Successful desensitisation to Anastrozole

To the Editor:

Many breast cancers have oestrogen receptors and their growth can be stimulated by oestrogen. In postmenopausal women, the principal source of circulating oestrogen is the conversion of adrenally-generated androstenedione to oestrone by aromatase in peripheral tissue, with further conversion to oestradiol. Treatment of breast cancer has included efforts to decrease oestrogen levels, by ovariectomy premenopausally and by use of anti-oestrogens and progestational agents both pre- and post-menopausally. These interventions lead to decreased tumour mass or delayed progression of tumour growth in some women[1].

Anastrozole (AN) is a potent and selective third generation reversible nonsteroidal aromatase inhibitor[2,3]. It lowers serum oestradiol concentration and has no detectable effect on the formation of adrenal corticosteroids or aldosterone. It has been shown to reduce intratumoural oestrogen levels[1]. AN has good oral absorption, with maximum plasma levels reached within 2 hours of intake. It is extensively metabolised in liver (85%) via N-dealkylation, hydroxylation and glucoronidation[1]. The most common adverse effects reported include: hot flushes (27%); nausea (19%); fatigue (16%); joint pain and stiffness (12%); bone, chest and back pain (11%); cough (11%), pharyngitis (10%) and dyspnoea (10%)[1].

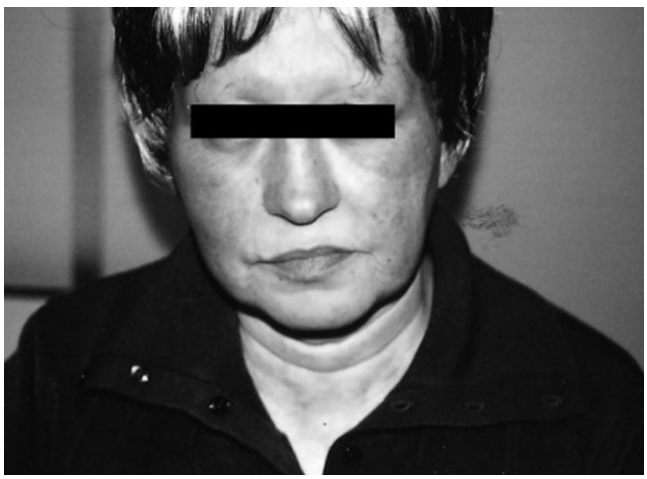

Figure 1. Facial exanthema 3 days after treatment with Anastrozole.

Table I. Desensitisation protocol to Anastrozole

Days	Dose	Cumulative dose
Day 1	10 μg	450 μg
	20 μg	
	40 μg	
	80 μg	
	100 μg	
	200 μg	
Day 2	200 μg	950 μg
	200 μg	
	200 μg	
	350 μg	
Day 3	500 μg	1 mg
	500 μg	

Third generation aromatase inhibitors are considered the most effective first-line endocrine treatment of advanced endocrine-responsive breast cancers since superior antitumoural activity has been repeatedly demonstrated versus tamoxifen in large phase III randomised trials in postmenopausal women[4-7].

The authors report the clinical cases of two patients (55 and 59 years old) with advanced breast cancer, submitted to surgery, chemotherapy (adriamycin, cyclophosphamide and docetaxel) and radiotherapy, always with good tolerance. In November 2006 they began adjuvant treatment with AN 1 mg/day. One of the patients referred a burning sensation on her face, macular exanthema, conjunctival hyperaemia, periorbital oedema, and watery discharge (fig. 1), three days after beginning the treatment. Due to progression of cutaneous symptoms to the neck and upper thorax, AN was discontinued on day 9 and oral antihistamines and corticosteroids were started with total resolution of symptoms.

The second patient referred macular exanthema on the face, neck and thorax two months after the treatment was started. AN was interrupted with total resolution of symptoms without any treatment.

Patch tests with 10% AN in white petrolatum were performed in both patients with negative results. Two exposed controls were also negative. Alternative treatment with tamoxifen was not possible because of its cardiotoxicity as one of the patients has heart disease. Letrazole, an alternative drug for both patients, was not available in our hospital. It was at this point that desensitisation to AN was proposed and performed. The desensitisation procedure (3-day protocol) was performed in the day care Hospital beginning with a 10 μg dose, progressing until the cumulative dose of 1 mg was achieved (Table). The patients continued taking AN 1 mg/day without any reactions. They have been followed on monthly basis consultations without any symptoms.

All drugs can induce hypersensitivity reactions, which can limit the use of essential drugs in the treatment of serious diseases like cancer. The choice of an alternative chemotherapy regimen is often limited by tumour sensitivity, presence of comorbidities or the availability of alternative drugs.

Drug desensitisation can be defined as the induction of a state of unresponsiveness to a compound responsible for a hypersensitivity reaction. The induction of temporary unresponsiveness to drug antigens allows patients to be treated with medications to which they have presented hypersensitivity reactions[8]. This is achieved by gradual reintroduction of small doses of drug antigens at fixed time intervals, allowing the delivery of full therapeutic doses and protecting patients against previous severe drug reactions.

The desensitised state can only be maintained by continuous administration of the drug[9]. In spite of the amount of literature on drug desensitisation, the mechanisms behind this procedure are still not completely understood.

With regard to chemotherapy drugs there are some published data about successful desensitisation protocols to

taxenes, platinum salts, L-asparaginase and monoclonal antibodies involving anaphylactic or anaphylactoid reactions[8]. To date no desensitisation protocols have been published on third generation aromatase inhibitors like AN.

In these case reports both patients referred late reactions to AN with mainly cutaneous symptoms. To clarify the underlying mechanism of these reactions, patch tests with 10% AN in white petrolatum were performed with negative results. This could have several explanations: the final responsible agent for the reaction could be a metabolite of AN; poor penetration of the drug into the epidermis; low drug concentration, use of inappropriate vehicle[10,11] and immunosuppression state of patients. Although no immune mechanism could be proven in our patients, a desensitisation procedure was tried with success. This result reinforces the fact that desensitisation to drugs that induce delayed cutaneous hypersensitivity reactions is possible and safe, as we have observed many times in patients with HIV infection and delayed cutaneous reactions to cotrimoxazol.

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Lymphoma as presentation of common variable immunodeficiency

To the Editor:

Common variable immunodeficiency (CVID) is a heterogeneous disorder characterized by deficient antibody synthesis. It manifests as recurrent bacterial respiratory infections and an increased incidence of neoplasms — particularly lymphomas, autoimmune processes and granulomatous diseases[1-3]. We report a clinical case of CVID of special interest in paediatrics due to its initial manifestation as non-Hodgkin lymphoma.

A four-year-old boy presented with headache, asthenia and anorexia for the previous 15 days. The oncological history among his grandparents revealed leukaemia and stomach, lung, and testicle cancer. The paternal grandmother suffered diabetes mellitus and chronic arthritis; the maternal grandmother presented hypothyroidism. There were no personal disease antecedents of interest other than very intense varicella at 18 months of age, and repeat bronchitis up to three years of age. Vaccinations were correct and well tolerated.

Physical examination revealed a poor general condition, 2/6 systolic murmur, oral candidiasis, submandibular adenopathies and abdominal distension with hard and painful 4 cm hepatomegaly associated with nodular areas. The neurological exploration proved normal.

The initial complementary explorations revealed intense anaemia in the blood tests (haemoglobin 9.7 mg/dl, haematocrit 34%), important lactate dehydrogenase elevation (LDH 1936 U/l), abdominal ultrasound findings in the form of diffuse hepatomegaly of both lobes and multiple nodular images compatible with liver metastasis. The brain CT scan in turn showed oedema and a hypodense nodular image containing calcifications in the left cerebellar hemisphere, suggestive of metastasis.

The initial diagnostic impression was lymphoma, in view of the age of the patient, the important family antecedents of oncological disease, and the aggressivity of the clinical condition.

The study was continued with brain and spinal MRI, which revealed expansive lesions in the left hemicerebellum with nodular contrast uptake and an oedematous halo, compatible with lymphoma (fig. 1).

There was no spinal involvement. The abdominal CT scan identified nodular lesions in the liver and kidneys, as well as mesenteric adenopathies (fig. 2). The bone marrow biopsy confirmed the existence of a blast cell infiltrate with an immunophenotype corresponding to leukaemia/B lymphoma, with FAB L3 morphology.

At that point, the immune study revealed a decrease in all immunoglobulins, with normal lymphoid populations (IgG 2810 mg/l, IgM 180 mg/l, IgA 220 mg/l, lymphocytes 1697/mm^3, B lymphocytes 350/mm^3, T lymphocytes 1273/mm^3 CD8 593/mm^3; CD4 680/mm^3), and natural killer cells 74/mm^3. Of note was the absence of anti-rubella IgG antibodies and of anti-tetanus IgG and IgM antibodies, despite previous vaccination against those diseases. The titres of those antibodies were measured three times after double checking that the patient was correctly vaccinated and re-vaccinated