Novel treatment (new drug/intervention; established drug/procedure in new situation)

Metyrapone: a management option for ectopic ACTH syndrome in small cell lung cancer treated with intravenous etoposide

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Summary

Small cell lung cancer (SCLC) with ectopic adrenocorticotrophic hormone (ACTH) syndrome and resultant hypercortisolism carries a poor prognosis with a short median survival and high incidence of infective complications. The combination of etoposide with either carboplatin or cisplatin is the current standard chemotherapy used for the management of SCLC. Etoposide is metabolised by cytochrome P450 3A4. Ketoconazole is an imidazole derivative possessing antifungal properties and also causes inhibition of adrenal corticosteroid and androgen production. There is an additional increased risk of toxicity due to a potential interaction between etoposide and ketoconazole, which is a strong inhibitor of cytochrome P450 3A4, and theoretically can lead to greater myelosuppression. Metyrapone can be a safe alternative in such settings.

BACKGROUND

Ectopic adrenocorticotrophic hormone (ACTH) syndrome (EAS) associated with small cell lung cancer (SCLC) results in worse prognosis, increased risk of infection and decreased response to treatment. The poor survival is considered to be related to the high tumour burden, chemoresistance and higher incidence of infective complications even without neutropenia often resulting in discontinuation

of cytotoxic treatment. Anticancer treatment alone rarely provides adequate control of endogenous hypercortisolism and steroid synthesis inhibitors such as ketoconazole and metyrapone have to be used for the optimum control of hormonal abnormalities. It is therefore prudent to control ectopic ACTH hypersecretion, which can be challenging if concomitant chemotherapy can result in potentially increased toxicity due to interaction between ketoconazole

Figure 1 Urinary free cortisol response to metyrapone and chemotherapy.

Figure 2

Figure 2 Adrenal steroidogenesis pathway illustrating the sites of action for steroidogenic enzyme inhibitors.

and etoposide. Sustained suppression of corticosteroid and improvement of performance status can be achieved while potential toxicity can be avoided when metyrapone is used with chemotherapy for the management of EAS.

CASE PRESENTATION

A 50-year-old woman with a history of bilateral flank pain, abdominal distension, constipation, lower limb oedema, poor mobility and approximately 10 kg of weight gain was referred to the hospital by her general practitioner. She had a history of osteoporotic crush fractures of lumbar spine and poorly controlled hypertension as reflected by the use of multiple antihypertensives including atenolol, frusemide, irbesartan, perindopril and prazosin. She was also taking methadone, amitriptyline and paracetamol for backache. She lived alone and had experienced a substantial decline in her activities of daily living (Eastern Co-operative Oncology Group, ECOG, status 3). She had a 35-pack years history of smoking and consumed six standard drinks of alcohol per day for the past few years.

On examination, she had cushingoid appearance with facial plethora, centripetal obesity, interscapular fat pad, distended abdomen with purple striae and bilateral lower limb oedema. Her weight was 90 kg.

She was hypertensive with blood pressure of 180/115 mm Hg on multiple occasions. She did not have any hyperpigmentation or proximal muscular weakness.

INVESTIGATIONS

The random morning cortisol (802 nmol/l), random evening cortisol (761 nmol/l), 23:00 salivary cortisol (54 nmol/l) and 24 hours urinary free cortisol (2419 nmol/ 24 h) were all elevated. ACTH was normal. A 1 mg and an 8 mg dexamethasone suppression test failed to suppress with the morning serum cortisol values of 904 nmol/l and 840 nmol/l, respectively. Follicle-stimulating hormone, luteinising hormone, thyroid-stimulating hormone along with free T4 were in the normal range. CT abdomen/pelvis showed bulky adrenal glands bilaterally with normal appearance of other organs. Pituitary gland was normal on an MRI scan. CT chest showed a 2.2×5.2 cm right middle lobe mass and bulky mediastinal and ipsilateral hilar lymphadenopathy. Whole body bone scan showed multiple osteoporotic fractures of the lumbar spine and ribs but there was no evidence of metastatic disease in the bones. Bronchial biopsy of the right middle lobe lung lesion confirmed SCLC on histological analysis. An immunoperoxidase stain for ACTH showed scattered tumour cells with weak granular immunoreactivity in keeping with ectopic ACTH production. On the basis of this a definitive diagnosis of (EAS) secondary to limited-stage SCLC was made.

DIFFERENTIAL DIAGNOSIS

Pseudo-Cushing syndrome was ruled out due to the loss of evening nadir in the serum cortisol levels. Normal MRI

suggested pituitary-independent Cushing syndrome. High-dose dexamethasone suppression test was negative, suggesting an ectopic ACTH-dependent cause.

TREATMENT

She was started on ketoconazole for the management of hypercortisolism but it was stopped prior to the first cycle of chemotherapy with the anticipation that treatment of the underlying malignancy should result in normalisation of cortisol levels.

She received her first cycle of chemotherapy with intravenous etoposide and carboplatin as an inpatient without any untoward side effects. She was admitted 3 weeks later for her second cycle of chemotherapy but at that time she was found to be increasingly short of breath with productive cough and fever up to 39°C. A CT pulmonary angiogram was done, which showed multiple small pulmonary emboli and a necrotic right middle lobe mass suggestive of a possible lung abscess, although she was not neutropenic. Bronchial washings grew *Staphylococcus aureus* and she was started on intravenous flucloxacillin for 2 weeks followed by 4 weeks of oral dicloxacillin. Her chemotherapy had to be delayed by 4–5 weeks. During this delay in chemotherapy, she was re-started on ketoconazole but it was changed to metyrapone prior to second cycle of chemotherapy due to the potential interaction between ketoconazole and etoposide (the former being a potent inhibitor of CYP 3A4 system responsible for the metabolism of etoposide).

She was started on enoxaparin for the pulmonary emboli and was on potassium supplements due to hypokalaemia most likely related to EAS.

In brief, her continued management included

- ▶ Chemotherapy: intravenous etoposide and carboplatin (a total of six cycles)
- ▶ Radiotherapy
- ▶ Metyrapone 250 mg three times a day, eventually increased to 500 mg three times a day
- ▶ Bisphosphonate: risedronate 35 mg weekly
- ▶ Intravenous flucloxacillin for lung abscess
- ▶ Enoxaparin for pulmonary embolism
- ▶ Occupational therapy and physiotherapy input.

OUTCOME AND FOLLOW-UP

The dose of metyrapone was increased during the course of treatment for better control of cortisol levels.

Patient had good response with declining 24-h urinary free cortisol level that eventually normalised (figure 1).

She had improvement in her mobility and performance status (ECOG 1) and body weight. Her blood pressure was better controlled and perindopril was stopped. She was managing at home independently.

DISCUSSION

SCLC is responsible for approximately 20% of all bronchogenic cancers.¹ Hypercortisolism occurs in up to 50%

of patients with SCLC,^{2,3} however, clinically apparent EAS occurs in about 5% of patients with SCLC.⁴

Patients developing EAS in association with SCLC have a much higher rate of complications during therapy and worse survival than those patients with SCLC not associated with an EAS.^{1–5} This is due to an increased risk of infection, gastrointestinal toxicity, decreased response to chemotherapy and poor performance status in the presence of hypercortisolism.

Treatment of EAS is difficult in the presence of malignant tumours along with severe hypercortisolism.⁶ Bilateral adrenalectomy is sometimes required if hypercortisolism cannot be controlled medically.⁶ Ketoconazole blocks steroid synthesis by inhibiting 14-demethylation of cholesterol.^{1,7} Metyrapone is an inhibitor of 11-beta-hydroxylase, an enzyme required in the terminal step for the conversion of 11-deoxycortisol to cortisol.^{6–8} Traditionally, both of these drugs have been used for the treatment of ACTH-dependent and ACTH-independent Cushing's syndrome (figure 2).

The use of intravenous etoposide and platinum-based chemotherapy is the current standard therapy used for the management of SCLC. CYP 3A4 is the major metabolic pathway of etoposide as it catalyses 3-demethylation of etoposide.⁹ Ketoconazole, like cyclosporin, is a strong inhibitor of CYP 3A4.¹⁰ Studies have shown that cyclosporin increases the area under the concentration–time curve of etoposide by 1.8-fold, and as a result, increases the frequency of leukopenia,¹¹ hence, therapy modification is required.

The data studying the use of ketoconazole with intravenous etoposide is limited. One study involving the use of ketoconazole with oral etoposide concludes that ketoconazole reduces the clearance of oral etoposide but does not alter its toxic profile.¹² Whether this is also true with intravenous etoposide has not been verified.

Metyrapone has an inhibitory effect on steroid synthesis. As seen in our patient, metyrapone can provide an effective means to control hypercortisolism associated with EAS secondary to SCLC and allow administration of etoposide at standard doses.

Increased susceptibility of infection is one of the effects related to corticosteroids.⁶ Our patient also developed a lung abscess, which is likely to be the combined result of hypercortisolism and cancer. The infection was successfully treated with antibiotics. However, interruption in chemotherapy was encountered as a consequence of infection. Whether it can be interpreted as an indication for routine prophylactic use of antibiotics in these groups of patients is debatable.

Overall, the management of EAS secondary to SCLC with chemotherapy and metyrapone resulted in the improvement of the patient's well-being and performance status, which is indicative of a positive response to chemotherapy. Whether it has improved survival benefit, is yet to be seen.

Learning points

- ▶ EAS in association with SCLC can be debilitating, with poor performance status, decreased chemotherapy response and increased risk of infections.
- ▶ Metyrapone given with intravenous etoposide and carboplatin is effective in suppressing steroid synthesis and can be considered instead of ketoconazole.
- ▶ There may be a role of pre-chemotherapy use of steroid synthesis inhibitors in order to reduce the rates of infectious complications related to cytotoxicity from chemotherapy and altered immune response secondary to endogenous hypercortisolism.
- ▶ Whether ketoconazole increases the toxicity profile of intravenous etoposide requires further clarification.
- ▶ To facilitate continuation of chemotherapy without interruption, the routine use of prophylactic antibiotics in patients with EAS secondary to SCLC can be considered but there is no general consensus.

Competing interests None.

Patient consent Obtained.

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