Combination hormonal therapy involving aromatase inhibitors in the management of women with breast cancer

J N Ingle, V J Suman, V C Jordan and M Dowsett

Mayo Clinic, Rochester, Minnesota 55905, USA
1Northwestern University, Chicago, Illinois 60611, USA
2Royal Marsden Hospital, London SW3 6JJ, UK

Abstract
Numerous comparative clinical trials have been conducted evaluating combination hormonal therapy involving the aromatase inhibitor aminoglutethimide, but there is no evidence for any superiority of this approach over single-agent therapy alone. The advent of new aromatase inhibitors with greater potency, selectivity, and better tolerability has prompted a reconsideration of the combined therapy approach, with attention being focused on pharmacologic and endocrinologic clinical research. The value of combining newer aromatase inhibitors with other hormonal agents remains to be established.

Introduction
Hormonal therapy remains an integral part of the management of most women with breast cancer both in the adjuvant and metastatic settings. A variety of hormonal agents are in clinical use today including antigestogens, progestins, androgens, estrogens, luteinizing hormone-releasing hormone analogs, and aromatase inhibitors. Despite the availability of multiple agents and multiple classes of agents, a sizeable proportion of tumors will not respond to treatment and those tumors that do respond will, in all likelihood, become resistant to treatment. The desirability of finding more efficacious hormonal therapy regimens is indisputable. The existence of multiple classes of agents with different mechanisms of action and excellent tolerability which can be given at full therapeutic doses in combination has formed the basis for the interest in studying combination hormonal therapy.

The mechanism of action of the aromatase inhibitors is well defined in terms of reduction of circulating estrogens. The existence of aromatase activity in a substantial proportion of breast carcinomas (Lipton et al. 1987) is an additional incentive for their study. Recent advances in aromatase inhibitor research has led to the introduction of new more potent, more specific, and more tolerable agents (Goss & Gwyn 1994). The aromatase inhibitors are particularly attractive for combining with hormonal agents from other classes. In the case of combining aromatase inhibitors with tamoxifen (TAM), it is possible that the different mechanisms of action would be complementary, with the aromatase inhibitor decreasing estrogen levels and thus allowing TAM to act more effectively as a competitive inhibitor with estradiol.

Numerous reports have been published evaluating aromatase inhibitors in combination with other hormonal agents but the most informative are those of a comparative nature. This report will review the experience of randomized trials evaluating combination hormonal therapy involving aromatase inhibitors and discuss preliminary studies utilizing letrozole plus TAM.

Randomized clinical trials evaluating combination hormonal therapy involving aromatase inhibitors

The randomized trials evaluating combination hormonal therapy involving aromatase inhibitors are given in Table I. The aromatase inhibitor utilized in all these studies was aminoglutethimide (AG) along with hydrocortisone. Five trials evaluated TAM alone or combined with AG (Corkery et al. 1982, Milsted et al. 1985, Ingle et al. 1986, Rose et al. 1986, Alonso-Muñoz et al. 1988). The trial with the largest sample size was that of Rose et al.
Ingle et al.: Combination hormonal therapy with aromatase inhibitors

Table 1 Randomized clinical trials of combination hormonal therapy involving aminoglutethimide

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No of evaluable patients</th>
<th>Objective response rate (%)</th>
<th>Median duration of response (months)</th>
<th>Time to treatment failure* or progression** (months)</th>
<th>Median survival (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAM vs TAM + AG</td>
<td>97</td>
<td>34</td>
<td>~24</td>
<td>10(^A)</td>
<td>NA</td>
<td>Rose et al. (1986)</td>
</tr>
<tr>
<td>TAM vs TAM + AG</td>
<td>49</td>
<td>43</td>
<td>15</td>
<td>7.2(^B)</td>
<td>21.9</td>
<td>Ingle et al. (1986)</td>
</tr>
<tr>
<td>TAM vs TAM + AG</td>
<td>34</td>
<td>53</td>
<td>NA</td>
<td>15(^B)</td>
<td>NA</td>
<td>Alonso-Munoz et al. (1988)</td>
</tr>
<tr>
<td>TAM vs AG</td>
<td>29</td>
<td>48</td>
<td>NA</td>
<td>13</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>TAM vs TAM + AG</td>
<td>31</td>
<td>38</td>
<td>NA</td>
<td>14</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>TAM vs TAM + AG</td>
<td>26</td>
<td>19</td>
<td>86</td>
<td>NA</td>
<td>NA</td>
<td>Milsted et al. (1985)</td>
</tr>
<tr>
<td>TAM vs TAM + AG</td>
<td>9</td>
<td>33</td>
<td>NA</td>
<td>6(^A)</td>
<td>NA</td>
<td>Corkery et al. (1982)</td>
</tr>
<tr>
<td>TAM vs TAM + AG</td>
<td>11</td>
<td>36</td>
<td>NA</td>
<td>6</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>TAM vs TAM/AG/Danazol</td>
<td>99</td>
<td>30.6</td>
<td>~22.5</td>
<td>NA</td>
<td>NA</td>
<td>Powles et al. (1984)</td>
</tr>
<tr>
<td>AG vs AG + TAM</td>
<td>25</td>
<td>20</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Hisamatsu et al. (1992)</td>
</tr>
<tr>
<td>MA vs AG</td>
<td>21</td>
<td>19</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Russell et al. (1997)</td>
</tr>
<tr>
<td>MA vs MA + AG</td>
<td>75</td>
<td>6*</td>
<td>NA</td>
<td>5(^A)</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>AG vs MPA + AG</td>
<td>80</td>
<td>24</td>
<td>NA</td>
<td>4</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>MA + AG vs AG</td>
<td>80</td>
<td>23</td>
<td>NA</td>
<td>7</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>AG vs MPA + AG</td>
<td>62</td>
<td>32</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Wander et al. (1987)</td>
</tr>
<tr>
<td>MPA vs AG</td>
<td>29</td>
<td>31</td>
<td>9</td>
<td>NA</td>
<td>NA</td>
<td>Samonis et al. (1994)</td>
</tr>
<tr>
<td>MPA vs MPA + AG</td>
<td>28</td>
<td>36</td>
<td>9</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>MPA + AG vs AG</td>
<td>28</td>
<td>43</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

NA, not available; TAM, tamoxifen; AG, aminogluthimide; MA, megestrol acetate; MPA, medroxyprogesterone acetate.

*Response determined in total of 122 patients.

(1986) which involved 179 patients evaluable for time analysis and 166 patients evaluable for response. There was no indication of a therapeutic advantage, and the toxicity was greater with the addition of AG. The other four randomized trials (Corkery et al. 1982, Ingle et al. 1986, Milsted et al. 1985, Alonso-Munoz et al. 1988) contained smaller sample sizes but had similar results.

After the completion of these studies of TAM plus AG, Lien et al. (1990) reported a study of pharmacokinetic interactions between these two agents. They studied six postmenopausal women treated for more than 6 months with TAM as a single agent. AG was then added, using 250 mg four times a day in five patients and three times a day in one patient, along with cortisone acetate (50 mg twice a day for 2 weeks and 25 mg twice a day thereafter). AG was found to be associated with a significant (P=0.032) decrease in the area under the curve (AUC) for TAM, with the mean reduction being 73% (range: 56-80%), which corresponded to a mean increase in TAM clearance of 222%. The impact of AG on five metabolites of TAM, including N-desmethyl-TAM and 4-hydroxy-TAM, was also examined, and the AUC for most metabolites was also reduced, with a mean reduction of about 50%. The authors concluded that their data were most consistent with induction of TAM metabolism by AG. This reduction of TAM and its metabolites provided a potential explanation for the failure of the studies noted above to show superiority for TAM plus AG over TAM alone.
In a variation on the TAM plus AG theme, Powles et al. (1984) compared TAM plus AG plus danazol (a synthetic progestin) with TAM alone. The combination regimen produced a higher response rate (43 vs 31%, $P=0.05$) but no advantage in terms of duration of response. The authors concluded that the trial did not show a therapeutic advantage for the combination. Of note with respect to the reported higher response rate for the three-agent combination is that it was subsequently demonstrated that AG and danazol have opposing effects on the concentration of the free biologically active fraction of estradiol (Dowsett et al. 1986). Thus, the use of danazol in combination with AG would be expected to be counterproductive.

Three studies have evaluated the addition of AG to a progestin. The largest study compared megestrol acetate (MA) with AG or the combination of MA plus AG (Russell et al. 1997). They studied a select group of women who were required to have estrogen receptor positive tumors and prior treatment with TAM in the advanced disease setting with achievement of a partial response or stability for at least six months. The objective response rates were 6% (MA), 24% (AG), and 23% (MA plus AG), with no significant difference being identified ($\chi^2$, 2 df, $P=0.01$). In addition, there was no difference in time to treatment failure or survival. The other two studies compared medroxy progesterone acetate (MPA) with AG or the combination of MPA plus AG (Wand et al. 1987; Samonis et al. 1994). There was no significant advantage identified for the combination in terms of response rate in either study. Potentially relevant to these findings are reports that AG will substantially reduce levels of both MA and MPA. When MPA was administered orally, AG was found to reduce mean plasma levels of MPA by 50% (Van Deijk et al. 1985) and mean serum levels by 60% (Lundgren et al. 1990). Likewise, AG was found to reduce serum MA levels by 79% (Lundgren et al. 1990).

**Evaluation of letrozole in combination with TAM**

The availability of a new generation of aromatase inhibitors which are orally active, potent, specific, and well-tolerated raises the issue of readdressing the value of combination hormonal therapy. The agents of most interest are letrozole (Dombernowsky et al. 1998) and anastrozole (Buzdar et al. 1996) as these have been approved by the US Food and Drug Administration (FDA). Because of prior experience with letrozole (Ingle et al. 1997), we studied this agent in combination with TAM.

Lessons were learned from studies by Lien et al. (1990), which showed the adverse impact of AG on levels of TAM and its major metabolites, and Dowsett et al. (1986), which demonstrated the antagonistic affect of AG and danazol on estradiol levels. Before considering a phase III trial, it was considered necessary to evaluate patients for any pharmacokinetic interactions between TAM and letrozole. In order to examine the effects of letrozole on TAM, we performed a pilot study in which patients received TAM (20 mg daily) for 6 weeks followed by the addition of letrozole (2.5 mg daily) (JN Ingle, VJ Suman, PA Johnson, JE Krook, JA Mailliard, RH Wheeler, CL Loprinzi, EA Perez, VC Jordan & M Dowsett, unpublished work). Dowsett et al. (1997a) concurrently performed the complementary study evaluating the effect of TAM on letrozole levels.

In the former study which evaluated the impact of letrozole on TAM pharmacokinetics, levels of TAM, N-desmethyl-TAM, and 4-hydroxy-TAM were measured at 6 week intervals up to 18 weeks after the addition of letrozole. Seventeen patients were assessed with respect to week 6 levels (before addition of letrozole) and week 24 levels (18 weeks after addition of letrozole). There was no indication of a systematic decrease in TAM, N-desmethyl TAM or 4-hydroxy TAM following the addition of letrozole. The variability in the percent change in TAM and that of the two metabolites was substantial but generally consistent and the median percent changes were close to zero for most of the determinations. There was no evidence for a substantial detrimental impact of letrozole on TAM or the two metabolites as had been observed with AG (Lien et al. 1990).

In addition, in our study estrogen suppression induced by letrozole was substantial despite concomitant administration of TAM. All patients experienced a substantial reduction in estradiol after the addition of letrozole for 6 weeks with a median decrease of 88.5% (range 73.7-95.2%).

In the complementary study by Dowsett et al. (1997a), patients received letrozole 2.5 mg daily for 6 weeks followed by the addition of TAM at a dose of 20 mg daily. Letrozole pharmacokinetics were based on plasma samples taken 1 day before the addition of TAM and after 6 weeks of receiving both agents. Letrozole AUC decreased by a mean±S.D of 30.6±17.9%, with the reduction being seen in 9 of the 10 patients. The range of the AUC reduction was from −5% to +59.4% and was greater than 30% in seven patients. The authors noted that the reduced plasma levels of letrozole corresponded to the reduced plasma levels of letrozole followed by the addition of TAM at a dose of 20 mg daily. Letrozole pharmacokinetics were based on plasma samples taken 1 day before the addition of TAM and after 6 weeks of receiving both agents. Letrozole AUC decreased by a mean±S.D of 30.6±17.9%, with the reduction being seen in 9 of the 10 patients. The range of the AUC reduction was from −5% to +59.4% and was greater than 30% in seven patients. The authors noted that the reduced plasma levels of letrozole corresponded to the reduced plasma levels of letrozole.

**Future considerations**

Recent preclinical data raise concerns regarding the concept of combining aromatase inhibitors with TAM. Brodie et al. (1998) have utilized MCF-7 cells which are stably transfected with the aromatase gene in...
ovariectomized nude mice to study the antitumor effect of TAM and two aromatase inhibitors, letrozole and anastrozole. The pertinent finding relative to the topic under discussion was that there was no additional benefit from adding TAM to aromatase inhibitors over the aromatase inhibitors alone. Whereas the combination of TAM plus letrozole was significantly more efficacious than TAM alone, it appeared that letrozole alone was superior to the combination of TAM plus letrozole.

The concept of combining aromatase inhibitor with antiestrogens such as TAM remains attractive but further preclinical and clinical research with these agents is necessary. The value of combining aromatase inhibitors with other hormonal agents remains to be established.

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References


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