen Therapy: A Review of the ATLAS Trial. J Adv Pract Oncol 2014; 5(1): 57-60.
7. Suh DH, Kim JW, Kang S, Kim HJ, Lee KH. Major clinical research advances in gynecologic cancer in 2013. J Gynecol Oncol 2014; 25(3): 236-48.