LETTERS TO THE EDITOR

Comorbidity in elderly NSCLC patients

We read with interest the report by Janssen-Heijnen and associates on the effect of comorbidity on the treatment and prognosis of elderly patients with non-small cell lung cancer (NSCLC).1 The authors concluded that the number of comorbid conditions had no significant influence on the treatment chosen for patients with non-localised disease. We share the authors’ opinion that “comorbidity had no independent prognostic effect”.

In their report, the authors used the Charlson comorbidity index and analysed the number of comorbid conditions. However, they did not examine the scoring system of the index. We would like to know why the authors did not use the scoring of the system of the index. We would like to know why the authors did not use the scoring of the system. However, in two other recent studies 1,2 the hazard ratio for death for comorbidity was much lower for patients with a lethal tumour than for those with a tumour with a good prognosis.

We also included angina pectoris as a comorbid condition. We think it is important to include this condition in future studies.

In other studies hospitalisation for angina or treated angina was classified as high severity for mortality, and angina not requiring hospitalisation or untreated angina was classified as moderate severity.3,4 The severity index should be validated in future studies.

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References

Authors’ reply

Miyazaki and colleagues wonder why we did not use the scoring system of Charlson’s comorbidity index and whether the conclusion would be different if the scoring system was used. We did not use the scoring system of Charlson’s index because this was not available in the large population based database from which the data were derived. We were, however, able to analyse the prognostic impact of each condition and each combination of conditions. None of these had a significant prognostic impact.1 The conclusion might have been different if we had used the scoring system. However, in two other recent studies 1,2 the hazard ratio for death for comorbidity was much lower for patients with a lethal tumour than for those with a tumour with a good prognosis.

We also included angina pectoris as a comorbid condition. We think it is important to include this condition in future studies. In other studies hospitalisation for angina or treated angina was classified as high severity for mortality, and angina not requiring hospitalisation or untreated angina was classified as moderate severity.3,4 The severity index should be validated in future studies.

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References

Neutrophilic inflammation in childhood bronchial asthma

Although there is increasing evidence that neutrophilic inflammation is involved in enhanced bronchial reactivity and exacerbation of bronchial asthma, the definitive role of neutrophil mediated inflammation in the pathophysiology has not been fully established. To investigate this further, we performed a historical cohort study of 64 children with primary autoimmune neutrophilic (AIN) and compared the incidence of asthma with a control group. The study was approved by the Human Research Committee of Shishin University.

Between January 1997 and December 2000, 64 patients (31 boys and 33 girls) of the average (SD) age 6.1 (1.9) years (range 4.8–10.3) were recruited from our hospitals (table 1). They were followed up for at least 3 years. All were diagnosed with AIN by the age of 12 months, and they had no signs of other autoimmune diseases or haematological disorders. Neutropenia is defined as an absolute neutrophil count of less than 1000/μl blood lasting for 6 months. The diagnosis of AIN was determined by the presence of antineutrophil antibodies and bone marrow findings. Neutropenia resolved in 46 patients (71.9%) within 16–60 months after diagnosis. 415 control subjects (218 boys and 197 girls) were recruited from the patients who had no signs of other autoimmune diseases and other patients who were matched with each of the index children in terms of age, sex, and indoor family smoking. A diagnosis of bronchial asthma was established by interviewing the parents with the modified ATS-DLD structured questionnaire 4 and paediatric pulmonologists reviewed the clinical symptoms and responses to asthma medications under 5 years of age (before school age). The results were analysed using the χ2 test (with Yate’s correction) for categorical variables. The frequency of asthma and eczema in first degree relatives was identical for the two groups (8.2% vs 18.2%, respectively).

In controls, the prevalence of asthma was 9.9%. By contrast, none of the patients with AIN developed asthma (p=0.0243). During the neutropenic period and/or recurrent wheezing.

Our findings strongly suggest that neutrophilic inflammation contributes to the onset of childhood asthma. It is well known that, in infancy, common viral infections of the respiratory tract can cause acute airway obstruction. Persistent inflammation in infancy and childhood is responsible for short-term and long-term consequences and may be a risk factor for later atopy and asthma. Antineutrophil antibodies in AIN usually recognise HLA-NA-1 and HNA-2 antigens that are not detected on

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cosinophils and mast cells, and eosinophils are observed in the peripheral blood of patients with AIN. One possible explanation is that their propensity towards autoimmunity affects dysregulation of the Th1/Th2 balance. However, it has been reported that severe RSV bronchiolitis in infancy is highly associated with the development of asthma up to age 7. We hypothesise that a large proportion of asthma cases may be a result of neuromediatory airway inflammation in early childhood.

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doi: 10.1136/thx.2005.043075

This work was supported in part by Grants-in-Aid from the Japanese Ministry of Education, Culture, Sports and Science.

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3 Ferris BG. Epidemiology standardization project. 2. Recommended respiratory disease questionnaires for use with adults and children in epidemiological research. Am Rev Respir Dis 1978;118:7–53

Protein C in pneumonia

Pneumonia is characterised by a disturbed alveolar fibrin turnover which is the net result of activation of coagulation and attenuation of fibrinolysis. 1,2 We have recently shown, in patients developing ventilator associated pneumonia (VAP), that suppression of fibrinolysis precedes the clinical diagnosis while procoagulant effects mainly occur afterwards. 3 We have extended these findings by investigating the relationship in time between changes in the anti-coagulant protein C (PC) pathway and VAP. Levels of PC, activated protein C (APC), and soluble thrombomodulin (sTM) were measured in non-directed bronchial lavage fluid collected every other day from critically ill patients during mechanical ventilation. APC was measured with an enzyme capture assay using monoclonal antibody HAPC 1555 and chromogenic substrate Spectrozyme PCa (American Diagnostica, Greenwich, CT, USA); 4 PC activity was measured with an amidolytic assay using chromogenic substrate S2366 (Chromogenix, Milan, Italy); and sTM was measured with an ELISA (Diagnostica Stago, Asnières-sur-Seine, France). Serial data from patients were evaluated using analysis of repeated measures with a linear mixed model, as described previously. 5 Data are presented as medians (interquartile ranges).

The patient population was as previously described. 5 In short, specimen collection was initiated in 60 consecutive patients; 28 patients were selected for final analysis, which required at least three sample sets (minimum ventilation duration >5 days). Nine patients developed VAP and 19 showed no signs of pulmonary infection during the clinical course. There were no significant differences between patients who did and did not develop VAP with regard to baseline characteristics, mechanical ventilation settings, and baseline levels of PC, APC, and sTM. Median (IQR) baseline concentrations for patients without and with VAP were as follows: PC: 0.78 (0.69–0.89) v 0.82 (0.72–0.90) U/ml; APC: 0.52 (0.44–0.59) v 0.47 (0.36–0.59) ng/ml; sTM: 102 (79–123) ng/ml (differences not statistically significant). In patients who developed VAP the clinical diagnosis was preceded by a fall in pulmonary PC levels, as measured in lavage fluids, from 0.69 (0.45–0.86) U/ml before VAP to 0.47 (0.24–0.56) U/ml on the day of diagnosis of VAP (p<0.0001; fig 1). In patients who did not develop VAP, pulmonary PC levels remained unchanged (p = 0.07). The decline in PC levels in the infected lungs was accompanied by a decrease in levels of APC, which fell from 0.40 (0.25–0.46) ng/ml before VAP to 0.21 (0.13–0.32) ng/ml on the day of diagnosis (p<0.01; fig 1). The suppression of APC occurred before the clinical diagnosis of VAP was made. Furthermore, in patients who developed VAP a significant increase in sTM levels was observed. Local levels of sTM increased from 95 (120–151) ng/ml before VAP to 214 (186–312) ng/ml on the day of diagnosis (p<0.0001; fig 1), thereafter increasing to 274 (311–362) ng/ml 8 days after VAP was diagnosed. In patients who did not develop VAP during the study, sTM increased to a lesser extent from 102 (79–123) ng/ml at admission to 130 (102–156) ng/ml on day 10 of mechanical ventilation (p<0.01; fig 1).

In sepsis, low levels of APC contribute, at least in part, to the systemic procoagulant environment at the site of infection during pneumonia. Correction of the local PC system may be a target in the treatment of pneumonia.

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Table 1
No (%) of children diagnosed with infantile asthma and their history

<table>
<thead>
<tr>
<th></th>
<th>AIN</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>31</td>
<td>218</td>
</tr>
<tr>
<td>Girls</td>
<td>33</td>
<td>197</td>
</tr>
<tr>
<td>Asthma</td>
<td>0/64</td>
<td>41/415</td>
</tr>
<tr>
<td>(0.05)</td>
<td>(9.9%)*</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6.1 (1.9)</td>
<td>6.2 (0.3)</td>
</tr>
<tr>
<td>age (years)</td>
<td>12</td>
<td>84</td>
</tr>
<tr>
<td>Smoking in</td>
<td>19.4%</td>
<td>(20.2%)</td>
</tr>
</tbody>
</table>

*Significant difference between groups (p = 0.0243).

Human APC has been found to reduce mortality in patients with severe sepsis. 4 Our results show that, during the pathogenesis of pneumonia, the PC pathway is locally suppressed. We suggest that this is the net result of increased PC consumption, cleavage of PC by neutrophil elastase, as well as inadequate PC activation due to oxidation of TM and shedding of TM from the cell surface (resulting in soluble fragments of TM). 4 Presumably, the insufficient anti-coagulant PC system contributes to the local procoagulant environment at the site of infection during pneumonia. Correction of the local PC system may be a target in the treatment of pneumonia.

Figure 1
Levels of protein C (PC), activated protein C (APC), and soluble thrombomodulin (sTM) in non-directed bronchial lavage fluid prospectively collected in mechanically ventilated patients. Left panels: patients who did not develop pneumonia; day 0 denotes start of mechanical ventilation. Right panels: patients who developed ventilator associated pneumonia (VAP); day 0 corresponds to the day at which VAP was clinically diagnosed. Data represent medians with interquartile ranges.
The study protocol was reviewed and approved by the Central Oxford regional ethics committee.

This study was funded in part by the Oxford Health Services Research Committee (research project number 593).

doctor:10.1136/thx.2004.037341

References

Surgery for difficult persistent asthma

A 35 year old non-smoking woman was referred to hospital for advice regarding poorly controlled atopic asthma. Despite good compliance with fluticasone 2 mg/day, a long acting β2 agonist, anticholinergic agent, nebulised bronchodilators plus theophylline, she experienced persistent symptoms necessitating frequent courses of oral corticosteroids. It became apparent that her asthma control deteriorated following menopause—a pattern which was not influenced by premenstrual or continuous oral corticosteroids. Trials with various combinations of oral contraceptive pills failed to improve asthma control. Some improvement was observed with 6 months of treatment with a gonadorelin analogue (goserelin); however, premenstrual symptoms did persist, exacerbations were less marked resulting in a significant reduction in oral corticosteroid use. Gonadorelin analogues produce an initial phase of stimulation followed by downregulation of gonadotrophins, releasing hormone receptors, thereby reducing the release of gonadotrophins and subsequent inhibition of oestrogen production. On discontinuation of goserelin (contraindicated for use longer than 6 months) symptomatic asthma recurred, requiring repeated monthly courses of oral corticosteroids. Following discussion with the patient and her gynaecologist, it was decided that, given the cyclical severity of symptoms, the use of an oral hormone replacement was not appropriate. Consequently, the patient had a single exacerbation of asthma that coincided with the end of the effectiveness of her oestrogen implant (with consequent rise in hysterecmy due to lack of suppression by oestrogen). She was subsequently commenced on regular oestrogen only hormone replacement therapy to good effect. One year after surgery the patient has discontinued intermittent daily oral prednisolone, is asymptomatic, and maintained on 250 μg/day fluticasone combined with salmeterol. This unusual case highlights the importance of enquiring about the possible temporal relationship between worsening asthma control and the menstrual cycle. Premenstrual exacerbations of asthma are well recognised and do not always respond to more aggressive anti-inflammatory treatment. Some success has been achieved with the institution of oral oestrogen and intramuscular progesterone administration.

Four years after initial referral a bilateral oophorectomy and subtotal hysterectomy was performed without complication and an oestrogen-alone hormone replacement was implanted. In the year following surgery the patient had a single exacerbation of asthma that coincided with the end of the effectiveness of her oestrogen implant (with consequent rise in hysterecmy due to lack of suppression by oestrogen). She was subsequently commenced on regular oestrogen only hormone replacement therapy to good effect. One year after surgery the patient has discontinued intermittent daily oral prednisolone, is asymptomatic, and maintained on 250 μg/day fluticasone combined with salmeterol.

This unusual case highlights the importance of enquiring about the possible temporal relationship between worsening asthma control and the menstrual cycle. Premenstrual exacerbations of asthma are well recognised and do not always respond to more aggressive anti-inflammatory treatment. Some success has been achieved with the institution of oral oestrogen and intramuscular progesterone administration. We believe this to be one of the first documented cases of difficult asthma where marked improvement in asthma control has been achieved after a beneficial therapeutic trial of a gonadorelin analogue, followed by bilateral oophorectomy and subtotal hysterectomy plus oestrogen replacement. An initial improvement in asthma control was observed when gonadotrophin levels were low (as a result of the gonadorelin analogue) and a deterioration occurred when gonadotrophin levels were likely to have been rising (towards the end of the effectiveness of the oestrogen implant). This, in turn, suggests that high (or rapidly increasing) gonadotrophin levels, rather than oestrogen/progesterone, were implicated in adversely affecting asthma activity.

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References

Is there a relationship between Mycobacterium tuberculosis strain type and TB paradoxical reaction?

Paradoxical reaction (PR) in tuberculosis (TB) is defined as transient worsening of symptoms and signs or the appearance of new lesions after beginning appropriate anti-tuberculosis chemotherapy. Recent studies suggest that PR occurs in 10–35% of patients. It is more common and more severe in HIV co-infected individuals with disseminated disease. PR is thought to be an immune mediated phenomenon but the reasons for its occurrence are unknown. Infection by Mycobacterium tuberculosis (MTB) results in highly variable outcomes between individuals. The characterisation of MTB strains by molecular typing techniques suggests this may be a reflection of the infecting organism, as well as host response and environmental factors. Distinct genotypes have been shown to evoke different immunopathological events in mouse models and variable clinical manifestations in human population based studies.

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References
is needed to focus on both strain type and consequent host immune response.

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References

Table 1 Site of TB and HIV status of patients with and without clinically evident paradoxical reactions (PR)

<table>
<thead>
<tr>
<th>Pulmonary TB</th>
<th>Lymph node TB</th>
<th>Other primary site</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+</td>
<td>HIV-</td>
<td>HIV+/NK</td>
</tr>
<tr>
<td>PR</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>No PR</td>
<td>10</td>
<td>46</td>
</tr>
</tbody>
</table>

NIK, not known.

isopercin in inoperable chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is a devastating disease in which the pulmonary vasculature becomes obstructed by organised fibrotic material, presumed to be the consequence of incomplete resolution of pulmonary emboli. The ensuing increased pulmonary vascular resistance and right ventricular dysfunction results in severe exercise limitation, symptomatic right heart failure, and markedly impaired survival.

Recent studies suggest that the frequency of this condition is higher than previously appreciated, occurring in up to 3.8% of patients following acute pulmonary embolism after 2 years.1 The treatment of choice is pulmonary endarterectomy (PEA), a potentially curative surgical procedure in which the fibrotic material is removed from the proximal pulmonary arteries during periods of circulatory arrest.4

However, in response to increased flow and shear stress through vascular segments unobstructed by proximal thrombotic material, some individuals also develop a small vessel arteriopathy. This so called “distal CTEPH” has a pathophysiology not dissimilar to that of idiopathic pulmonary arterial hypertension.5 In such patients, PEA may be unsuccessful in alleviating the pulmonary hypertension, and at the present time there is no licensed medical treatment for this condition.

As the national referral centre for PEA for the UK, we sought to assess the efficacy of the oral endothelin receptor antagonist bosentan in patients with distal CTEPH. This agent has established efficacy in pulmonary arterial hypertension, and in distal CTEPH endothelin-1 is thought to play an equally important role in the progressive nature of pulmonary vascular remodelling.6

Twenty patients with established distal CTEPH were recruited to the study, 15 deemed inoperable because of the distribution of their disease on imaging and five with persisting pulmonary hypertension following PEA. All subjects received open label bosentan 125 mg twice daily for at least 3 months. Assessments of change in 6 minute walk distance (6MWD), modified New York Heart Association Classification (NYHA), and haemodynamics were made. After at least 3 months of treatment there were significant improvements in 6MWD, NYHA classification, cardiac index, total pulmonary resistance, and pulmonary vascular resistance (table 1). All patients were alive at 3 months and no significant adverse events were reported as a result of the treatment. In particular, hepatic transaminases, which were monitored on a monthly basis, remained within the acceptable range in all participants.

Although uncontrolled, these preliminary data suggest that treatment with bosentan in this otherwise progressive condition results in improvement in exercise capacity, function, and haemodynamic prognostic markers. It is likely that, by inhibiting the action of endothelin-1, bosentan reduces the abnormal endothelial and smooth muscle cell proliferation stimulated by high shear stress within non-occluded pulmonary arteries. This gradual reversal of vascular remodelling is the most likely reason for the reduction in pulmonary vascular resistance and right ventricular afterload and improved cardiac output observed in our subjects.

Pulmonary endarterectomy remains the treatment of choice for proximal CTEPH. However, in patients with established distal arteriopathy deemed unsuitable for this surgical intervention, bosentan may offer an option by which to delay the progression of this otherwise devastating disease.

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doi: 10.1136/thx.2005.046961

References

Table 1 Mean (SD) 6MWD and cardiac haemodynamics at baseline and after at least 3 months of treatment with bosentan

<table>
<thead>
<tr>
<th>Baseline</th>
<th>3 months</th>
<th>Change from baseline p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class I/II/III/IV</td>
<td>5/14/1</td>
<td>8/11/1</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>262 (106)</td>
<td>307 (100)</td>
</tr>
<tr>
<td>CI (l/min/m2)</td>
<td>1.9 (0.62)</td>
<td>2.3 (0.59)</td>
</tr>
<tr>
<td>TPR (dyne.s/cm5)</td>
<td>1165 (392)</td>
<td>918 (275)</td>
</tr>
<tr>
<td>PVR (n = 5) (dyne.s/cm5)</td>
<td>964 (406)</td>
<td>690 (271)</td>
</tr>
<tr>
<td>mPAP (mm Hg)</td>
<td>48 (13)</td>
<td>45 (11)</td>
</tr>
<tr>
<td>mRAP (mm Hg)</td>
<td>9.4 (6.5)</td>
<td>7.7 (4.8)</td>
</tr>
<tr>
<td>Mixed venous saturations (%)</td>
<td>59 (8.6)</td>
<td>63 (7.8)</td>
</tr>
</tbody>
</table>

6MWD, 6 minute walk distance; CI, cardiac index; TPR, total pulmonary resistance; PVR, pulmonary vascular resistance; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure.  
*two sided p values as indicated.*
Is there a relationship between *Mycobacterium tuberculosis* strain type and TB paradoxical reaction?

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*Thorax* 2005 60: 706-707
doi: 10.1136/thx.2005.044321