

LEADING ARTICLE

COX-2 INHIBITORS AND BREAST CANCER

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These simple drugs may represent a radical advance in breast cancer treatment, but potential therapeutic pitfalls need to be considered carefully.

The *cyclooxygenase (COX)-2* inhibitor celecoxib was recently approved in the USA for the prevention of polyp formation in familial adenomatous polyposis, a defined premalignant condition for colorectal cancer. The potential value of *COX* inhibitors in similar roles for other malignancies, particularly breast cancer, is therefore currently under intense scrutiny. Use of these medications in chemoprevention or treatment would represent a radical departure from established regimens because these drugs are readily accessible, inexpensive, and generally well-tolerated.

Epidemiological investigations of long-term non-steroidal anti-inflammatory drug (NSAID) use have given encouraging indications of a small, but significant protective effect against breast cancer. A recent meta-analysis of 14 studies found a risk reduction of around 18%.¹ A subsequent large case-control study has confirmed this approximate level of protection, and also found that risk reduction occurred with NSAID use for any duration, with strongest effect for use lasting >8 years.²

The *COX* enzyme system mediates the conversion of arachidonic acid into prostaglandins. There are two isoenzymes, *COX-1* and *COX-2*. The latter is generally termed 'the inducible isoenzyme', and is overexpressed in various pathological states including cancer.³ It is well-established that elevated levels of prostaglandins are associated with carcinogenesis;⁴ these molecules are thought to mediate tumorigenicity by various mechanisms.^{5,6}

There is now considerable evidence implicating dysregulation of *COX-2* expression as an aetiological factor in mammary carcinogenesis. Immunochemical analysis of human breast cancers reveals that a significant proportion express *COX-2*.^{7,8} Recent investigations have confirmed an association between the degree of *COX-2* expression and poor prognostic features of tumours⁷ and have determined that elevated *COX-2* expression occurs also in ductal carcinoma *in situ*.⁹ This suggests that abnormal *COX-2* expression has an early pathogenetic role in mammary carcinogenesis, and may have positive implications for *COX-2* inhibition. We have recently shown that elevated levels of *COX-2* mRNA are also present in the tissue adjacent to cancerous lesions in humans,¹⁰ indicating that tumour cells may have a paracrine *COX-2*-inducing influence on surrounding non-cancerous tissue. This may be a possible means by which a breast cancer may spread locally.

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Accepted for publication 14 April 2003.

COX inhibition in breast cancer could have two main roles: (i) primary prevention (to prevent onset of the disease in patients at high risk); and (ii) secondary prevention (treatment of established breast cancer with *COX-2* inhibitors to reduce aggressiveness and induce remission). Animal studies have demonstrated that chemoprevention strategies are both feasible and effective; prophylaxis with *COX-1/2* or selective *COX-2* inhibitors reduces tumour incidence and multiplicity,^{11,12} and treatment of established breast cancer with *COX-2* inhibitors leads to a reduction in tumour volume.¹³

These positive results will surely pave the way for clinical trials of *COX* inhibitors in breast cancer. There are, however, a number of potential therapeutic pitfalls that need to be considered.

First, is it necessary to create a distinction between selective versus non-selective *COX* inhibition? Not all tumours express *COX-2*, and some have been shown to produce elevated levels of *COX-1* only.⁸ Cell line experiments have shown that transfection with *COX-1* or *COX-2* leads to increasingly invasive behaviour of cells,¹⁴ while both *COX-1* and *COX-2* null cells can continue to overproduce prostaglandin E₂, due to increased transcription of the remaining functional gene.¹⁵

Also, would *COX* inhibition be useful in patients with tumours that are *COX*-negative? This particular strategy needs investigating to determine whether it would prevent breast tumours developing a more aggressive facet of malignancy. Recent studies have suggested that *COX-2*-expressing lesions may belong to a specific subset of tumours that overexpress *HER-2/neu*,¹⁶ indicating that specific genetic pathways to malignancy might exist for subgroups of breast cancers.

Moreover, *COX* has an inherent, physically and functionally distinct *peroxidase (POX)* activity.¹⁷ This activity can also lead to the production of carcinogens, and is not necessarily blocked by NSAIDs.¹⁸ The contribution of this particular function of the enzyme to mammary carcinogenesis needs to be clarified.

Primary prevention envisages long-term *COX* inhibition in relatively young women at high risk of breast cancer. Hence, the long-term consequences of sustained *COX* suppression in this population need to be addressed. Studies in mice with *COX-2* gene deletions suggest that *COX* isoenzymes play essential roles in organ development. *COX-2* deficiency retards blastocyst implantation¹⁹ and leads to failure of closure of the ductus arteriosus after birth.²⁰ *COX-2*-deficient mice develop severe renal disease, with a distinct pathology from NSAID-induced renal toxicity.²¹ Also, *COX-2* null mice are infertile and, although *COX-2*-deficient mice undergo follicular development, they demonstrate reduced ovulatory function.^{19,22} The degree of applicability of these results to humans is unclear and certainly merits further investigation.

Regarding other side-effects of NSAIDs, the results of the Celecoxib Long-Term Arthritis Safety Study (CLASS) favoured use of selective *COX-2* inhibitors over non-selective drugs, on the basis that fewer ulcer complications were noted in the celecoxib

group compared to reference NSAID users.²³ Of concern, recent reanalysis of these data has suggested that COX-2 inhibitors may not, as previously held, have a superior toxicity profile, especially with regards to peptic ulceration.²⁴ There is also concern regarding possible adverse cardiovascular effects of COX-2 inhibitors from the Vioxx Gastrointestinal Outcomes Research (VIGOR) study.²⁵ An excess of cardiovascular events occurred in the rofecoxib-treated group. The low number of total events precluded thorough statistical review, and it is possible that the comparator drug, naproxen, exerted a cardioprotective effect, hence influencing the final analysis.

COX suppression could represent a radical step away from current conventional treatment and prevention modalities; but we clearly need to await the outcome of clinical trials involving these drugs to allow a more balanced and complete appraisal of their suitability in the physician's armamentarium of anti-cancer treatments.

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