Biological and clinical evaluation of Lanreotide (BIM 23014), a somatostatin analogue, in the treatment of advanced breast cancer

A pilot study by the I.T.M.O. Group

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Summary

Biological data support the development of clinical trials designed to evaluate the activity of somatostatin (SMS) analogues in advanced breast cancer (ABC). Although previous clinical trials have failed to show antitumor activity, various factors may have biased their results. In an attempt to improve our understanding of the role of SMS analogues in ABC, 10 patients with favourable prognostic factors and who had not been heavily pretreated for advanced disease were treated with lanreotide 30 mg i.m. fortnightly (depot formulation). Blood samples were periodically taken to evaluate the effect of the drug on growth hormone (GH) and insulin-like growth factor 1 (IGF-1) and to determine drug serum levels. Although the drug was well tolerated, no clinical activity was observed. Serum GH and IGF-1 levels were not properly suppressed over time and drug serum concentrations fluctuated widely. In conclusion, SMS analogues cannot be recommended even as palliative treatment of ABC. Further studies should be undertaken to investigate the effect of higher drug doses, given subcutaneously or by means of continuous infusion, in suppressing GH and IGF-1 serum levels.

Introduction

Over the last few years, laboratory data have shown that the growth of breast cancer cells is locally regulated by a series of molecules acting through the autocrine and paracrine pathways [1, 2], and this has given a substantial impulse to the search for new drugs capable of interfering with the local regulation of breast cancer cells. In particular, it has been shown that insulin-like growth factor-1 (IGF-1), a peptide produced by the tumoral stroma, can stimulate the growth of breast cancer cells by means of specific receptors located within the membrane of tumoral cells [3]; these receptors are frequently found in estrogen receptor positive tumors [4]. Furthermore, it has been suggested that median plasma IGF-1 concentration is higher in a primary breast cancer population than in a control group [5]. However, recent data have also shown that breast cancer cell proliferation is a very complex mechanism involving both of the IGFs so far isolated, IGF binding proteins, and other molecules [6, 7].

Somatostatin (SMS), a tetra-decapeptide produced in many parts of the body, is capable of inhibiting the secretion of growth hormone (GH) and consequently of IGF-1, but the fact that its half-life is only about 3 min has hampered the development of clinical trials [8, 9]. However, the chemical syn-
thesis of SMS analogues with a longer half-life, which are more capable of inhibiting GH secretion than the original peptide, has recently prompted clinical trials aimed at evaluating these molecules in various diseases [10]. Both octreotide and lanreotide, the first two analogues available for clinical trials, have been shown to be active in the treatment of acromegaly, and lead to a significant reduction in serum GH and IGF-1 levels [11, 12]. These endocrinal effects have been shown using thrice-daily subcutaneous doses ranging from 0.1 to 0.5 mg, or continuous intravenous infusion [13].

In addition to the suppression of serum IGF-1 levels observed in the treatment of acromegaly, the cytostatic effect of both SMS and its analogues on human breast cancer cells has further supported the development of clinical trials in the treatment of advanced breast cancer [14]. The antiproliferative activity is probably mediated by specific SMS receptors located within the membrane of tumor cells [14, 15]; indeed SMS, octreotide, and lanreotide binding receptors have been found in 15–90% of human breast tumor samples [16, 17].

Previous clinical trials have not found that either of the analogues has any significant activity in the treatment of advanced breast cancer [18–22]. However, the inability to draw any definitive conclusion concerning their anti-tumor activity may be due to the fact that the enrolled patients were heavily pre-treated for their metastatic disease [19, 21] and/or that the SMS analogues were associated with other anti-tumor drugs [18, 22].

It therefore seemed reasonable to test single-agent therapy with lanreotide in a pilot study involving patients with favourable prognostic factors. Lanreotide was chosen instead of octreotide because of the availability of an intramuscular depot formulation to be given weekly. Previous studies using depot lanreotide 30 mg i.m. fortnightly have shown its optimal activity in suppressing serum GH and IGF-1 levels in patients with acromegaly [23].

In addition to evaluating the drug’s clinical efficacy, the study protocol also included a biological section aimed at evaluating the activity of depot lanreotide in suppressing serum GH and IGF-1 levels and determining serum drug levels at pre-established times.

Patients and methods

Eligibility criteria

Pre or postmenopausal advanced breast cancer patients who were ER and/or PgR positive and who had measurable lesions were considered eligible for this treatment program. Lanreotide was given as either first or second-line treatment (in the latter case, only if the first-line consisted of hormonal therapy). The patients may have received any form of neo-adjuvant or adjuvant medical treatment and previous or concomitant radiotherapy (in the case of multiple measurable lesions) was also admitted. A PS (ECOG) of 0–1 and a disease-free interval >12 months were required; in the case of patients whose ER/PgR status was unknown a disease-free interval ≥24 months was necessary. Informed consent was obtained from each patient, and the trial received local Ethical Committee approval.

Staging procedures and treatment plan

Baseline staging included physical examination, chest X-ray, bone X-ray, liver ultrasound, complete hemogram, and blood chemistry survey. After proper tumor staging, the patients were treated with lanreotide 30 mg i.m. fortnightly. The drug was administered by nurses at the time of their outpatient visit (i.e. every two weeks). The lanreotide (Ipsen Biotech) was a lyophilized white powder (30 mg per vial) to be reconstituted in a solvent containing carboxymethyl cellulose sodium, polysorbate 80, mannitol, and water for injection (2 g.). Response was evaluated according to WHO/UICC criteria [24] every three months by repeating the baseline examinations; in the case of progressive disease, the patients were transferred to conventional therapy, otherwise lanreotide treatment was continued for a further three months. In case the symptoms or signs noted during the regular fortnightly visit suggested an early or inter-evaluation progression, further exams were promptly performed and, if progressive disease was documented, the patients were switched to conventional treatment.