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CLINICAL TRIAL REPORT

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Phase I–II study of the somatostatin analogue lanreotide in hormone-refractory prostate cancer

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Abstract Lanreotide (BIM 32014), a somatulin analogue, was found to be as effective as castration in a rat prostate tumor model. Therapeutic benefit was also demonstrated in the hormone-resistant phase of this tumor model. The activity of lanreotide may be due to a reduction in the levels of growth factors such as insulin growth factor 1 (IGF1). A total of 30 patients with hormone-refractory prostate cancer were treated with a slow-release formulation of lanreotide. The mean age was 71 years. Patients were treated with one intramuscular injection of 30 mg BIM 23014 once a week and were followed for prostate-specific antigen (PSA) level evolution until disease progression or WHO grade 3 or 4 toxicity and for survival. The patients were treated for a mean duration of 12 weeks (range, 2–60 weeks). The performance status and bone pain were improved in 40% and 35% of patients, respectively. In all, 20% of the patients had a decrease of $\geq 50\%$ in PSA levels and 16% showed a stabilization. The biological response was correlated with clinical improvement. The 1-year global survival rate was 72%, with the rate being 89% in the group of patients who were responders on PSA plasma level and 64% in patients with progressive disease. The response duration ranged from 16 to 60 weeks. Toxicity was minor, with transient grade I digestive side effects being noted in a few patients. Lanreotide given at 30 mg once a week to patients with metastatic hormone-refractory prostate cancer was well tolerated. The response rate was higher than that reported in recent published series. Higher doses of lanreotide should be evaluated.

Key words Prostate cancer · Hormone-refractory status · Somostatin analogues

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Introduction

Prostatic carcinoma is the most common malignancy in elderly men. Treatment of the metastatic cancer with hormone therapy temporarily controls cancer symptoms in 70%–80% of patients [7]. Nevertheless, after a remission period, a relapse of the disease invariably occurs. After progression, no effective treatment is available. The median survival is about 6 months in duration; therefore, progressive metastatic hormone-refractory disease remains a therapeutic challenge. Recent advances in prostate cancer research support the role of autocrine/paracrine growth factor in tumor progression, suggesting the potential effectiveness of growth inhibitors such as somatostatin or its analogues [8, 17]. Particularly the somatostatin analogue lanreotide (BIM 23014) was found to be as effective as castration in the R 3327-H rat prostate tumor model [2]. Therapeutic benefit was also demonstrated in the hormone-resistant phase of this tumor following castration [2]. Moreover, clinical tumor response was observed in advanced breast cancer [18]. The activity of lanreotide may be due in part to a reduction in levels of endocrine (insulin growth factor 1) [17] and paracrine growth factor products. We report herein the results of a French multicenter pilot study performed between 1991 and 1993 to assess the efficacy of lanreotide on progressive metastatic hormone-refractory prostate cancer.

Patients and methods

Patient selection

From November 1991 through January 1993, 30 patients with histologically confirmed prostate cancer and hormone-refractory metastatic status according to National Prostatic Cancer Project (NPCP) criteria were included. The patients characteristics are reported in Table 1. In all, 18 patients (60%) had been treated with pelvic radiotherapy and 3 patients (10%), with radical prostatectomy. All patients were treated with hormone therapy as follows: orchidectomy, 15 patients (50%); analogues, 21 patients (70%); antiandrogens, 26 patients (87%); estrogens, 3 patients (10%); and aminoglutethimide, 2 patients (6%). The numbers of previous hormonal regimens were 1 in 4 patients (13%), 2 in 16 patients (55%), 3 in 9 patients (35%), and 4 in only 1 patient. In all, 5 patients (16%) had previously been treated with chemotherapy. The age ranged from 49 to 85 (mean, 71) years. The Eastern Cooperative Oncology Group (ECOG) performance status (PS), was 0 in 75 patients, 1 in 9 patients, 2 in 3 patients, 3 in 2 patients, and 4 in 1 patient. Nine patients complained of dysuria related to a persistent primary tumor. Altogether, 17 patients (57%) presented with bone pain, which was slight in 4 cases, moderate in 6 cases, and severe in 6 cases requiring opioid treatments. The mean interval between bone metastasis occurrence and the beginning of lanreotide administration was 25 (range, 1–91) months. There was no patient with visceral metastasis and no patient had hypercalcemia. All patients had basal prostate-specific antigen (PSA) plasma levels above 10 ng/ml (mean, 402 $\pm$ 1016 ng/ml, range, 10.3–5700 ng/ml). Testosterone plasma levels were assessed in 14 patients, 12 of whom had castration levels. Exclusion criteria were life-threatening renal, liver, or cardiac disease or other malignancies, as well as diabetes because of the risk of lanreotide-induced hyperglycemia.

Treatment

Eligible patients received a slow-release formulation of lanreotide (30 mg) given once a week by intramuscular injection. Sites of injection were frequently changed and were looked after closely. Treatment was continued for 6 months, and patients who achieved a partial remission or remained stable continued receiving treatment until disease progression or death. Medical castration with luteinizing hormone-releasing hormone (LHRH) agonists was maintained throughout the study for previously treated patients. Initiation of therapy by antiandrogens, chemotherapy, or estrogen, therapy was not allowed during the study. The treatment was discontinued in cases of patients refusal, acute life-threatening grade 3 or 4 toxicity according to WHO criteria, or progression of the disease.

Table 1 Characteristics of the 30 patients entered in the present study

	Patients (*n*)
Prior chemotherapy	5
Prior radiotherapy	18
Prior hormonal treatment	30
Orchidectomy	15
LH-RH agonists	21
Antiandrogens	26
Estrogens	3
Number of line of treatment before lanreotide:	
1	4
2	16
3	9
4	1
ECOG performance status:	
0	15
≥ 1	15
Pain	17
Dysuria	9

Investigations

Patients were assessed before initiation of the treatment, at day 14, at 1 month, and then every month for PS, pain evaluation, urinary symptoms, physical examination, complete blood count (CBC), biochemistry, PSA levels (radioimmunoassay), and testosterone plasma levels. A bone scan and radiological investigations were performed at study entry and every 3 months according to the clinical evolution. Informed written consent was obtained from each patient before treatment.

Assessments

Therapeutic efficacy was assessed by ECOG PS, bone pain intensity, urinary symptoms, and PSA doses. An objective response was defined as a decrease of 50% or more in the PSA plasma level. A complete response was defined as normalization of PSA plasma levels along with the complete disappearance of all clinical symptoms. Progression was defined as an increase of 25% or more in PSA plasma levels. A decrease of 25% or more and less than 50% was considered as stabilization.

Statistical analysis

Analysis was performed in March 1994. Survival was evaluated from the date of inclusion into the study. Survival curves were calculated using the actuarial method and were compared with the log-rank test.

Results

From three French medical centers, 30 patients were included in the study. All patients were evaluable for response and toxicity. The mean duration of treatment was 12 weeks (range, 2–60 weeks). Five patients progressed rapidly and were withdrawn from the study within the 1st month of treatment. One patient received only two injections because of the occurrence of severe coagulopathy.

Response

Among the 15 patients with a basal PS of > 0, the PS improved in 6 patients (40%) and remained unchanged in 6 subjects; aggravation was noted in 3 patients. Among the 17 patients who presented with bone pain, this symptom resolved in 5 patients, was improved in 1 patient (response, 35%), and remained unchanged in 8 cases; aggravation was observed in 3 patients. This symptom appeared during the study in 3 cases. Among

the 9 patients who presented with dysuria, improvement was seen in 6 patients; dysuria was unchanged in 1 patient and worsened in another case. This symptom appeared during the study in 1 patient.

Among the 25 patients who received at least 6 weeks of lanreotide treatment, a decrease of $\geq 50\%$ in the pretreatment PSA plasma level was observed in 5 patients (20%). For these patients, the PSA plasma levels were 24, 120, 264, 285, and 425 ng/ml before treatment; they decreased to 2.1, 38, 95, 106, and 58 ng/ml, respectively, during the treatment. The PSA plasma levels remained stable in 4 patients. A bone scan showed total relief at 5 months after the start of treatment in 1 patient. The biological response was correlated with clinical improvement. Among the 5 patients who responded on PSA level, the ECOG PS improved in 3 of 4 subjects with a PS of ≥ 1 and was unchanged in 1 case.

Survival

At the time of the analysis, 12 patients had died with progressive disease and 18 patients remained alive. The 1-year global survival rate was 72% (see Fig. 1). As shown in Fig. 2, the 1-year survival was 89% in responders on PSA level and 64% in patients with progressive disease ($P < 0.0003$). The mean survival duration was 71 ± 16 weeks in responders and 48 ± 28 weeks in nonresponders. There was no significant difference in the baseline clinical characteristics or in the initial levels of PSA between these two groups.

Tolerance

Toxicity was minimal. Transient WHO grade I nausea, diarrhea, and abdominal pain were reported by 4, 10 and 5 patients, respectively. Local pain at the site of injection was reported by two patients. No diabetes was seen.

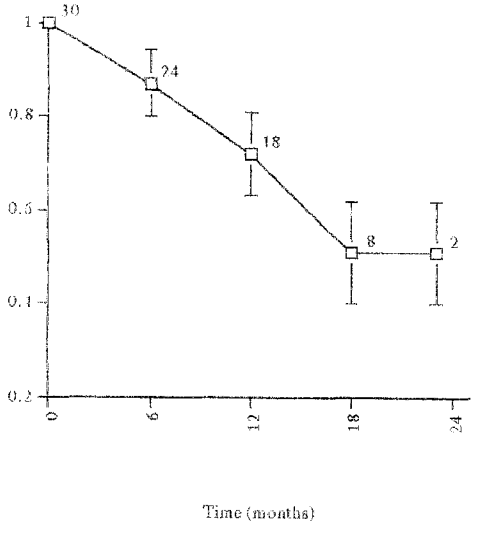

Fig. 1 Overall survival for all patients

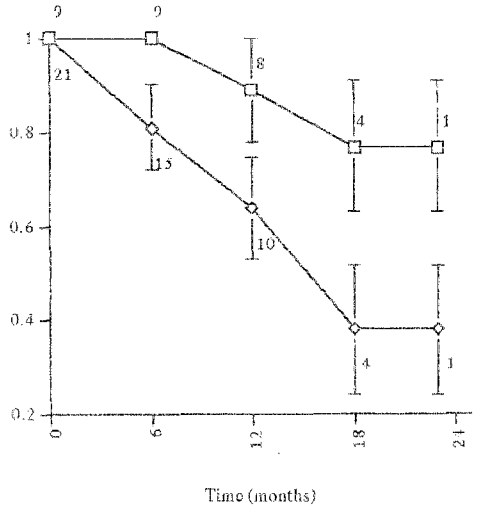

Fig. 2 Comparison of overall survival between responders (□–□) and nonresponders (◇–◇)

Discussion

In 1973, Brazeau and Vale [3] isolated somatostatin, an inhibitor of growth hormone from hypothalamic cells. Subsequently, somatostatin analogues with a longer half-life such as lanreotide were developed [1]. The efficacy of these somatostatin analogues is related to their interactions with type I or II somatostatin receptors [16]. Anticancer effects of somatostatin analogues, observed in vitro and in vivo, involve complex mechanisms: angiogenesis inhibition and direct inhibition of cell growth [5, 10]. Furthermore, plasma concentrations of some growth factors such as Somatomedin C (insulin growth factor, IGF1) and epidermal growth factor (EGF), which stimulate the growth of some types of tumor cells such as mammary or pancreatic tumor cells, may decrease during chronic treatment [12]. Moreover, somatostatin as well as its specific receptors have been detected in the prostate of rats and humans [15]. The physiological significance of somatostatin in the male reproductive system remains unknown. However, its ubiquitous and broad spectrum of biological activities indicate that somatostatin is an endogenous regulatory hormone of growth factor and suggest that somatostatin may inhibit the growth of prostate tumors. This antiproliferative effect has been confirmed in vivo in the Dunning R-3327H prostatic tumor implanted in male rats, notably in the hormone-refractory phase of this tumor following castration [2]. In this model, a supra-additive effect was observed with a lanreotide plus LHRH analogue combination.

These promising experimental data led us to start a pilot clinical study in patients with evolutive hormone-refractory prostate cancer. Therapeutic approaches capable of controlling pain and improving the quality of life without producing major side effects are somewhat restricted. An antitumor response induced by chemotherapy is generally limited and of short duration in prostate cancer [11]. Moreover, because of its mediocre tolerance, chemotherapy is not always feasible in such elderly patients. Only a few series on patients treated with somatostatin analogues for metastatic prostate cancer have been published. A pain decrease was observed in 5 patients after intrathecal administration, and a posologic reduction in opioid treatment was possible for 3 of 11 patients treated with subcutaneous injections of octreotide [9, 14]. For Dupond et al. [4], the clinical efficacy of octreotide combined with bromocriptine was limited, although a significant decrease in plasma IGF1 levels was seen. A recent phase II study including 25 patients treated with lanreotide mentioned normalization of PSA levels for 2 patients and stabilization of disease in 3 additional patients [13]. The potential efficacy according to clinical criteria was not specified in this trial.

In our series, the ECOG PS was improved and pain was relieved in more than one-third of the patients. These clinical results were correlated with a decrease in PSA levels. Kelly et al, [6] recently reported the prognostic value of a PSA-level decrease for median survival in metastatic hormone-refractory cancer after treatment, underlining the role of PSA as an objective criterion of response. We observed a clinical antitumor effect of lanreotide after the failure of successive "classic" hormonal treatments and a survival benefit for responders. We did not observe any difference in baseline clinical characteristics or in initial levels of PSA between responders and nonresponders and thus failed to demonstate prognostic criteria of response. Lanreotide was well tolerated; gastrointestinal side effects were mild and transient. Moreover, the slow-release formulation of the drug, allowing weekly administration in ambulatory patients, is simple to use and nonconstraining. A phase II trial including patients with a good performance status who have received only one line of hormonal treatment could help to define better the place of this somatostatin analogue in metastatic prostate cancer.

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