Do the results of BIG 1-98 assist with patient management decisions?

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It goes without saying that the primary purpose of clinical trials is to provide data that indicates which treatment provides the best outcome for patients (ideally the individual patient); and in the context of adjuvant treatment for breast cancer this means maximisation of the chance of overall survival or 'cure'. In the real world such conclusions may be difficult to reach for a variety of reasons. These include the need to adhere to ethical principles of research in humans and the massive cost and logistics of undertaking trials large enough to demonstrate relatively small incremental gains of new over established effective treatments. The BIG 1-98 trial has been influenced by these difficulties but has dealt with them in an effective manner and as a result must be considered a resounding success, providing not only answers to the questions it set out to look at, but also useful additional information that guides an individual patient's treatment choice.

It is nearly 14 years since the first patient was randomised in the BIG 1-98 trial, a large global study designed to determine whether breast cancer outcomes are improved by using 5 years of letrozole rather than 5 years of tamoxifen or whether treatment sequences of the two drugs provide additional benefit. Now, after 8.1 years median follow up, answers to these questions have been published (1) and further follow up is providing consolidation and additional clarity (2). This most recent report (3) indicates that there is a statistically significant disease free and overall survival benefit for letrozole over tamoxifen, but neither treatment sequence provides additional breast cancer related benefits over letrozole alone. The trial also provides data that supports treatment individualisation with tamoxifen alone or sequentially being satisfactory for some patients, again confirmed by the current analysis.

These conclusions are drawn despite the difficulties that have perturbed the trial conduct; particularly that trial randomisation was disrupted by the allowance of ethically guided selective crossover, thereby reducing the validity of results obtained by standard intention-to-treat (ITT) analysis. This issue has been addressed using a relatively new statistical technique which is discussed further below. Additionally, as tamoxifen is an effective adjuvant treatment for breast cancer, the extra benefit of an alternative agent targeting the same pathway can only be expected to be of relatively small size, as has been demonstrated by the lack of overall survival benefit seen in other aromatase inhibitor (AI) adjuvant trials (4,5) and also when all such trials are subjected to meta-analysis (6). The large size of the BIG 1-98 study and relatively long follow-up have contributed to its statistically significant outcome.

Adjusting for selective crossover

Selective crossover arises where the analysis of the primary outcome for the trial (or another similar trial) demonstrates a significant benefit for the new treatment, and in order to ensure the best interests of all trial participants, patients randomised to the inferior treatment arm are provided the opportunity to crossover to the superior treatment. What an individual patient decides to do will depend on many disease- and patient-related factors, thereby introducing significant bias. As a result, the value of randomisation is partly lost and the trial becomes partly observational.

The problems associated with selective crossover have been seen in a number of breast cancer studies and in other oncology and non-oncology trials (7). It is likely that future trials will also be similarly affected and it is therefore

important that analysis methods are refined, widely used and accepted so that the contribution of these trials is not reduced or lost. The issues arising from selective crossover are well explained by Finkelstein and Schoenfeld in their editorial (8) that accompanied the publication of the BIG 1-98 analysis adjusting for selective crossover (9).

In order to adjust for selective crossover, Colleoni *et al.* (9) have analysed the BIG 1-98 trial data using the inverse probability of censoring weighted (IPCW) modelling method. This is the first time that this method has been used in a breast cancer field. This methodology was introduced by Robins *et al.* (10) and has been widely used in analyses of HIV/AIDs and cardiovascular clinical trials (7). Standard ITT analysis in the setting of selective crossover will tend to underestimate the benefit of the new treatment as participants crossing over from the control arm (less effective treatment) to the experimental arm (more effective treatment) will do better than those remaining on the control arm but their improved outcome will be attributed to the control treatment - thus reducing the difference in outcomes between the two arms. Censoring is often used to account for selective crossover. However, this can also result in inaccurate interpretation, particularly where the crossover is non-random - with higher risk patients crossing over thus removing their outcomes from the control group, also resulting in a better outcome for this group, and a reduced difference between this and the experimental arm. In summary, the standard approaches to analysis of the BIG 1-98 will tend to underestimate the benefit of letrozole.

IPCW analysis has been designed to allow for selective crossover and attempts to provide the result that would have occurred if there had been no crossover. It does this by weighting the follow-up for the patients who do not cross over, so they account not only for themselves but also for the censored follow-up and events of matched patients who crossed over. A critical assumption of this methodology is that all important confounders of both crossover and outcome are used to estimate these weights. In the BIG 1-98 study, it is likely that the majority of these factors are known and that the estimates obtained from this analysis are a very good approximation of the trial result had there been no crossover. Further support for this contention comes from the 8.1 year follow up indicating that even using the ITT analysis, both OS and DFS benefits are statistically significant.

This is an important outcome for several reasons. These results begin to build confidence in the IPCW methodology in the breast cancer field and lend support for its use in other trials affected by selective crossover. Thus, valuable new treatment benefits can be accurately measured. It is also important that the ethical imperative to allow crossover in such situations need not mean that valid trial results will be lost.

Follow up of adjuvant endocrine trials

Long term follow-up of adjuvant aromatase inhibitor trials appears to be warranted for a number of reasons. The authors note in the publication of the 8.1 year analysis of BIG 1-98 (3) that the hazard ratios for DFS, OS, distant relapse free interval (DFRI) and breast cancer free interval (BCFI) have not changed from the analysis done two years previously, but the longer follow up has allowed narrowing of the confidence intervals, as more events have occurred. As more than half of the relapses in patients with estrogen receptor (ER) positive breast cancer occur after 5 years, follow up, during this time can be expected to have the potential to influence outcomes more than follow-up in the early years. In addition, the longer term influence of ceasing treatment at five years, which might manifest quite some years later, needs to be further assessed. Indeed, the 2011 EBCTCG update (11) suggests that the carryover effect of tamoxifen may not persist after 10 years of follow-up.

In contrast, longer follow-up of the ATAC trial (4) has not resulted in a statistically significant OS benefit. The reasons for this remain unknown, but potentially include differences in the populations treated, and differences in the efficacy and life threatening toxicity of the two AIs. The ATAC population (12,13) was on average three years older and had slightly lower risk disease, (with less chemotherapy use - 21% *vs.* 25%) although they underwent more mastectomies (48% *vs.* 25%) and as a consequence fewer received radiotherapy (62% *vs.* 72%). In terms of efficacy, any difference, remains to be determined by the outcome of the FACE trial (14). A recent meta-analysis of AI-related toxicity (15) has indicated an increased risk of cardiovascular disease and bone fractures, although at five years the increased risk of death without recurrence in AI treated patients seen in this analysis was not significant. There is also no data to indicate that patterns of toxicity are different between the different AIs; however, it is a further potential reason for the lack of OS benefit in the ATAC study and another reason why the longer follow up of these trials is important.

Translating BIG 1-98 results for the clinic

In the clinic, the crucial question is whether to treat an

individual patient with an AI or not and whether this should be up front or in sequence. The BIG 1-98 study has provided considerable guidance on this question in a previous analysis of the data: A composite risk score (16) was allocated to each individual patient (using standard pathological tumour characteristics including lymphovascular invasion, ER, PR, HER2 and KI67 and patient age) and outcomes analysed using the Subpopulation Treatment Effect Pattern Plot (STEPP) method. These results indicate that 5-year DFS was similar for all four treatments for patients at lowest risk and all three letrozole-containing schedules for patients at intermediate risk; however for those at high risk letrozole monotherapy was associated with the best 5-year DFS outcome. The 8.1 year analysis further reinforces these conclusions.

Longer follow up is needed to further inform the possibility raised by Amir and colleagues (15) that serious toxicities may contribute to a potential increase in risk of non-breast cancer death. Other commentators have raised the concern that the size of the benefits of AIs over tamoxifen does not warrant their additional expense. It is interesting to reflect, however, that the absolute survival benefit seen with tamoxifen *vs*. no endocrine treatment reported in the EBCTCG overview at 5 years (11) was only 3.3%, and this has increased to 9.2% at 15 years, which translates into hundreds of thousands of lives saved globally. The absolute OS benefit of 4% at 8 years demonstrated in the IPCW analysis of the BIG 1-98 could potentially also translate into many lives saved.

The concerns of toxicity and expense, remain important but it is hoped they will be well countered by maturing BIG 1-98 results which should provide further guidance as to which patients can safely be treated either with tamoxifen alone or with a sequence. The sequence of letrozole followed by tamoxifen appears to be emerging as a very suitable option for many patients with intermediate-risk early breast cancer.

Remaining questions

The most important questions in the clinic are regrettably still the ones we have been struggling with for quite a number of years: "which patients *must* be treated with an AI?" and "how long must anti-oestrogen treatment continue?" and the 8.1 year BIG 1-98 publication does not address these. However, in the further translational research that is ongoing with BIG 1-98 data and tumour material, it is hoped that fresh evidence will emerge as to why letrozole

is superior to tamoxifen and whether the benefit can be seen to be confined to a sub-group of patients that can be defined biologically. Further research is needed to answer the duration question, although the Study of Letrozole Extension (SOLE) trial which will complete recruitment this year will provide some useful data.

In conclusion, the publication of the 8.1-year follow-up of the BIG 1-98 trial adds to our confidence in presenting the benefit of adjuvant letrozole to patients; further confirms the adequacy of the option of sequential treatment with letrozole and tamoxifen or tamoxifen alone for some patients and at the same time provides some validation of the IPCW analysis methodology in an oncology setting. However, it does not contribute to the perennial adjuvant AI questions.

References

1. BIG 1-98 Collaborative Group, Mouridsen H, Giobbie-Hurder A, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N Engl J Med 2009;361:766-76.
2. Regan MM, Price KN, Giobbie-Hurder A, et al. Interpreting Breast International Group (BIG) 1-98:

a randomized, double-blind, phase III trial comparing letrozole and tamoxifen as adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive, early breast cancer. Breast Cancer Res 2011;13:209.

3. Regan MM, Neven P, Giobbie-Hurder A, et al. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8•1 years median follow-up. Lancet Oncol 2011;12:1101-8.

4. Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol 2010;11:1135-41.

5. Boccardo F, Rubagotti A, Guglielmini P, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial. Ann Oncol 2006;17:vii10-4.

6. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol 2010;28:509-18.

7. Rimawi M, Hilsenbeck SG. Making sense of clinical trial data: is inverse probability of censoring weighted analysis the answer to crossover bias? J Clin Oncol 2012;30:453-8.

8. Finkelstein DM, Schoenfeld DA. Correcting for discretionary treatment crossover in an analysis of survival in the Breast International Group BIG 1-98 trial by using the inverse probability of censoring weighted method. J Clin Oncol 2011;29:1093-5.

9. Colleoni M, Giobbie-Hurder A, Regan MM, et al. Analyses adjusting for selective crossover show improved overall survival with adjuvant letrozole compared with tamoxifen in the BIG 1-98 study. J Clin Oncol 2011;29:1117-24.

10. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-717.

11. Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet 2002;359:2131-9.

12. Breast International Group (BIG) 1-98 Collaborative Group, Thürlimann B, Keshaviah A, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005;353:2747-57.

13. Monnier A. FACE: the barefaced facts of AI potency. Cancer Manag Res 2010;2:267-76.

14. Amir E, Seruga B, Niraula S, et al. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. J Natl Cancer Inst 2011;103:1299-309.

15. Viale G, Regan MM, Dell'Orto P, et al. Which patients benefit most from adjuvant aromatase inhibitors? Results using a composite measure of prognostic risk in the BIG 1-98 randomized trial. Ann Oncol 2011;22:2201-7.

16. Vitry AI, Thai LP, Lu CY. Time and geographical variations in utilisation of endocrine therapy for breast cancer in Australia. Intern Med J 2010. [Epub ahead of print].

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