Budesonide versus Placebo in a High-risk Population with Screen-detected Lung Nodules

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Abstract

Screening computed tomography (CT) enables the detection of small peripheral lung nodules. The nature of these nodules is uncertain, but it seems reasonable that some of them, in particular non-solid nodules, could represent pre-cancerous lesions. A previous trial showed a reduction in the size of peripheral nodules by inhaled budesonide in subjects with bronchial dysplasia. We tested inhaled budesonide 800µg or placebo twice daily in a randomised, double-blind, placebo-controlled phase IIb trial, which enrolled 202 current and former smokers with stable CT-detected lung nodules. The primary end-point was the one-year change in target nodule size in a per-subject analysis. Treatment was well tolerated and >80% of participants received at least 50% of total drug dose. Initial observations seem to show a promising effect on non-solid target nodules in individuals at high risk of lung cancer. As non-solid nodules may represent precursors of adenocarcinoma, further investigations in this population are warranted.

Keywords

Budesonide, chemoprevention, lung cancer

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Lung cancer is the most common cause of cancer-related death in both men and women,[1] and smoking is the largest avoidable cause of death worldwide.[2] Smoking has consistently been recognised as the main aetiological factor for lung cancer, accounting for ~85–90% of cases, and the increased risk of developing lung cancer persists many years after stopping smoking.[3] Thanks to smoking cessation programmes, the rate of decrease in the prevalence of adult smoking in the US increased significantly in recent years, but from 2004 to 2007 this rate remained at about 20%.[4] This plateau of decline in smoking has been explained by a possible levelling-out in smoking cessation success,[5] suggesting that the remaining population of smokers can be considered unable or unwilling to quit.[6] Both current and former smokers are the target population who may benefit from a chemopreventative strategy because of its potential to arrest or revert the cancerogenesis progression. Unfortunately, researchers have yet to succeed in developing an effective chemopreventative strategy against lung cancerogenesis. Moreover, the majority of trials conducted so far were focused on the potential effect on bronchial dysplasia and not on the peripheral lung, where most lung cancers actually arise.[7]

Computed Tomography and Screening

The screening computed tomography (CT) is a non-invasive test with low radiation exposure and no contrast medium. It provides the opportunity to study the peripheral lung area despite the limitations of characterising the nature of small lesions that cannot undergo biopsy. So far, many observational studies have demonstrated that low-dose CT is a sensitive tool for the identification of early lung cancer,[8–13] and a 10-year survival rate of 88% was estimated for stage I screen-detected cases.[14]

The Corticosteroid Budesonide and Lung Cancer Chemoprevention

Inflammation is a common reaction in local tumour environments.[15] On the one hand, inflammatory diseases increase the risk of developing many types of cancers; on the other, oncogenic alterations can induce an inflammatory microenvironment that has many tumour-promoting effects.[16] Inflammatory networks may in fact influence survival, growth, mutation, proliferation, differentiation and motility of both tumour and stromal cells. Furthermore, promotion of angiogenesis and metastasis and subversion of adaptive immune responses and hormone sensibility seem to be modulated by flogosis.[17] For all these reasons, drugs that could target cancer-related inflammation, such as inhaled corticosteroids, have the potential to modulate a tumour-promoting inflammatory infiltrate or to prevent such cells from migrating to the tumour site. They may also be able to re-align a tumour-promoting microenvironment to become a tumour-inhibiting microenvironment and to enhance tumour-specific adaptive immune response.[17]

Budesonide is a glucocorticoid (see *Figure 1*), a compound that binds to and activates the cytosolic glucocorticoid receptors. Inhaled budesonide is a potentially important approach to cancer chemoprevention that is widely used in asthmatic patients, and it

Figure 1: Skeletal Formula of Budesonide

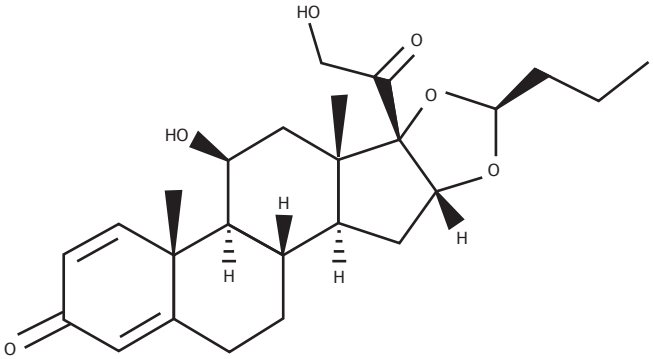


Figure 2: Undetermined Lung Nodule Detected at Computed Tomography (CT) Scan and Persistent at Second-year CT Scan

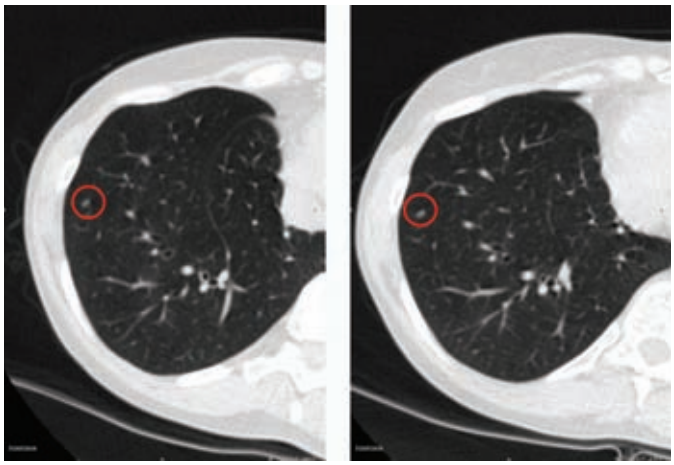
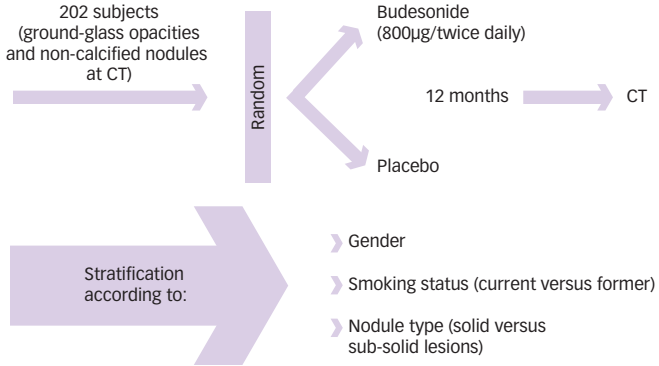


Figure 3: Study Design



CT = computed tomography.

has been demonstrated to inhibit all stages of lung carcinogenesis in various mouse models.[18–20]

A long-term epidemiological trial on chronic obstructive pulmonary disease (COPD) suggested that patients treated with budesonide had a lower incidence of lung cancer, although the low number of events did not allow a definitive conclusion.[21] In 2004, Lam et al.[22] conducted a phase IIb trial to determine the effect of budesonide in smokers with bronchial dysplasia, which is considered the main precursor of squamous cell carcinoma. A total of 112 smokers with ≥1 site of bronchial dysplasia >1.2mm in size identified by autofluorescence bronchoscopy-directed biopsy were randomly assigned to receive placebo or budesonide 800µg twice daily inhalation for six months. The primary end-point was the change in the histopathological grade on repeat biopsy of the same sites at six months. Despite the lack of efficacy in reversing bronchial dysplasia, a subgroup analysis indicated that inhaled budesonide had a favourable tendency in reducing peripheral lung nodules detected by CT. Eleven subjects (21%) in the budesonide group and 19 subjects (36%) in the placebo group had one or more non-calcified lung nodule on their spiral CT at baseline. Retrospectively, 30 nodules were observed in nine of 11 subjects in the budesonide group in the baseline or follow-up CTs, whereas 74 nodules were observed in 15 of 19 subjects in the placebo group. The nodules that were seen in retrospect were very small (>80% were ≤4mm). Interestingly, 16 of the 60 nodules (27%) in the budesonide group became smaller or resolved by the final follow-up compared with 14 of 117 (12%) in the placebo group. The difference in the percentage of nodules that were smaller was statistically significant (p=0.024), although the absolute number of nodules that were smaller was no different between the budesonide and the placebo groups. Recently, in another randomised study,[23] subjects with bronchial squamous metaplasia or dysplasia who received fluticasone, another glucocorticoid, showed a decrease in nodule size and fewer had an increase in the number of nodules detected at chest CT, although this trend did not reach statistical significance.

The European Institute of Oncology Experience – Randomised Phase II Clinical Trial of Budesonide Pulmicort Turbuhaler versus Placebo in High-risk Population with Undetermined Lung Nodules Detected at Computed Tomography Scan

Since October 2004 at the European Institute of Oncology we have been conducting a single-centre screening study (the Continuous Observation of Smoker Subjects [COSMOS] study), which in the first year enrolled 5,201 volunteers at high risk of lung cancer. Subjects underwent baseline multidetector low-dose CT, repeated annually according to protocol for five or more years.[13] In particular, our group analysed 'persistent' nodules detected at low-dose CT scan at the second year (see *Figure 2*) as target markers to test the activity of budesonide.

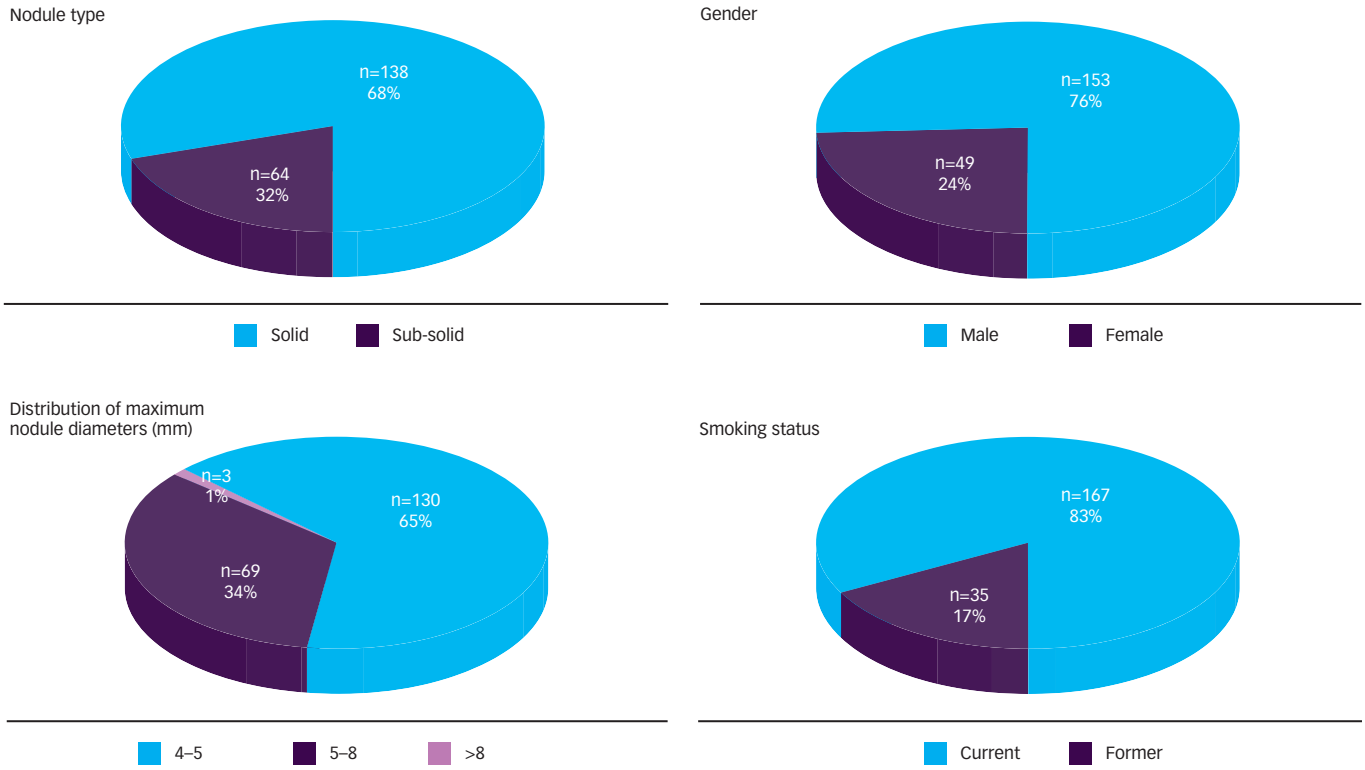
Design

We conducted a randomised, double-blinded phase IIb study in which subjects received either budesonide 800µg twice daily or placebo using a turbuhaler device. Randomisation was stratified according to sex, smoking status (current versus former smokers) and type of nodule (non-solid and partially solid versus solid nodules). The trial design is summarised in *Figure 3*.

Eligibility Criteria

Participants were asymptomatic current smokers or former smokers who had stopped within the last 15 years with a smoking history of more than 20 pack-years and >50 years of age. Subjects should have had persistence of lung nodules (>4mm) detected on low-dose CT scan in the second year of the screening trial; that is, the nodule(s) should be stable in two serial CT scans. Subjects with solid nodules >8mm should have had a negative positron emission tomography (PET) scan. We excluded subjects with lung nodules with clearly benign morphological features at CT scan (i.e.

Figure 4: Subject Characteristics (n=202)



homogenous calcifications, solid nodules with regular and round or polygonal margins and distance from the pleura <1cm), subjects currently suffering from malignant disease or having had malignant disease within the last five years and regular/chronic users of oral or inhaled corticosteroids.

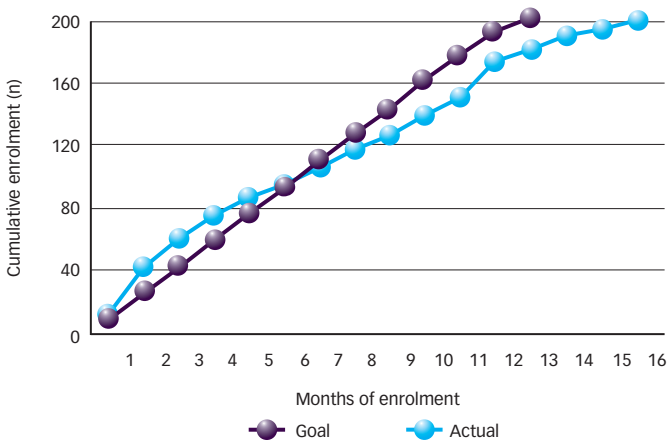
End-points

The primary end-point of the study was the response rate in target nodules in a per-person specific analysis. Secondary end-points included the evaluation of per-lesion analysis by application of Response Evaluation Criteria In Solid Tumors (RECIST) criteria and the average decrease in size of the target lesions, the modulation of biological markers of lung cancer in serum and sputum after treatment (aberrant promoter methylation of retinoic acid receptor beta [RARβ], p16 and RASSF1A genes, ultrasensitive C-reactive protein) and the correlation of these findings with modification of lung nodule sizes. The toxicity of budesonide was also assessed in this cohort of subjects; in addition, since a link between lung cancer and COPD has been documented,[24] we evaluated the effect of budesonide on COPD by both spirometry and spiral CT. The effect of inhaled budesonide on respiratory function was studied by comparison of pulmonary function tests (PFTs), diffusing capacity of the lung for carbon monoxide (D_LCO) and oxygen saturation (SaO_2) before and after one year of treatment; the role of the CT scan in estimating the grade of respiratory impairment and emphysema was analysed by comparing it with PFTs and symptoms.

Patient Characteristics

Among the 4,821 subjects who underwent the second annual low-dose CT screening in the COSMOS study, a total of 527 subjects were screened for protocol inclusion given the presence of persistent undetermined nodules at second CT, and 392 were eligible according to nodule characteristics. Two hundred and two were randomised

Figure 5: Accrual – April 2006 to July 2007



from April 2006 to July 2007; 101 participants were allocated to each study arm. The characteristics of the participants are shown in *Figure 4*. There was no statistically significant difference in median age, sex, smoking history, type of nodule, size of nodule and risk assessment for lung cancer. Overall, 198 subjects completed the 12-month study and were included in the analysis. Three subjects were lost to follow-up and one participant withdrew consent to the trial (drop-out rate 2%).

What We Know So Far

Lam's results are definitely encouraging, but there are some important matters that should be mentioned about the trial. Over 80% of nodules were <4mm, most nodules on low-dose CT were evaluated retrospectively, only three nodules were non-solid type and the vast majority were new nodules, most of which may represent acute inflammation. Thus, the degree of reduction in nodule size obtained

in Lam's study may be attributable in part to the effect of budesonide on inflammatory lesions. To avoid this misinterpretation, the nodules we used as target lesions were stable after one year in two consecutive CTs, one-third were of sub-solid/ground-glass opacity type and all had a diameter >4mm. Although the histology of these nodules cannot be determined and there are other causes for small lung nodules, including adenomatous hyperplasia, all of these latter characteristics were supposed to be less attributable to an inflammatory tissue alteration and more probably to precursor lesions of adenocarcinoma.

Our preliminary results indicate the feasibility of an innovative approach to testing chemopreventative agents in high-risk individuals. While prior chemoprevention trials addressed central squamous carcinogenesis by the use of bronchial dysplasia as an outcome measure,[22,23,25,26] this was the first attempt to focus on prevention of lung cancer by using CT-detected peripheral lung nodules. The study was nested into a screening project with clear advantages in terms of participant accrual and reduction of costs. The study methodology has been successful, with a single-centre accrual of 13 cases per month, showing that the screened population was highly motivated to participate in a chemoprevention trial (see *Figure 5*). Furthermore, the retention rate and compliance were extremely high due to the excellent toxicity profile. In fact, treatment was well tolerated, with the vast majority of adverse events being grade 1, according to the most recent version of the National Cancer Institute (NCI) toxicity criteria (CTCAE version 3.0, published 12 December 2003). The only significant drug-related events were altered taste, voice change and cortisol suppression. No serious adverse events were considered drug-related. Compliance was similar in the two groups, with 84.6% of the population receiving at least half of the study drug dose (83.1% in the budesonide arm and 86% in the placebo arm; p=0.697).

The aim of testing the potential activity of budesonide on sub-solid nodules (partially solid and non-solid) is an important factor, especially if we consider that these lesions represent a frequent finding of CT screening and have a higher probability of progressing to lung malignancies.[27,28] In addition, some of these lesions may represent multifocal indolent bronchioalveolar adenocarcinoma,[29] for which local systemic treatment is not always successful. The use of a chemoprevention intervention to limit progression of these lesions may have important clinical implications. The detailed results of the study will be published shortly. ■

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