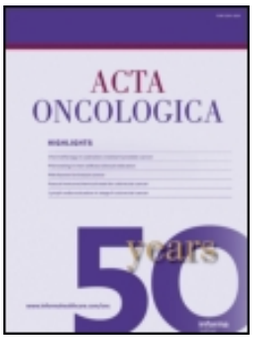

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LETTER TO THE EDITOR

Treatment and treatment considerations in a patient with advanced breast cancer and acute intermittent porphyria

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To the Editor

The porphyrias represent a collection of seven disorders due to genetic defects, each resulting from a partial deficiency of a specific enzyme in the haem biosynthesis pathway [1], this leads to over-production syndromes with the formation of toxic haem precursors. Haem is synthesised in every human cell and about 85% are made in erythroid cells, where the majority are used for haemoglobin formation. Most of the remainder is produced in the liver, where 80% is used for the creation of different cytochromes. The porphyrias can be divided into two subgroups – hepatic or erythropoietic – according to the organ in which accumulation of porphyrins and their precursors mainly appears. The three most important entities are an acute porphyric attack and acute and chronic skin symptoms. The prevalence of porphyrias varies from 0.5 to 10 per 100 000 in different populations.

The hepatic porphyrias (acute intermittent porphyria, variegate porphyria and hereditary coproporphyria) can induce acute attacks, where porphyrin precursors are excreted massively from the liver because of induction of haem biosynthesis [2]. An acute attack begins with minor behavioural changes such as anxiety, restlessness, and insomnia and proceeds rapidly to symptoms of autonomic and sensomotoric neuropathy. Abdominal pain – usually followed by vomiting and constipation – is common and severe, mimicking acute abdominal crisis. Pain in the back or in the extremities is frequently present. Hypertension and tachycardia are associated with the activity of the disease.

About 75% of acute attacks have identifiable precipitants, e.g. porphyrinogenic drugs, infections, malignancies, alcohol, tobacco, illicit drug use, fasting, pre-menstrual stress. One of the possible mechanisms by which drugs can precipitate acute attacks is by induction of the cytochrome P450-mediated oxidation leading to depletion of liver haem concentrations and thus induction of the haem biosynthesis pathway [2]. Measurements of urinary porphobilinogen must be undertaken during an acute attack, porphobilinogen and 5-aminolaevulinic acid. They are porphyrin precursors and will always be increased under an acute attack. To confirm the diagnosis of an acute attack, porphobilinogen has to be measured by a quantitative test and it is usually markedly increased and to a lesser extent 5-aminolaevulinic acid [1]. The majority of patients with acute intermittent porphyria will have a slightly increased urinary porphobilinogen during the symptomless phase. Treatment is administration of haem, which is infused daily for three to four consecutive days. There are limited information on cytotoxic chemotherapy and the porphyrias [3–5]. We here describe and discuss an attempt to avoid potentially porphyrinogenic drugs but at the same time give an optimal antineoplastic and palliative treatment to a patient with dissiminated breast cancer.

At age 42 years, a woman with acute intermittent porphyria since the age of 31 was diagnosed with cancer of her right breast. She was treated with metoprolol because of hypertension associated with porphyria, but was apart from the disease mentioned

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otherwise healthy. Histology showed a 2.5 cm, grade 3 invasive ductal carcinoma. The tumour was oestrogen receptor and progesterone receptor positive and with axillary node involvement. It was not possible to perform a radical operation of the axilla. She was diagnosed with liver metastases by ultrasound before the initiation of chemotherapy. Bone scan and x-ray of the chest was normal. HER-2/neu overexpression 3+ was measured in this patient by immunohistochemistry using the Hercep test.

The patient commenced treatment with weekly trastuzumab. After seven weeks of treatment staging CT scan showed disease progression in the liver. Paclitaxel was added to the trastuzumab regime. The first treatment was given during hospitalisation and with 150 grams of glucose intravenously in order to depress gluconeogenesis. It was decided not to use antihistamines because they are all degraded via the cytochrome P450 system. Initially there was regression of the liver metastases, but later there was progression. It was decided to change the regime to epirubicin in reduced dose. After six regimes of epirubicin administered every three weeks there was again progression of her disease. A bone scan showed bone metastases to the spine and pelvis. Due to the pain she received radiotherapy with a single fraction of 8 Gy to L4-S1. Ionising irradiation is thought to be safe [6]. Pain was treated with morphine and ketobemidone.

Treatment was changed to trastuzumab and vinorelbine [7]. The patient was hospitalised with febrile neutropenia after the second treatment. Her infectious disease was treated with intravenous antibiotics of pentrexyl and gentamicin. Ultrasound of the liver showed progression and the treatment was changed to letrozole 2.5 mg.

She was hospitalised 1 year and 9 months after diagnosed with breast cancer with terminal disease, cerebral symptoms, nausea and vomiting. A CT and MR-scan of cerebrum showed no metastases. The patient was transferred to the department of endocrinology at a nearby university hospital. The urine was analysed for porphyrins but the patient was found not to be in an acute attack of porphyria. In accordance to the wish of her family and herself she was referred to home, where she died six days later of progressive cancer disease (three weeks after letrozole treatment was initiated).

This patient experienced no attacks of porphyria despite an antineoplastic treatment primary focusing on her breast cancer. This patient was treated with epirubicin, trastuzumab as monotherapy and trastuzumab in combination with paclitaxel and later vinorelbine. The treatment was well tolerated with no further increase in porphobilionogen and 5-aminolaevulinic acid in the urine. Porphobilinogen was slightly increased in our patient at baseline and during treatment. These regimes are all well documented regimes in the treatment of breast cancer. This patient suffered no porphyric attack but had an aggressive, Her2 positive breast cancer and died of her progressive disease.

The standard treatment for advanced breast cancer at the time of admittance (2003) at our institution would have been cyclophosphamide, epirubicin and fluorouracil if the patient had not had porphyria. But cyclophosphamide is an unsure drug to use with porphyria. In one case report of a patient with acute intermittent porphyria it triggered a porphyric crisis, but the drug was given in combination with doxorubicin and carboplatin and the possible mechanism could be febrile neutropenia, [8], in other cases it has been well tolerated [9,10]. Trastuzumab was considered because the patient had Her2 positive disease. Trastuzumab has no metabolites and need no antiemetic treatment. There was no information available at that time, but it was theoretically found to be safe for patients with porphyria. After progression after chemotherapy the patient was treated with letrozole. Tamoxifen was chosen not to be used because the possibility of inducing porphyric crisis [10]. Furthermore letrozole offer efficacy advantages over tamoxifen [11].

The treatment of patients with underlying porphyria is complicated by the fact that many drugs may precipate acute porphyric crises. There was no available data on vinorelbine, paclitaxel or trastuzimab and porphyria by a search by Pubmed. Extensive lists of such drugs are available on the Internet and are revised on a regular basis. One from South Africa: http://web.uct.ac.za/depts/porphyria/, from Australia: http://www.uq.edu.au/porphyria/, from Norway: http://www.drugs-porphyria.org/ and from Europe: http://www.porphyria-europe.com/.

However there are individual differences between patients with acute porphyria for the tolerance to a drug, many patients have been treated with possible porphyrinogenic drugs without having an attack. There is very limited published literature on the use of cytotoxic drugs in patients with porphyria.

This case further strengthens the view that several cytotoxics can be administered safely in prophyric patients. The presence of hepatic porphyria should not discourage chemotherapy for the treatment of neoplastic disease. As the reaction of a patient with acute intermittent porphyria to certain drugs cannot be predicted, monitoring urinary porphyrin excretion may help to prevent porphyritic attacks.

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