Appropriate chemotherapy for palliating advanced cancer

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Patients, doctors, and nurses often express concern about the value of cytotoxic drugs in treating cancer that is beyond hope of cure. How much investigations contribute to patients' care under these circumstances is also frequently questioned. The costs (physical toxicity, psychological morbidity, social disruption, and economic) have to be weighed against the possible benefits (tumour regression, symptom relief, improved activity, and prolongation of life).¹ Decisions on appropriate management may be difficult. Ideally, appropriate management should be clear from the published papers, particularly clinical trials. But although trials provide information that is useful when treating an individual patient, the protocols are often highly exclusive (quite properly in scientific experimental design), and this limits their wider application to the many clinical circumstances affecting patients with cancer. To establish criteria for appropriate treatment and investigation, evidence from clinical trials needs to be supplemented by scrutiny of the collective experience of clinicians and nurses working in this specialty.

We met on several occasions to discuss these issues and identify areas of broad agreement and disagreement. The resulting draft paper was widely circulated for consultation and this final version incorporates the comments received (see acknowledgments). We attempt to outline what is considered to be good clinical practice in the United Kingdom at the present time. It is not feasible to give a comprehensive bibliography in an article such as this, but we believe that its content is consistent with the extensive literature.² Under recent legislation the commissioning and provision of health care in this country are to be separated.³ These guidelines should be of assistance to health authorities and general practitioners in commissioning care for their patients, as well as acting as standards for medical audit.

The role of chemotherapy can only be palliative when used for the following cancers: breast (advanced disease), lung (with the possible exception of limited stage small cell cancer), alimentary tract (all sites including liver and pancreas), ovarian, endometrium, uterine cervix, head and neck, kidney, urinary bladder, brain, melanoma, soft tissue sarcomas, and low grade non-Hodgkin's lymphoma. We are not concerned here with chemotherapy aimed at curing (as in acute leukaemia, Hodgkin's disease, high grade lymphoma, testicular cancer, or some childhood cancers), nor with preoperative or postoperative (adjuvant) chemotherapy.

Age by itself is not a factor when considering chemotherapy for advanced cancer, but in elderly patients frailty and coexisting medical problems need to be considered. Such patients are likely to be intolerant of intensive treatment. Poor performance status correlates with a poor outcome from chemotherapy, but how this should be taken into account in planning treatment depends on the causal relation between the low activity status and the malignant

Chemosensitive cancer before and after treatment. Patients would probably judge treatment worthwhile despite side effects

disease and whether it is potentially reversible by treatment. Hence poor performance status as a result of symptoms from progressive metastatic disease should not necessarily have a major influence on starting primary chemotherapy when treatment is intended to relieve symptoms and improve activity.

We have considered the investigations that are appropriate before and during palliative chemotherapy, what the intentions of treatment should be, what is reasonable treatment for the different cancers, and how this may be modified by other factors in individual patients. We recognise that other types of treatments are not only appropriate but crucial in the

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Intention of palliative chemotherapy

To justify using palliative chemotherapy one or more of the following criteria must exist and should be explicitly recorded.

Relief of symptoms is considered to be the primary intention of chemotherapy in advanced cancer. A decision to use cytotoxic drugs should be based on a knowledge of the probability of response of the tumour concerned. If a patient has no symptoms then the use of chemotherapy is questionable.

Prevention of expected problems—In an asymptomatic patient with metastatic disease chemotherapy to avoid imminent problems may sometimes be worth while. For example, the progression of pulmonary metastases seen on chest radiography will probably cause respiratory symptoms in due course and, for a chemosensitive cancer, timely chemotherapy may be appropriate. Such a judgment will depend inter alia on previous observations of the pace of the patient's disease. Another example is the appearance of early symptoms and signs of brachial plexopathy in a patient with breast cancer, when regression of the tumour by chemotherapy may prevent irreversible neurological damage.

Prolongation of life—Although prolongation of life may be an aim, this is often not achieved with palliative chemotherapy and is not necessarily its primary intention. Nevertheless, in a patient whose metastatic pattern is immediately life threatening, such as extensive diffuse pulmonary infiltration or fulminating liver disease, response to chemotherapy can prolong life. In certain cancers, notably small cell lung cancer and ovarian cancer, response to chemotherapy may confer a small, but significant, extension of survival and this may be the intention for individual patients.

Phase I and II studies—Promising treatments developed in the laboratory must ultimately be tested in the clinic. Ethical considerations require that new drugs are first tested in patients who have no further prospect of benefiting from established treatments. For motivated patients it may be appropriate to prescribe new drugs in phase I and II studies approved by local ethics committees. The studies should be designed, as far as possible, to give a reasonable chance of showing activity for the new drug by employing appropriate inclusion and exclusion criteria in the protocol.⁵ Patients should understand the experimental nature of the treatment, be content to contribute to furthering knowledge, and have some hope of a beneficial effect. Unfortunately, results are often disappointing, but the inherent support given to patients and the interest shown in them by the staff undertaking these studies will often be much appreciated by them and their relatives and may, incidentally, improve the quality of remaining life.

Doctor-patient communication

Honest, careful, and compassionate explanation of the patient's disease and the aims and possible side effects of palliative chemotherapy are important prerequisites to giving treatment. The rate at which such explanation is delivered and its detail should vary according to patients' desire for information, their ability to make sense of it, and their emotional states. Such assessment also enables doctors to judge how much patients may wish to participate in decisions about their medical treatment. Communication of information about palliative chemotherapy needs to emphasise the quality of the patient's life and to foster realistic hope. An individual patient's survival cannot

Utility of treatment

When considering palliative treatment it is important to take account of the views of the

- Patient
- Relatives
- Nurses
- Doctors

Are they the same?

be accurately predicted, and it may be destructive to remove the uncertainty surrounding prognosis.

Including a close relative or friend in discussions about treatment can help patients remember information. It also improves communication within families and facilitates realistic planning for the future. Patients' ability to make decisions and cooperate with treatment may be increased by giving them the opportunity to discuss disease and treatment related issues with other members of the medical team, including trained and supervised nurse counsellors and chemotherapy nurse specialists; regular communication between the hospital and the general practitioner is essential. Discussion allows important information to be reinforced and gives the patient differing perspectives on management. Some patients find it helpful to talk to others who can give authoritative and impartial information, such as the cancer information services,⁶ or to use other supportive therapies—for example, relaxation. In this way patients may feel that they can contribute to their own management.

Some patients who are not eligible for phase I and II trials, or for whom no trial is available, insist on chemotherapy despite a negligible chance of response and in the face of an honest and compassionate explanation of this reality. In these circumstances any treatment should not be demanding on patients or resources and should have minimal toxicity.

Assessing quality of life

The potential benefits of palliative chemotherapy should always outweigh the cost in terms of patient suffering. The quality of life of a patient undergoing palliative chemotherapy should be considered in terms of patients' reports of their symptoms from cancer, adverse physical effects of treatment, and level of physical functioning. Reports of social, psychological, and sexual adjustment and global wellbeing should also be taken into account.

Assessment of quality of life using standardised methods should be incorporated into phase III trials. It is important to be aware of the problems inherent in measuring quality of life in clinical trials in advanced cancer. These include the high loss of patients from studies before they are completed and the dilemma of balancing quality of life issues against modest gains in terms of objective regression and survival. Few clinical trials have assessed the quality of life of patients undergoing palliative chemotherapy.

Duration of treatment

An explicit statement of the treatment plan and subsequent amendments to it should be clearly documented in the case records. The intended duration of palliative chemotherapy should be determined at the outset, although circumstances may require it to be altered later. For example, a change in a patient's clinical state, such as progression of disease or unacceptable toxicity, would necessitate curtailing the treatment. On the other hand, a slow response or

stabilisation of disease with improvement of symptoms and good tolerance of treatment may justify extending the treatment programme. We have attempted to give guidelines on duration of treatment in the discussion of individual cancers below.

Intention of investigations

Laboratory, radiological, and other investigations performed before and during palliative chemotherapy should have a clear purpose that will fall into one of four categories:

- Those needed to give cytotoxic drugs safely. Blood counts are essential for the safe planning of chemotherapy and should be repeated before each course of treatment. Hepatic and renal biochemistry tests should be performed before treatment as impairment of function affects handling of cytotoxic drugs and could alter the drugs selected. Generally, routine biochemical testing with each course of treatment is not necessary
- Those appropriate to monitor response to treatment
- Those needed to diagnose intercurrent problems
- Those only for research.

Supportive care

In palliative chemotherapy the response to treatment has to be balanced against the side effects. Attention must be given to mitigating toxicity. As well as antiemetic drugs, prevention and treatment of infection, and management of alopecia, psychological distress must be monitored and treated. This requires appropriately trained staff, as found in specialist oncology units. In addition, the medical and nursing members of the team should be skilled at counselling both patients and their relatives. Patients with clinically significant psychological problems may benefit from referral to a psychiatrist.

Symptom control and support from palliative care teams are becoming more widely available. Their experience helps doctors to remain positive in outlook as the use of appropriate drugs enables the quality of remaining life to be enhanced. The patient has continuing support at home and can spend less time attending hospital.

Breast cancer

Breast cancer is the most prevalent cancer in the United Kingdom. It often has a chronic course and places great demands on health service resources. Palliative chemotherapy is used in patients with distant metastatic disease and extensive locoregional recurrence not amenable to radiotherapy or surgery.

Postoperative adjuvant endocrine treatment or chemotherapy is increasingly used in operable breast cancer and may modify the response of advanced disease to systemic treatment. But at the present time use of these treatments does not influence decisions on palliative chemotherapy. Many patients with advanced

disease requiring systemic treatment will first be given endocrine therapy, but for those with aggressive visceral metastases (diffuse pulmonary metastases causing dyspnoea or hepatic disease associated with jaundice or raised serum enzyme concentrations) chemotherapy provides the only chance of reversing progression of disease.

Cytotoxic drugs that have an established place in treating advanced breast cancer include cyclophosphamide, anthracyclines (particularly doxorubicin and epirubicin), fluorouracil, methotrexate, mitomycin, and mitozantrone. They are often used in combinations—for example, CMF (cyclophosphamide, methotrexate, and fluorouracil). Few clinical trials have investigated the contribution of each component of these combinations, although prospective trials have shown that vincristine has no contribution in certain combinations. There are no clear data supporting the use of combinations over single drugs. When selecting drugs, the side effects which are important to avoid should be considered. For example, the existence of bone marrow disease or previous skeletal radiotherapy, may preclude drugs that are toxic to marrow, particularly those causing long term marrow suppression such as mitomycin. In other patients avoiding alopecia may be most important, precluding the use of anthracyclines. With uncertainty about the best approach to chemotherapy for advanced breast cancer, decisions rest on the experience of the user and considerations of toxicity.

When no differences exist in disease response other aspects of treatment can influence quality of life, including the scheduling of chemotherapy. Three weekly regimens of doxorubicin have been shown to confer better quality of life than equal dose intensities given weekly. There is some evidence that the quality of life of patients with advanced breast cancer is improved by achieving tumour response even when the side effects are relatively severe. This has been shown in comparisons of endocrine and cytotoxic chemotherapy as well as those of continuous and intermittent therapy.

The optimal duration of chemotherapy is not known. If after six weeks a response is observed or the disease has remained static continuation is appropriate, provided that it is acceptable to the patient. If the disease is progressing treatment should be stopped. In patients responding to treatment there is no evidence to support long term treatment and regimens lasting four to six months are appropriate.

With regard to secondary, or even tertiary, chemotherapy three groups should be considered: (a) responders to primary chemotherapy or those with stable disease having a long time to relapse of six months or more; (b) responders with a short time to relapse; (c) non-responders. In the first group it is reasonable to consider using the same drugs as used initially, but in the other groups alternatives will be needed. In comparison with primary chemotherapy, which gives response rates of about 50% with a median duration of six months, secondary and tertiary treatments give lower response rates, less than 20%, of median duration two to three months.

Chest radiography before starting treatment is a simple and useful examination that may give information on pulmonary or skeletal disease. Initial bone scintigraphy or a radiological skeletal survey are appropriate, but not essential, to screen for skeletal lesions, some of which may need additional local treatment. Bone scintigraphy during treatment is not useful unless needed to elucidate a specific diagnostic problem. Radiography of baseline lesions throughout treatment is helpful in assessing response. Liver scintigraphy or ultrasonography is not indicated unless liver disease is suspected clinically or as the result of

Investigation and treatment

For treatment to be appropriate the benefits expected must exceed the unwanted side effects by a worthwhile margin. Investigations must be done only for valid reasons. How do we decide what is appropriate?

- Medical literature
- Clinical trials
- Collective clinical experience

biochemical tests. Analyses of steroid receptors are not essential for managing metastatic breast cancer.

Lung cancer

SMALL CELL LUNG CANCER

Small cell lung cancer is conveniently subdivided into two stages, "limited" when only locoregional disease is apparent and "extensive" when widespread metastases are present. Cytotoxic chemotherapy prolongs survival in limited stage disease; 20-25% of patients remain alive two years after diagnosis but less than 5% are alive at five years. Extensive small cell lung cancer cannot be cured with current treatments. Nevertheless, chemotherapy may prolong survival from a median of about two to nine months, although most patients have died within 18 months.

The most commonly used drugs for small cell lung cancer include doxorubicin, vincristine, etoposide, cyclophosphamide, and ifosfamide, either alone or in combination. Objective response is usually evident within three weeks of starting chemotherapy and if not evident after six weeks, treatment should be stopped. Few non-responders respond to second line treatment. In responding patients four to six cycles of treatment at three weekly intervals is usually optimal; there is no evidence that more intensive chemotherapy regimens improve the results in small cell lung cancer. After responders have relapsed, secondary chemotherapy is likely to achieve only a short response. Poor performance status and low serum albumin and sodium concentrations indicate poor prognosis, and in patients with these features the cost-benefit ratios for chemotherapy are often unfavourable.

Chest radiography, bone scintigraphy, and liver ultrasonography are appropriate for staging the disease before treatment but computed tomography of the brain has no value unless the patient has symptoms. Chest radiography should be repeated at each course of treatment and other tests that have previously given abnormal results may be repeated such as selected skeletal radiographs or liver ultrasonography after completing treatment.

NON-SMALL CELL LUNG CANCER

A routine role for chemotherapy in treating adenocarcinomas and large cell anaplastic and squamous cell cancers of the lung has not been established, and cytotoxic drugs should be used for these tumours only in clinical trials. Regimens which do show activity are highly toxic and give only short modest responses making cost-benefit considerations unfavourable.

Gynaecological cancer

EPITHELIAL OVARIAN CANCER

In stages I, II, and III epithelial ovarian cancer the intention of primary treatment is curative. However, some elderly patients present with bulky stage III disease and are not suitable for radical treatment. These patients, those with primary stage IV disease, and those with relapse are considered primarily for palliative treatment.

In both the curative and palliative chemotherapy of ovarian cancer no advantage has been shown for combinations of cytotoxic drugs over single drugs. The most active drugs are the platinum compounds, including cisplatin and carboplatin, but toxicity can be severe. Carboplatin is better tolerated and can be given to outpatients; its efficacy is similar to that of cisplatin. In patients with a poor performance status, particularly elderly patients, single alkylating agents (for example, chlorambucil or cyclophosphamide) can be considered for palliation. Intraperitoneal chemotherapy is being evaluated in patients with minimal

residual disease and ascites, but no role has yet been established.

Objective response to treatment in ovarian cancer is difficult to measure. Sometimes clinical assessment by an experienced observer is helpful, but usually either computed tomography or ultrasonography is needed to monitor progress. These tests should therefore be undertaken before treatment to identify baseline reference lesions. When circulating concentrations of the antigen CA 125 are raised, serial measurements can give useful additional information on response to treatment.

If a response has not occurred after three cycles further treatment is unlikely to be beneficial and should be stopped. In responding patients treatment should be continued for a further three cycles. Several drugs—for example the anthracyclines—have been tested as second line treatment after failure of cisplatin or alkylating drugs, but few patients respond to them. At present there is no routine second line treatment other than within phase II clinical trials.

CARCINOMA OF THE CERVIX

Chemotherapy can be considered for palliative treatment of carcinoma of the cervix either when the disease has relapsed after previous surgery and radiotherapy or in primary stage IVb disease. It is a moderately chemosensitive tumour and modern regimens using combinations including bleomycin, ifosfamide, cisplatin, and methotrexate can achieve response rates of about 60% but at the risk of substantial toxicity. Median duration of response is five to six months. These regimens should be used only to relieve symptoms of progressive disease—for example, pain or lower limb oedema. Relief of symptoms is more common than objective response, and in patients with no symptoms the toxicity of these treatments, which may be considerable, outweighs any possible benefit. Four to six cycles of treatment are probably optimal, but if no response is seen after three cycles treatment should be abandoned. There is no routine place for second line cytotoxic treatment. To supplement clinical examination in assessing response to treatment baseline and serial computed tomograms or ultrasonograms are helpful.

OTHER GYNAECOLOGICAL CANCERS

Routine chemotherapy has no established place in the palliative treatment of carcinoma of the endometrium or vulva.

Alimentary tract cancer

COLORECTAL CANCER

Before chemotherapy is used for palliating rectal cancer, pelvic radiotherapy and standard analgesic techniques should be considered. Chemotherapy should not be given for asymptomatic metastatic colorectal cancer, but for symptomatic disease fluorouracil may be appropriate. No clearly superior schedule has been identified and intermittent injections or continuous infusions are acceptable. Doctors should note that though the drug is inexpensive, infusion pumps are costly. Absorption of fluorouracil from the gastrointestinal tract is unreliable making oral administration inappropriate. The highest chances of response are achieved by combining fluorouracil with folinic acid.

Various schedules are used for fluorouracil either alone or in combination with folinic acid. In general, higher doses lead to higher response frequencies but at the expense of increased toxicity. These regimens can be continued for several months, four to six months being reasonable in responding patients. If disease progresses after a good response further treatment with

Palliative chemotherapy is aimed at improving quality of life. The relative importance to patients of the various side effects from different regimens must be considered

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response to two cycles of treatment it should be stopped, otherwise a total of four to six courses should be given. Baseline investigations should include chest radiography and computed tomography.

Soft tissue sarcomas

Cytotoxic drugs can be considered for palliating locally recurrent or unresectable soft tissue sarcomas that are beyond the scope of radiotherapy or when distant metastases have occurred. Regimens using doxorubicin, dacarbazine, cyclophosphamide, and ifosfamide give reported response rates of 10-40%, but it is often not clear what this achieves in terms of palliation. Randomised trials have shown no significant differences between single drugs and combinations. When local symptoms such as pain and ulceration are severe and radiotherapy is not appropriate or if pulmonary metastases are causing dyspnoea, chemotherapy may relieve symptoms. If there has been no response after two or three cycles of treatment it should be stopped, otherwise it is reasonable to give four to six cycles. Given the low response rates and the high toxicity of such treatment the benefits from palliative chemotherapy must be regarded as marginal.

fluorouracil may be appropriate if the patient has symptoms. No advantage has been shown for giving fluorouracil or other drugs by hepatic artery infusion, and this technique should be considered as a research procedure undergoing evaluation. Although lomustine, semustine, and mitomycin have been used, particularly in combinations, they are not established for routine use. Chemotherapy is appropriate only for patients of reasonable performance status. Appropriate baseline investigations include chest radiography and ultrasonography of the liver.

GASTRIC CANCER

Gastric cancer is only moderately chemosensitive. Short objective regressions can be achieved with various drugs including fluorouracil (with or without folinic acid), doxorubicin, cisplatin, and mitomycin used alone or in combination. Chemotherapy can be considered for patients with symptomatic progressive disease, depending on performance status. Although platinum has activity, its toxicity makes it unsuitable for most patients with this disease. Use of any other drugs for advanced gastric cancer is inappropriate except in clinical trials.

OTHER ALIMENTARY TRACT CANCERS

There is no standard chemotherapy for routine use in cancers of the oesophagus, liver, or pancreas and its use should be restricted to clinical trials.

Bladder cancer

Palliative systemic chemotherapy for carcinoma of the urinary bladder may be considered for relapse in the pelvis after previous surgery and radiotherapy or for extrapelvic disease that is not amenable to irradiation. Combinations of methotrexate, vinblastine, doxorubicin, and cisplatin give high response rates, but toxicity can be considerable. Nevertheless, severe symptoms such as pain or oedema in a young patient may warrant using one of these regimens. Haematuria is controlled better by radiotherapy than chemotherapy. Patients without symptoms—for example, those with asymptomatic pulmonary metastases—should not be given chemotherapy. In patients with a poor performance status the potential toxicity of chemotherapy must be balanced against the possibility of symptom relief. The best palliative results are achieved with drug combinations. If there has been no

Malignant melanoma

The disease has a very variable course. Responses to chemotherapy are poor with commonly used drugs such as dacarbazine, cisplatin, and vindesine and are usually confined to cutaneous or pulmonary disease. Higher response rates have been reported with some regimens combining procarbazine, vincristine, and lomustine, but a routine role for chemotherapy in this disease has not been established. Arterial limb perfusion with cytotoxic drugs can occasionally be of palliative value.

Head and neck cancer

Chemotherapy may provide useful palliation of head and neck cancer, particularly when local recurrence has developed after radical surgery or radiotherapy. The standard drug combinations include cisplatin, bleomycin, fluorouracil, and methotrexate. Though these combinations give higher response rates than either methotrexate or cisplatin used alone, there is little evidence that this is reflected in an increase in survival. Response rates vary between 20% and 40%, lasting about three months. In patients with good performance status, four to six cycles of treatment are optimal, but if there is no response after three, treatment should be stopped. Responses are monitored by clinical measurement and chest radiography if pulmonary metastases are present.

Lymphoma

The intention of primary chemotherapy of Hodgkin's disease and high grade non-Hodgkin's lymphoma is curative. After relapse the curative potential for chemotherapy is much less, but with intensive treatment supplemented by autologous bone marrow transplantation cure may still be realistic. By contrast, disseminated low grade non-Hodgkin's lymphomas are relatively resistant to eradication by chemotherapy. Cytotoxic treatment, usually chlorambucil with or without prednisolone, should be reserved for symptomatic disease not amenable to palliative radiotherapy. Recently more intensive combinations containing anthracyclines have been used in low grade non-Hodgkin's lymphoma, but the morbidity is considerable and it is too early to know the results achieved with this approach.

Myeloma and other cancers

For most patients with multiple myeloma treatment is palliative and comprises combined melphalan and prednisolone. Despite several clinical trials the evidence on more intensive combinations is conflicting. Nevertheless, in younger patients the results of trials of high dose chemotherapy with bone marrow transplantation seem promising.

Cytotoxic drugs have no established role in the palliative treatment of cancers of the thyroid, kidney, and prostate. The lipid soluble nitrosoureas have been used for treating gliomas, but evidence that they improve quality of life or survival is unconvincing.

Conclusions

Systemic cytotoxic treatment has been remarkably successful in curing a few uncommon disseminated tumours, notably testicular cancer, acute lymphoblastic leukaemia, and Hodgkin's disease. This has encouraged the widespread use of chemotherapy for other more common cancers, but progress has been slow despite the enormous clinical research effort worldwide. We have therefore cautioned against the uncritical use of chemotherapy and stressed the importance of giving it selectively and only with adequate supportive care. The guidelines suggested in this paper should encourage the more effective use of chemotherapy in the palliation of advanced cancer and be useful as predetermined standards for medical

audit; commissioners of health care may also find them useful when deciding how best to deploy available resources. They should be considered as complementary to innovative clinical research directed towards finding more active and less toxic treatments for disseminated cancer.

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Lesson of the Week

Acute angle closure glaucoma associated with nebulised ipratropium bromide and salbutamol

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Coadministration of nebulised ipratropium bromide and salbutamol may cause acute angle closure glaucoma in susceptible patients

Nebulised ipratropium bromide and salbutamol have become standard drugs for managing acute exacerbation of chronic obstructive airways disease. We report five cases of patients who presented with acute angle closure glaucoma provoked by the combined administration of these drugs.

treated with intensive pilocarpine (4%) topically, intravenous acetazolamide (500 mg), and analgesia. After initial control of intraocular pressure, all patients had bilateral peripheral iridotomies with a neodymium-YAG (yttrium aluminium garnet) laser.

Discussion

We have observed five patients who developed acute angle closure glaucoma (bilateral in three cases) after receiving nebulised salbutamol and ipratropium bromide. There have been two previous case reports of this condition associated with these drugs: in one case after using nebulised salbutamol and ipratropium bromide¹ and in the other case after using only nebulised ipratropium bromide.²

Ipratropium is an anticholinergic drug and is known to cause pupil dilatation. Salbutamol is a β_2 adreno-receptor agonist and increases production of aqueous humour. Eyes which are anatomically predisposed to acute angle closure glaucoma have shallow anterior chambers, narrow anterior chamber drainage angles, and are often hypermetropic. By semidilating the pupil, ipratropium will partially block the flow of aqueous humour from the posterior to the anterior chamber, which will result in the peripheral iris bowing anteriorly and obstructing the drainage angle. Salbutamol will compound this problem by increasing production of aqueous humour. Acting together these two drugs will increase intraocular pressure and precipitate acute angle closure glaucoma. The concomitant administration of other drugs with anti-

Case reports

All five patients had been admitted by general physicians with a diagnosis of acute exacerbation of chronic obstructive airway disease and had been started on combined nebulised ipratropium and salbutamol six times a day. Each patient was referred to the ophthalmic department after a sudden reduction in visual acuity and severe ocular pain and periorbital headache on the affected side(s). Three patients also had nausea and vomiting. All patients had congested conjunctivae, hazy corneas, shallow anterior chambers, and fixed mid-dilated pupils in the affected eyes. Angle closure glaucoma was bilateral in three patients (table). The patient in case 3 gave a history suggestive of abortive attacks of acute angle closure glaucoma over the three months preceding admission. In case 4 the patient had had symptoms of abortive angle closure during his admission (before the development of acute angle closure glaucoma) that were related to the administration of nebulised drugs. The table shows the time between starting nebulised therapy and the onset of symptoms. The drugs received by all patients were reviewed to identify any other drugs that could contribute to angle closure. All patients were initially

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