Role of combination therapy with aromatase and cyclooxygenase-2 inhibitors in patients with metastatic breast cancer

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Aromatase inhibitors (AIs) are well established in the treatment of metastatic hormone-sensitive breast cancer in postmenopausal women. Cyclooxygenase (COX)-2 inhibitors have demonstrated efficacy in reducing cancer risk in animal and human studies. In several preclinical studies, combination Al plus COX-2 inhibitor therapy has shown a synergistic antitumor effect. This review describes the utility of AI plus COX-2 inhibitor therapy and discusses the completed and ongoing clinical trials investigating treatment with the AI exemestane and the COX-2 inhibitor celecoxib in the neo-adjuvant and metastatic breast cancer settings. In general, combination therapy had comparable or better efficacy compared with AI monotherapy using the end points of progression-free survival, overall response rate, clinical benefit rate, time to progression, and duration of clinical benefit. All therapies were well tolerated. There appeared to be a beneficial impact on serum lipid levels for patients receiving combination therapy in a neo-adjuvant trial despite the known cardiovascular toxicity risk associated with COX-2 inhibitors. In conclusion, AIs plus COX-2 inhibitors have shown promising efficacy and safety for the treatment of patients with metastatic breast cancer. Careful monitoring during future trials will be necessary to accurately assess the risk–benefit ratio of combination therapy.

Key words: adjuvant, advanced breast cancer, aromatase inhibitor, celecoxib, exemestane

introduction

Breast cancer is the leading cause of cancer death in women. As of 2002, breast cancer had an estimated worldwide prevalence of 18% and accounted for ~13% of all female cancer deaths [1]. Although early detection and treatment improve survival [2, 3], the long-term prognosis for breast cancer remains poor. Among patients with a favorable prognosis, risk for distant disease ranges from 10% to 20% [4–7]. In patients with axillary node involvement, the 5-year relapse rate can be 40%–50% [4, 8]. For patients with estrogen receptor-positive (ER+) disease, the annual breast cancer mortality rates during years 0–4 and 5–14 are equal [4]. Recurrent or metastatic disease remains incurable, with a median survival time of ≤2 years [9].

Third-generation aromatase inhibitors (AIs) are now widely recommended for adjuvant therapy in postmenopausal breast cancer patients with hormone-sensitive disease [10–13]. Moreover, they are considered the standard first-line treatment for patients with metastatic disease. Several case–control studies have demonstrated that cancer risk may be reduced in individuals who routinely take nonsteroidal antiinflammatory drugs (NSAIDs), such as aspirin or cyclooxygenase (COX) inhibitors [14–16]. Also, a meta-analysis of six cohort studies and eight case–control studies showed a slight reduction in relative risk (RR) for breast cancer incidence associated with NSAID use (RR 0.82; 95% CI 0.75–0.89) [17]. These findings have prompted considerable research into the potential utility of combining AIs with COX inhibitors when treating breast cancer. A particular focus has been placed on the potentially synergistic effects of combined treatment with AIs and COX-2 inhibitors.

In this review, the preclinical evidence that supports the use of combined AI and COX-2 inhibitor therapy in the treatment of breast cancer precedes a summary of the clinical evidence for the efficacy and safety of combined treatment with the AI exemestane and the COX-2 inhibitor celecoxib. PubMed was searched for clinical trial manuscripts using the search terms ‘aromatase inhibitor AND COX-2 AND breast cancer’, and all articles returned in the search were included in the clinical data summary of the article.

aromatase and COXs in breast cancer pathogenesis

Most of the circulating estrogen in postmenopausal women is derived from adrenal and ovarian androgens through the action of aromatase [18]. In malignant breast tissues, aromatase expression is primarily governed by the cyclic adenosine
monophosphate-dependent promoters I.3 and PII, whereas in normal tissue, aromatase expression is primarily governed by promoter I.4 [19, 20]. Aromatase expression and activity are both higher in tumors than in normal breast tissue [21, 22]. It is hypothesized that increases in local estrogen levels induced by elevated aromatase activity stimulate tumor growth and development [23].

COX, also known as prostaglandin endoperoxide synthase, is the rate-limiting enzyme in the conversion of arachidonic acid into prostaglandin H2. COX-1 is expressed ubiquitously, but expression of COX-2 is induced by the presence of mitogens, cytokines, hormones, and serum [24]. Overexpression of COX-2 has been detected in a number of solid tumors, including breast cancer [25–28], although there is a recent conflicting report of reduced COX-2 expression in a small sampling of human breast tumors [29]. Because COX-2 is inducible, levels measured from initial biopsies or tumor specimens may not accurately reflect expression at a later stage of the disease process. Prostaglandin E2, produced by COX-1 and COX-2 isoenzymes, stimulates estrogen biosynthesis by increasing expression of the cytochrome P450 (CYP) 19 (aromatase) gene in breast stromal cells [30]. There is a strong correlation between messenger RNA expression of COX-2 and CYP19 in vivo [31]. Elevated COX-2 expression in breast cancer tumors is associated with increased tumorigenic transformation [32, 33], higher grade tumors, and decreased overall and progression-free survival (PFS) time [28, 34]. Expression of COX-2 is also related to angiogenesis [35], increased proliferation (measured by Ki67 expression), high expression levels of p53 and human epidermal growth receptor 2 (HER2), and the presence of axillary node metastases [28, 36]. HER2, a known marker for aggressive disease and poor patient prognosis, stimulates COX-2 transcription via the Ras → Raf → mitogen-activated protein kinase pathway [37]. Furthermore, inhibition of COX-2 but not COX-1 increases apoptosis [38]. However, a neo-adjuvant study of celecoxib in early breast cancer did not corroborate an increase in apoptosis levels [39]. Taken together, these findings suggest that aromatase and COX have interrelated pathways and indicate that both enzymes figure prominently in breast cancer pathogenesis.

**rationale for combination therapy with AIs and COX-2 inhibitors**

Preclinical studies have demonstrated that the aromatase and COX-2 pathways are interconnected and that there is overlap between aromatase and COX-2 activities in breast tumors (Figure 1). *In vitro* studies in human and animal breast tumor models have shown a strong positive correlation between COX-2 and aromatase expression [40–42]. In cultured human breast cancer cells, COX-2 inhibitors decrease aromatase expression and activity [43]. These preclinical data provide support for the hypothesis that the aromatase-suppressive effects of COX-2 inhibitors may permit a more complete suppression of local estrogen biosynthesis, with concomitant clinical benefit, in patients with advanced breast cancer (or operable disease). Combination treatment with celecoxib and

**Figure 1.** Schematic illustration of the interconnected COX and aromatase pathways and the enzymes’ involvement in cancer pathogenesis. Ang, angiopoietin; Bax, Bcl-2-associated X protein; Bcl, B-cell chronic lymphocytic leukemia/lymphoma; COX, cyclooxygenase; CYP, cytochrome P450; ER, estrogen receptor; Flt-1, fms-related tyrosine kinase 1; HER2, human epidermal growth receptor 2; INK4a, inhibitor of cyclin-dependent kinase CDK4; VEGF, vascular endothelial growth factor.
the nonsteroidal AI exemestane was more effective in reducing the incidence and growth of tumors in an animal model of hormone-dependent breast cancer than either agent alone [44].

In addition to COX-2 being an activator of aromatase, COX-2 may advance breast cancer through several aromatase-independent mechanisms, such as decreased apoptosis and the activation of angiogenesis. COX-2 inhibitors have shown antitumor efficacy in cancer types not related to aromatase function, such as adenoma of the colon; this suggests that COX-2 inhibitors’ anticancer effects may be through multiple mechanisms.

clinical studies of combination therapy with an AI and a COX-2 inhibitor

Several clinical trials have investigated the efficacy of combination AI plus COX-2 inhibitor therapy in patients with breast cancer. The Celecoxib Anti-Aromatase NeoAdjuvant (CAAN) trial compared the treatment efficacy of exemestane (25 mg once daily [QD]) in combination with celecoxib (400 mg b.i.d.), exemestane alone (25 mg QD), and letrozole alone (2.5 mg QD) in the neo-adjuvant setting for postmenopausal hormone receptor-positive patients. Patients underwent surgery 57 days after the 3-month neo-adjuvant treatment period. In a preliminary report (n = 12) from the CAAN trial, treatment with exemestane plus celecoxib, exemestane alone, or letrozole alone for 3 months was equally effective in decreasing tumor area [45]. One patient treated with exemestane plus celecoxib had a complete clinical response as indexed by total tumor resolution. In a subsequent analysis from the CAAN trial, clinical response rates of 62%, 60%, and 55% were reported in postmenopausal women treated for 3 months (n = 31) with exemestane plus celecoxib, exemestane monotherapy, or letrozole monotherapy, respectively [46].

The efficacy of combined exemestane plus celecoxib was also examined in a feasibility study of combined exemestane (25 mg QD) plus celecoxib (400 mg b.i.d.) as first-line therapy for postmenopausal women with advanced breast cancer [47]. Treatment success, as measured by the percentage of patients who neither discontinued nor progressed at 6 months, was 60% at 6 months and 46% at 12 months. Overall PFS was 72% at 6 months and 53% at 12 months; overall survival was 87% at 6 months and 71% at 12 months.

Results from a randomized phase II trial of exemestane 25 mg QD plus celecoxib 400 mg b.i.d. compared with exemestane alone (25 mg QD) in patients with advanced breast cancer (n = 111) suggested a trend in favor of combination therapy [48]. The determination of response was based on the response evaluation criteria in solid tumors system [49]. More precisely, stable disease was defined as less than a 30% reduction and less than a 20% increase in the sum of longest diameters of all measured lesions and the appearance of no new lesions diameters. In assessable patients (n = 100), clinical benefit—the sum of complete responses, partial responses, and stable disease lasting ≥24 weeks—was comparable across treatment groups (exemestane plus celecoxib 47%; exemestane monotherapy 49%). Median time to disease progression (23.4 versus 20.0 week) and median survival time (73.9 versus 74.1 week) in the combination and monotherapy groups, respectively, were comparable. The lack of a clear added benefit with celecoxib in this study along with recent findings from a small COX-2 expression study have raised questions about whether COX-2 expression levels are indeed frequently elevated in breast tumors [29]. However, advantages with the combination in this study were evidenced by an approximately two-fold longer duration of clinical benefit (median duration, 96.6 week for combined therapy versus 49.1 week for exemestane alone, Table 1). The longer duration of clinical benefit in patients receiving the combination may be consistent with contributing cytostatic properties of celecoxib by either the inhibition of angiogenesis or other mechanisms targeted within the tumor cells.

Falandry et al. have reported on a phase III Groupe d’Investigateurs Nationaux pour l’Etude des Cancers Ovariens (GINECO) clinical trial comparing exemestane 25 mg QD plus either celecoxib 400 mg b.i.d. or placebo in postmenopausal patients with metastatic breast cancer [50]. This trial was

### Table 1. Efficacy end points that are improved by combined AI plus celecoxib therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>End point</th>
<th>Efficacy results</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Dirix et al.</td>
<td>Duration of clinical benefit</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exemestane 25 mg QD</td>
<td>49.1 week</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Exemestane 25 mg QD plus celecoxib 400 mg b.i.d.</td>
<td>96.6 week</td>
<td></td>
</tr>
<tr>
<td>Falandry et al. [50]</td>
<td>Overall response rate</td>
<td>35%</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>Exemestane 25 mg QD plus placebo</td>
<td></td>
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<tr>
<td></td>
<td>Exemestane 25 mg QD plus celecoxib 400 mg b.i.d.</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Falandry et al. [50]</td>
<td>PFS*</td>
<td>12.2 month</td>
<td>0.09</td>
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<tr>
<td></td>
<td>Exemestane 25 mg QD plus placebo</td>
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<tr>
<td></td>
<td>Exemestane 25 mg QD plus celecoxib 400 mg b.i.d.</td>
<td>9.8 month</td>
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<tr>
<td>Falandry et al. [50]</td>
<td>PFS#</td>
<td>4.7 month</td>
<td>0.019</td>
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<tr>
<td></td>
<td>Exemestane 25 mg QD plus placebo</td>
<td></td>
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<tr>
<td></td>
<td>Exemestane 25 mg QD plus celecoxib 400 mg b.i.d.</td>
<td>8.4 month</td>
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</table>

*As measured by study investigators; difference was not significant when assessed by an independent panel.

PFS for subgroup of patients treated for at least 3 months before study termination.

PFS for subgroup of patients progressing under tamoxifen or within 12 months after tamoxifen stopping.

QD, once daily; NR, not reported; PFS, progression-free survival.
terminated prematurely, however, after enrolling only 157 patients, following the announcement of increased cardiovascular risks associated with celecoxib in other trials, but the data collected from the exemestane plus celecoxib treatment group were promising. A significantly higher overall response rate was observed by investigators in patients who received exemestane plus celecoxib versus those who received exemestane alone (35% versus 20%, respectively; \( P = 0.034; \) Table 1). However, the overall response rates were not significantly different upon review by an independent panel (24% versus 17%; \( P = 0.18 \)). This discrepancy was due to a tendency by the investigators to ascribe partial responses to some patients who were assessed by the independent panel as having had stable disease. Rates of stable disease determined by independent review were similar between arms (35% for combined therapy versus 56% for exemestane alone) and were comparable to those assessed by the investigators. Median PFS was 9.8 months for both treatment groups. However, in a subgroup of 60 patients treated for at least 3 months before the termination of the study, PFS tended to be slightly longer with combination therapy (exemestane plus celecoxib, 12.2 month; exemestane monotherapy, 9.8 month). In another subgroup of patients progressing under tamoxifen or within 12 months after tamoxifen stopping there was a significant difference in PFS favoring patients receiving combination therapy versus those receiving exemestane monotherapy (8.4 versus 4.7 month, respectively; \( P = 0.019 \)). It should be noted that in the study of Dirix et al. [48], inclusion criteria required progression on tamoxifen therapy, which may explain the enhanced duration of clinical benefit observed within the exemestane plus celecoxib arm in that trial. Future trials with COX-2 and AI combinations may focus on postmenopausal women with advanced, hormone-positive breast cancer who have progressed on tamoxifen therapy.

The cardiovascular safety issues observed in some long-term non-breast cancer clinical trials have resulted in a relative scarcity of published clinical data on COX-2 inhibitor–AI combination therapy. However, because the data just discussed demonstrate that this combination can be effective, investigation of this therapy is justified in future trials. At present, there are several ongoing and planned clinical studies evaluating the efficacy and safety of exemestane plus celecoxib treatment in various stages of breast cancer. One phase II study (NCT00201773) is designed to evaluate the safety and efficacy of exemestane in combination with celecoxib as neo-adjuvant treatment in postmenopausal women with stages II, III, and IV breast cancer. This nonrandomized, open-label study began in 2003 and is actively recruiting patients (total enrollment is currently 34 patients). The NeoAdjuvant Trial of Preoperative Exemestane or Letrozole ± Celecoxib in the Treatment of ER-Positive Postmenopausal Early Breast Cancer trial (NEO-EXCELL) began recruiting patients in 2007 and has a proposed sample size of 1000 patients. The NEO-EXCELL trial is designed to determine whether exemestane is superior to letrozole as neo-adjuvant therapy in postmenopausal ER+ breast cancer patients and whether the efficacy of AIs in this setting maybe enhanced by the addition of celecoxib. The primary outcome measure for NEO-EXCELL is an objective clinical response to the neo-adjuvant treatment. Finally, the phase III Randomized European Celecoxib Trial, which evaluates the effects of 2 years of either celecoxib or placebo in combination with exemestane switch in metastatic breast cancer, is scheduled to resume enrollment in 2007.

**compatibility of COX-2 and AIs**

The greatest safety concern with the administration of COX-2 inhibitors has been the risks of serious arterial thrombotic events that have been reported with NSAIDs. So far >180 patients have received the full-dose combination of celecoxib 400 mg b.i.d. plus exemestane 25 mg QD in the clinical trials reviewed in this paper, resulting in a minimal appearance of cardiovascular events. In the study of Dirix et al. [48], one patient receiving celecoxib and exemestane had grade 3 congestive heart failure leading to discontinuation. In the GINECO trial, one patient with a history of cardiopathy who received exemestane plus celecoxib experienced paroxysmal supraventricular arrhythmia without any cardiac complication [50]. No cardiac events were observed in the feasibility study. Cardiovascular events with COX inhibitors are relatively infrequent and have been observed with varying incidence across COX-2 inhibitors and in different studies; therefore, a more complete understanding of the impact of AIs on risks associated with COX-2 inhibitors will likely require greater clinical experience with the combination.

The overall safety and tolerability of the AI plus COX-2 inhibitor combination in advanced breast cancer has so far been comparable to treatment with an AI alone. In the feasibility study by Canney et al. [47], adverse events (AEs) reported by >10% of treated patients included hot flushes/night sweats (25%), nausea (13%), and dyspepsia/heartburn (11%). Only two patients discontinued treatment because of AEs, one after 4 weeks because of esophagitis and one at 24 weeks because of diarrhea (Table 2). Similarly, in the study reported by Dirix et al. [48], both treatments were generally well tolerated; hot flashes were the most commonly reported AE (exemestane monotherapy, 9.4%; exemestane plus celecoxib, 11.3%). AEs leading to treatment discontinuation occurred in four patients in each treatment group. There were no significant reports of gastrointestinal AEs or hematologic or biochemical toxicity in any of the trials.

In the CAAN trial, patients treated with exemestane plus celecoxib had significantly lower total cholesterol and low-density lipoprotein levels after 3 months of treatment compared with those treated with exemestane alone or with letrozole [46]. Treatment with exemestane plus celecoxib was also associated with a significant decrease in overall cholesterol levels (\( P = 0.026 \)) 5 weeks after posttreatment surgery compared with presurgical levels. These preliminary findings seem to suggest that combination treatment involving celecoxib plus an AI has a beneficial effect on serum lipid levels compared with AI monotherapy.

COX inhibitors are also widely prescribed for analgesic effects in rheumatoid arthritis and osteoarthritis; therefore, the addition of a COX-2 inhibitor may actually improve some of the musculoskeletal AEs associated with AIs, such as arthralgia. In the GINECO trial, the most commonly reported AEs for patients...
Table 2. Adverse events leading to treatment discontinuation

<table>
<thead>
<tr>
<th>Study</th>
<th>Celecoxib + exemestane</th>
<th>Exemestane</th>
</tr>
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<tbody>
<tr>
<td>Canney et al.</td>
<td>Esophagitis (n = 1), diarrhea (n = 1)</td>
<td>N/A</td>
</tr>
<tr>
<td>Dirix et al.</td>
<td>Skin recurrence and chest pain (n = 1), acute respiratory failure associated with PD (n = 1), DVT associated with PD (n = 1), congestive heart failure (n = 1)</td>
<td>Pain and jaundice with skin recurrence (n = 1); ascites, jaundice, nausea, vomiting, and tremor (n = 1); skeletal pain, weakness, disorientation, and difficulty walking (n = 1); vomiting, weakness, nausea, and fatigue (n = 1)</td>
</tr>
<tr>
<td>Falandry et al.</td>
<td>Rash (n = 2), purpura (n = 1), dyspnea (n = 1), other (n = 1)</td>
<td>Digestive (n = 3), rash (n = 1), asthenia (n = 1), other (n = 1)</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis; N/A = not applicable; PD = progressive disease.

receiving exemestane plus celecoxib were pain (70% versus 77% for exemestane placebo, P = 0.33), arthralgia (32% versus 43%, P = 0.16), asthenia (43% versus 48%, P = 0.54), and insomnia (39% versus 49%, P = 0.2) [50]. Fewer patients receiving celecoxib experienced grade 2 or 3 pain, arthralgia, asthenia, and insomnia than patients receiving placebo. Recent reports from the Consortium on Breast Cancer Pharmacogenomics have shown that musculoskeletal toxicity associated with AIs may lead to a discontinuation rate of 13% [51].

summary and conclusions

Although AIs have significantly enhanced the efficacy of adjuvant endocrine therapy in postmenopausal patients, the prognosis for patients with recurrent or metastatic disease remains poor. Interactions between aromatase and COX pathways play a crucial role in tumorigenesis and the progression of breast cancer in postmenopausal women. This suggests that combination therapy with AIs and COX inhibitors could be beneficial in the treatment of breast cancer in postmenopausal women. The cardiovascular risks associated with long-term treatment with COX-2 inhibitors may limit their potential as cancer-preventive agents in healthy patients. A recent review noted that the use of COX-2 inhibitors produces 28%–66% reductions in advanced adenomas over 3 years of treatment in patients at high risk for colorectal cancer but increases the risk for serious cardiovascular events 1.3- to 3.4-fold [52]. To date, combination therapy with exemestane and celecoxib has also shown promising efficacy in advanced breast cancer. The poorer prognosis of these patients and their potentially greater likelihood of benefit may create a more ethical setting for the clinical development of this combination. Although additional trials will be needed to further clarify the risks of combination AI and COX-2 inhibitor therapy, the safety concerns associated with COX-2 inhibitors may be manageable in this population of patients with careful monitoring and patient selection. The recent safety fears associated with COX-2 inhibitors have limited the amount of clinical data available to assess the effectiveness of COX-2 inhibitor–AI combination therapy. However, this review aims to highlight the fact that the current data are promising and that further research in this area is warranted.

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references


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