the UK and Australia and is being considered for approval in Canada.

QUARTZ is a Medical Research Council Phase III, randomised controlled trial designed to assess whether optimal supportive care alone is as effective as WBRT in combination with optimal supportive care in the treatment of patients with inoperable brain metastases from NSCLC. This is a pragmatic study in which the primary eligibility requirement is that the clinician and patient should be uncertain of the role of WBRT in their particular case. This should allow the majority of patients with inoperable brain metastases from NSCLC to be considered for inclusion in this trial and thus allow QUARTZ to produce robust evidence for or against the inclusion of WBRT in standard management. Patients with histologically or cytologically proven NSCLC and inoperable brain metastases are randomised between optimal supportive care with WBRT (standard treatment arm) and optimal supportive care alone (experimental arm). Patients who have previously received systemic treatment for their lung cancer are eligible. In the context of the QUARTZ trial, optimal supportive care is defined as the use of dexamethasone, titrated down to the lowest dose required to control symptoms, and: specialist nursing support; open access to follow-up in a specialist clinic; and access to a specialist palliative care multidisciplinary team. The primary end point of the QUARTZ trial is patient assessed quality adjusted time (QALY). Secondary end points are overall survival, Karnofsky Performance Status and neurological symptoms.

SUMMARY

Brain metastases from NSCLC are, sadly, all too common. They have a devastating effect on quality of life and functional ability and median survival of patients with unresectable disease is between 2 and 3 months. It is not clear whether whole brain radiotherapy adds anything to the quality or length of survival of such patients and a randomised clinical trial has just begun which is designed to address this issue. It is essential that the QUARTZ trial recruits as many eligible patients as possible if the results are to be meaningful. Patients with inoperable brain metastases from NSCLC should be discussed at a lung cancer multidisciplinary meeting. This provides an opportunity to debate the likely benefit of WBRT in each individual case and if there is uncertainty then entry into QUARTZ should be considered.

Competing interests: None.
Rachael Barton is a member of the QUARTZ Trial Management Group

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Aspirin sensitivity and eicosanoids

Sophie Farooque, Tak H Lee

Aspirin sensitive respiratory disease (ASRD) was first described in 1922 by the French physician Widal.[1] It is characterised by asthma, chronic rhinosinusitis and nasal polyps on a background of aspirin sensitivity. The condition is a distinct, often aggressive, clinical syndrome, and it is rare in childhood with a peak age of onset in the early 30s.[2] Rhinorrhoea and nasal congestion are typically the first symptoms with asthma usually manifesting 1–5 years after the onset of rhinitis.[3] Once the disease is established, ingestion of aspirin induces the release of critical mediators that provoke an acute exacerbation of rhinosinusitis and asthma. It is estimated that 5–10% of all patients with asthma are aspirin sensitive.[4] Often poorly responsive to treatment, patients with aspirin sensitivity are over-represented in the severe asthma group and 50% are steroid dependent.[5]

The aetiology of ASRD is complex, but most investigators are agreed that the reaction to aspirin is not mediated by allergic mechanisms. Most evidence points towards an abnormality of arachidonic acid (AA) metabolism. AA is a substrate for both the production of leucotrienes (via the 5-lipoxygenase (5-LO) pathway) and prostanoids (via the cyclooxygenase (COX) pathway).

ASRD is characterised by excessive cysteinyl leucotriene (CysLT) production both in the steady state and for several hours after aspirin challenge.[6] Urinary leucotriene E4 (LTE_4) levels, as a measure of total body production of CysLTs, are a mean sixfold higher in patients with ASRD, increasing fourfold higher still after aspirin challenge.[7] To date, the question of whether ASRD is associated with a fundamental predetermined abnormality in the production of CysLT[8] or whether it is an expression of particularly severe disease remains unresolved.[9 10] Furthermore, while the mucosal cellular infiltrate resembles that of asthma and rhinitis generally, there is even greater

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increased expression of asthma-relevant cytokines such as interleukin (IL)-5 and granulocyte-macrophage colony stimulating factor.[11] On bronchial biopsy, increased numbers of eosinophils and mast cells are noted in the mucosa of aspirin-sensitive patients.[10]

Eighty-five years after being first described, ASRD remains both a clinical and scientific conundrum, and the traditional concept outlining the "diversion" of AA metabolism away from prostanoid synthesis towards leucotriene synthesis by COX-1 inhibitors such as aspirin has become increasingly refined. For instance, COX-1 inhibition resulting in reduced prostaglandin E_2 (PGE_2) production has been postulated as one mechanism for aspirin-induced exacerbations of asthma and rhinitis.

In support of this hypothesis is the finding that PGE_2 has been shown to inhibit CysLT biosynthesis by inhibiting 5-LO translocation to the nucleus.[12] Furthermore, administration of aerosolised PGE_2 prevents aspirin-induced bronchoconstriction and urinary LTE_4 excretion,[13] so PGE_2 "braking" in ASRD may be critically deficient. This could be due to abnormal PGE_2 receptor expression and/or deficient PGE_2 production.

There are four G-protein coupled PGE_2 receptors designated EP1–4.[14] Global mucosal expression of EP1 and EP2 (but not EP3 and EP4) are increased in nasal biopsies from both aspirin-sensitive and non-aspirin-sensitive patients compared with normal controls.[15] This is interesting because PGE_2 protects epithelial cells from injury and promotes wound healing and repair in the gastrointestinal and respiratory tracts,[16 17] consistent with a general response to inflammation. Despite a global increase in the expression of the EP2 receptor in the nasal epithelium in rhinosinusitis, a reduction in the expression of this receptor was observed in a wide range of mucosal inflammatory leucocytes including eosinophils, neutrophils, mast cells and T cells in aspirin-sensitive patients.[15] A functional single nucleotide polymorphism of the EP2 gene associated with a decrease in the transcription level of the receptor is apparently associated with an increased risk of aspirin-sensitive asthma and rhinosinusitis.[18]

PGE_2 therefore has the potential to reverse at least three of the cardinal features of ASRD: enhanced cysLT production, smooth muscle hyperplasia (smooth muscle cells from patients with asthma overexpress PGE_2 receptors) and airways epithelial damage. The question of whether aspirin-sensitive patients at baseline and after exposure to aspirin are deficient in PGE_2 production still remains equivocal.

Previous in vivo studies have directly quantified PGE_2 production in aspirin-sensitive and aspirin-tolerant patients by measuring PGE_2 release in nasal lavage fluid. One study found no significant decrease in local PGE_2 production in aspirin-sensitive and aspirin-tolerant patients after oral aspirin challenge,[19] but a second study reported inhibition in local PGE_2 production in both aspirin-sensitive and aspirin-tolerant groups following the administration of nasal aspirin.[20] In vitro studies addressing PGE_2 production in aspirin-sensitive patients have involved prolonged culture of structural cells (nasal polyp epithelial cells and bronchial fibroblasts) in vitro[21 22] or stimulation of peripheral blood cells,[23 24] which are remote from the site of the disease, and these studies have also yielded conflicting results. Some in vitro studies with peripheral blood leucocytes from aspirin-sensitive and aspirin-tolerant patients have shown no difference in PGE_2 release both at baseline and following incubation with aspirin,[23] while others have demonstrated diminished PGE_2 release from peripheral blood cells and nasal polyps taken from aspirin-sensitive subjects.[24]

In this issue of *Thorax* Mastalerz *et al*[25] have analysed PGE_2 production in aspirin-sensitive and aspirin-tolerant patients from a novel perspective and with unexpected results (***see page 27***). Specifically, two urinary metabolites of PGE_2 (PGE_2-M and urinary tetranor-PGE-M) were measured both before and after oral challenge with aspirin and celecoxib (a COX-2 inhibitor) as a reflection of systemic PGE_2 production. They found that, at baseline, there was no significant difference in measurable PGE_2 metabolites between aspirin-tolerant and aspirin-sensitive patients. Second, following aspirin challenge a decrease in levels of PGE_2-M and urinary tetranor-PGE-M was found only in aspirin-tolerant patients but not in patients with ASRD. Third, in contrast to the results following aspirin challenge, oral challenge with the celecoxib led to a decrease in measurable urinary PGE_2 metabolites in both groups. Finally, there was no correlation between the urinary levels of PGE_2-M and tetranor-PGE-M and urinary LTE_4.

Mastalerz *et al*[25] suggest that the striking difference in the response to aspirin between the two cohorts is due to aspirin simultaneously inhibiting COX-1 while also directly activating mast cells in the target organs of aspirin-sensitive patients. The authors do not specify a mechanism by which aspirin differentially activates mast cells and increases PGE_2 production only in the ASRD group. They propose that the increase in PGE_2 production is further augmented by cytokines and mediators released by degranulating mast cells which induce a secondary upregulation in PGE_2 biosynthesis in inflammatory cells.

A number of studies have demonstrated using oral challenges that patients with ASRD are normally able to tolerate COX-2 inhibitors,[26 27] and it has been suggested that this is because COX-2 activity is very low in this phenotype.[28] Studies examining the expression of COX-2 in patients with ASRD have, however, yielded conflicting results. In two studies using surgically resected nasal polyps/nasal mucosa, COX-2 expression and activity has been shown to be diminished in aspirin-sensitive patients.[29 30] In contrast, when the expression of COX-2 was examined in the bronchial mucosa of aspirin-sensitive and aspirin-tolerant patients with asthma, enhanced COX-2 expression was observed in aspirin-sensitive subjects. A mean fourfold increase in the percentage of COX-2 expressing cells that were mast cells and a 2.5-fold increase in the number of eosinophils expressing COX-2 was noted.[31]

Although it is not possible to discern whether the findings of Masterlerz *et al* can be directly extrapolated locally to the nasal and bronchial mucosa, and EP2 receptor expression was not quantitated, their findings challenge the notion that the reason why patients with ASRD tolerate selective COX-2 inhibitors is because expression of COX-2 is significantly diminished in the nasal and bronchial mucosa and therefore these drugs induce only a trivial diminution in PGE_2 levels. The novel observations will encourage new avenues of research into the regulatory role of PGE_2 in ASRD and why aspirin-sensitive subjects react to COX-1 but not to COX-2 inhibitors.

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New tests for tuberculosis: local immune responses have greater specificity

Graham H Bothamley

We all want a good test for tuberculosis. Sputum smears are negative in half of those with lung involvement.[1] How can we detect tuberculosis if there are $<10^5$ bacilli per ml of sputum? We could use either a more sensitive test for something the tubercle bacillus produces or use the host's response to amplify the signal. Mycobacterial culture, DNA-based amplification,[2] breath tests for volatile organic chemicals[3] and lipid profiles[4 5] exhibit the first approach. Chest radiographs, non-specific inflammatory markers and tests based on the specific immune response (such as tuberculin testing) exploit the second option.

Local immune responses have previously been shown to have greater potential for diagnostic assays than systemic responses from peripheral blood.[6 7] Studies using cells isolated from human granulomas have demonstrated the importance of early secretory antigen target-6 (ESAT-6) in the CD4+ T cell response,[8] as have bronchoalveolar lavage (BAL) cells with ESAT-6, culture filtrate protein-10 (CFP-10) and a number of other proteins.[9] New tests for tuberculosis have exploited the ESAT-6 and CFP-10 antigens found in region of difference 1 (RD1), which is deleted in BCG but found in all pathogenic strains of the *Mycobacterium tuberculosis* complex.

Two papers which have studied BAL in patients with suspected but smear-negative pulmonary tuberculosis have therefore excited much interest. The earlier paper examined BAL cells from 37 patients with suspected tuberculosis.[10] Eight culture-positive and four culture-negative patients who responded to anti-tuberculosis treatment all gave positive responses (>5 cells stained per 200 000 cells) when incubated with the peptides from ESAT-6 and CFP-10. Although false-positive responses were found in peripheral blood from those with previous tuberculosis, pneumonia or lung cancer in concurrent tests, there were no false-positive results from BAL fluid. Even if the higher cut-off value suggested by other workers were used,[11] the sensitivity of the

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