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Current directions for COX-2 inhibition in breast cancer

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Abstract

Chemotherapy is effective against breast cancer. COX-2 has been implicated in the progression and angiogenesis of cancers. Celecoxib, a cyclooxygenase type 2 (COX-2) inhibitor, has both apoptotic and antiangiogenic activities, and may be of use in treatment of breast tumors which overexpress the COX-2 enzyme. Preliminary clinical trials have shown that the combination of chemotherapy with celecoxib has minimal additional toxicity and it may enhance the effects of the chemotherapy. Beside chemotherapy, celecoxib may promulgate the effect of aromatase inhibitor in breast cancer cells. Animal studies have shown that there are fewer and smaller tumors treated by combining exemestane and celecoxib. Larger clinical trials should be initiated to study the potential anti-cancer effects of celecoxib in breast cancer.

Keywords: Current directions; COX-2 inhibition; Breast cancer

1. Introduction

Breast cancer is the leading cause of death [1,2]. Breast cancer has become such a major health care issue that researchers and clinicians all over the world have shown great efforts in the past decades to find out a safe, cheap and effective treatment option [3–20]. The cyclooxygenase enzymes are important for the conversion of arachidonic acid to prostaglandins, and their metabolites play a pivotal role in multiple physiologic and pathophysiologic processes [16,21–23]. The inducible isoform, COX-2, is commonly over-expressed in breast cancer [16,24,25]. Recent work suggests that COX-2-derived metabolites may contribute at multiple points throughout tumorigenesis, including premalignant hyperproliferation, transformation, maintenance of tumor viability, growth, invasion, metastatic spread [16,21–25]. COX-2 has been implicated in the inhibition of apoptosis and prolongs survival of malignant cells by inducing anti-apoptotic protein bcl-2 and reducing proapoptotic proteins bax [26,27]. It may also promote tumor-specific angiogenesis, inhibit apoptosis and induce proangiogenic factors such as vascular endothelial growth factor (VEGF), inducible nitrogen oxide synthetase promoter (iNOS), IL-6, IL-8 and TIE-2 [28–33]. Results from epidemiological studies suggest that use of nonsteroidal anti-inflammatory drugs, such as aspirin and indomethacin that inhibit COX-2 activity, reduces the incidence of breast cancer as well as colon cancer in humans [34–41]. Celecoxib is a selective COX-2 inhibitor. It has chemopreventive and chemotherapeutic properties in rodent models of breast cancer [36,37]. In patients with familial adenomatous polyposis, 6 months of twice-daily treatment with 400 mg of celecoxib leads to significant reduction in the number of colorectal polyps [42,43].

2. Preclinical studies of anti-cancer effects of COX2 inhibition in breast cancer

COX-2 protein was detected in breast carcinomas from mouse mammary tumor virus (MMTV)/neu mice. Treatment with celecoxib significantly reduces the incidence of mammary tumors in MMTV/neu mice with increased tumor cell apoptosis and decreased proliferation in vivo [34–41,44–46]. In vivo apoptosis correlated with significant decrease in activation of protein kinase B/Akt, a cell survival signaling kinase, with increased expression of the proapoptotic protein bax and decreased expression of the antiapoptotic protein bcl-2 [44–46].

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Prostaglandin E2 (PGE2) is expressed during mammary gland development and mammary glands from MMTV/neu mice express all four receptor subtypes [34–41,47–49,50–53]. These receptors were also up-regulated in tumor tissue [47–49]. PGE2 maybe involved in promoting invasion by activating metalloproteinase and CD44, resulting in destruction of extracellular matrix for invasion and metastasis [21–25,54,55]. Celecoxib causes reduction in mammary PGE2 levels and hence, signaling through PGE2 receptors may be an important pathway for mammary tumorigenesis and spread [50–53]. PGE2 also stimulates the expression angiogenic regulatory genes in mammary tumor cells isolated from COX-2 transgenic mice suggesting that COX-2-derived PGE2 maybe a potent inducer of angiogenic switch during mammary cancer progression [47–49]. Extensive studies conducted over the past few years have found that the overexpression of COX-2 and VEGF in cancer might be the leading factor of angiogenesis via induction of multiple proangiogenic regulators [21–25,44]. COX-2 regulates the activities of several important proangiogenic factors such as VEGF and fibroblast growth factor and it has been shown that celecoxib reduces microvessel density [21–25]. Therefore, therapy combining angiogenesis inhibitors targeting COX-2, VEGF, and bFGF pathway should be considered [21–25,44].

Cyclooxygenase-2 (COX-2) inhibitors are rapidly emerging as a new generation of therapeutic drug in combination with chemotherapy or radiation therapy for the treatment of cancer [34–41,45,56–59]. The mechanisms underlying its antitumor effects are not fully understood and more thorough preclinical trials are needed to determine if COX-2 inhibition represents a useful approach for prevention and/or treatment of breast cancer [45,56–59].

3. COX-2 inhibition and chemotherapy

Enhancement of the therapeutic effect of conventional drugs is currently an active treatment strategy for breast cancer, as shown in the clinical application of trastuzumab with chemotherapeutic agents, which prolonged survival even for metastatic disease [27–29]. A proof-of-concept study was conducted to determine if the addition of celecoxib is useful in improving the response rate of breast cancers to neoadjuvant cytotoxic treatment [60]. This is followed by a phase II study to determine the tolerability and cardiac safety of the use of celecoxib in such setting. These studies have shown that the addition of celecoxib to chemotherapy improves the response rate by close to 20%. The pathologic complete response rate was raised substantially. The levels of COX-2 gene expression were also determined in tumors of patients treated with celecoxib. It was found that among tumors that showed clinical response to the addition of celecoxib, a significantly higher level of COX-2 gene expression was observed versus non-responders. This finding was not seen in patients treated with chemotherapy alone. Moreover, the regimen was well tolerated. There were no clinically signs and symptoms of cardiac failure.

4. COX-2 inhibition and endocrine therapy

There is a linear relationship between aromatase activity and COX-1 and COX-2 expression within the human breast tissue [61–72]. This significant relationship between the aromatase and cyclooxygenase enzyme systems suggests that autocrine and paracrine mechanisms may be involved in hormone-dependent breast cancer development via growth stimulation from local estrogen biosynthesis [61–72]. Indeed, recent research on the signaling pathway in the regulation of aromatase and COX-2 expression showed that both the breast epithelial cells and the stromal cell compartment play important roles in the progression of tumor growth [61–72]. The interconnecting pathway may involve epidermal growth factor (EGF), transforming growth factor-β (TGF-β) and tetradecanoyl phorbol acetate (TPA) [61–72]. Overexpression of COX-2 contributes to increased expression of aromatase in the breast tumor [27–29,56–59]. COX-2 also promotes rich micro-vessels within the tumor through up-regulation of PGE2, VEGF and bFGF in cancer cells [29–31]. Since both rich vasculature and accelerated estrogen synthesis are thought to contribute to unfavorable conditions for the response to endocrine therapy, inhibiting COX-2 is a promising strategy to potentiate endocrine therapy [29–31].

The therapeutic potential of combining celecoxib and exemestane was tested in the DMBA rat model [73–76]. An objective response (OR) rate of 48% was achieved when the rats were treated with both exemestane and celecoxib. This contrasted with OR rates of only 5% when treated with exemestane alone and 0% when treated with celecoxib alone. The development of new tumors follows a similar pattern. The study demonstrated that the addition of celecoxib could enhance the inactivation of aromatase activity [73–76].

Celecoxib anti-aromatase neoadjuvant (CAAN) trial was conducted in postmenopausal hormonal sensitive breast cancer patients to investigate the efficacy of neoadjuvant therapy combining aromatase inhibitors with COX-2 inhibitor [56]. Recent studies using aromatase inhibitors as neoadjuvant therapy in postmenopausal women have demonstrated that these agents are effective [57–59]. Aromatase inhibitors have a better clinical and pathologic response than tamoxifen. Basing on these results, the CAAN trial is designed to study the neoadjuvant use of exemestane with and without celecoxib [56–59]. Exemestane is chosen because it is a type I agent and it has marked reduction of aromatization in malignant and non-malignant tissues [56–59]. A control arm using letrozole is added as control. The objectives of the study are to confirm the superior laboratory results from treatment combining exemestane with celecoxib, to determine whether the addition of celecoxib would cause different changes in angiogenesis and apoptosis markers and to evaluate the safety and side effects profiles of the three treatment arms. The preliminary report shows that all of the three anti-aromatase therapies are effective.

5. Summary

COX-2 is commonly expressed in breast cancer and may be an important factor of carcinogenesis, tumor angiogenesis and metastasis. COX-2 inhibitors may be a new direction of anti-cancer therapy for breast cancer, especially when combined with cytotoxic drugs or aromatase inhibitors.

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