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 polypt 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 carcino genesis;4 these molecules are thought to mediate tumorigenicty 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 cancer 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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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, it is 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.9 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.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. 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. There is also concern regarding possible adverse cardiovascular effects of COX-2 inhibitors from the Vioxx Gastrointestinal Outcomes Research (VIGOR) study. 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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