ELSEVIER

European Journal of Cancer 41 (2005) 694–701

European Journal of Cancer

www.ejconline.com

Effects of tamoxifen and octreotide LAR on the IGF-system compared with tamoxifen monotherapy

S.I. Helle [a], W. Mietlowski [b], J.P. Guastalla [c], I. Szakolczai [d], E. Bajetta [e], H. Sommer [f], E. Baltali [g], T. Pinter [h], M. Csepreghy [i], L. Ottestad [j], C. Boni [k], C. Bryce [l], J.G.M. Klijn [m], P.E. Lønning [a,*]

[a] *Department of Medicine, Section of Oncology, Haukeland University Hospital, N-5021 Bergen, Norway*
[b] *Novartis Pharmaceutical Corporation, East Hanover, New Jersey, USA*
[c] *Centre Leon Bernard, Lyon, France*
[d] *National Institute of Oncology, Budapest, Hungary*
[e] *Instituto Nazionale Tumori, Milan, Italy*
[f] *Universitats-Frauenklinik, Munich, Germany*
[g] *Hacettepe University Medical School, Oncology Institute, Ankara, Turkey*
[h] *Petz Aladar County Hospital, Gyor, Hungary*
[i] *Uzoki Hospital, Budapest, Hungary*
[j] *Det Norske Radiumhospital, Oslo, Norway*
[k] *Arcispedale S. Maria Nuova, Reggio-Emilia, Italy*
[l] *Vancouver Cancer Centre, Vancouver, Canada*
[m] *Daniel Den Hoed Klinick and Academic Hospital, Rotterdam, Netherlands*

Received 11 May 2004; received in revised form 23 November 2004; accepted 16 December 2004
Available online 21 January 2005

Abstract

The insulin-like growth factor (IGF)-system was evaluated in 150 breast cancer patients participating in a randomised phase III trial comparing octreotide pamoate and tamoxifen with tamoxifen + placebo. Alterations in the IGF-system in the two treatment arms and individual changes with respect to outcome were compared. Serum IGF-I and -II, free IGF-I, and insulin-like growth factor binding protein 1–3 (IGFBP1-3) were measured by radioimmmunoassay (RIA)/immunoradiometric assay (IRMA) and IGFBPs by Western ligand blots (WLB) before and during treatment. Combined treatment caused a higher increase in IGFBP-1 and larger suppression of total and free IGF-I, IGF-II, and IGFBP-3 ($P < 0.01$ for all), but less suppression of IGFBP-2 ($P < 0.05$) compared with tamoxifen monotherapy. An increase in IGFBP-2 $\geqslant 25\%$ was associated with decreased progression-free survival (PFS) in the total patient population and combined treatment group. Similar response rates and time to progression in the treatment arms suggests moderate suppression of circulating IGF-I has no influence on clinical outcome.

Keywords: Breast cancer; IGF-I; IGFBP-2; Tamoxifen; Octreotide

1. Introduction

Currently, ''targeted therapies'' against growth factor receptors receive much attention as treatment of solid tumours in general and breast cancer in particular. The antitumour effects of drugs like imatinib, cetuximab

* Corresponding author. Tel.: +47 55 972010; fax: +47 55 972046.
E-mail address: per.lonning@helse-bergen.no (P.E. Lønning).

0959-8049/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2004.12.015

and trastuzumab inhibiting receptors of the epidermal growth factor family in different tumours have provided "proof-of-principle" evidence revealing the therapeutic potential of growth factor receptor targeting [1]. Insulin-like growth factor (IGF)-I is one of the most potent mitogens to breast cancer cell lines *in vitro*, suggesting this system could be a suitable target in breast cancer [2]. High serum levels of IGF-I have been reported to be a risk factor for breast cancer development in healthy premenopausal women [3], but the effect of alterations in its serum levels on manifest breast cancer is incompletely understood.

A strategy of particular interest involves the combination of an anti-oestrogen and a somatostatin analogue. Somatostatin analogues may inhibit breast cancer cell proliferation *in vitro* [4,5]. Further to binding to the oestrogen receptor, tamoxifen [6], similar to somatostatin analogues [7], has been shown to suppress plasma IGF-I in humans. Oestrogens and IGF-I have been found to have synergistic effects on breast cancer cell growth *in vitro* [8,9], and there is evidence that tamoxifen and somatostatin analogues may have additive antitumour effects in animal models [4,10]. The effects of tamoxifen and somatostatin analogues are also complementary, as tamoxifen has a direct effect on hepatic IGF-synthesis,while somatostatin analogues act through suppression of growth hormone [7].

Recent studies found an additive effect of tamoxifen and somatostatin analogues in suppressing serum IGF-I levels without enhancing response rates or survival compared with tamoxifen monotherapy [11,12]. This lack of clinical benefit could potentially be due to the short plasma half-life of the analogue [13], resulting in insufficient through-levels of octreotide. In this randomised, double-blind phase III study, tamoxifen was combined with octreotide pamoate (OP-LAR), a sustained-release form producing stable trough-levels [7], and compared with tamoxifen plus placebo as first-line therapy in women with local recurrent or metastatic breast cancer who were positive for the oestrogen and/or progesterone receptor. The clinical results of this study has been given in a preliminary report in Ref. [14]. The main purpose of this study was to compare the effects of the different arms on the IGF-system in the subgroup of patients with available blood samples before and during treatment, and to establish whether any alterations in IGF-parameters were related to treatment response and outcome.

2. Patients and methods

2.1. Patients and protocol

The study was designed as a randomised double-blind placebo controlled phase III multicentre trial comparing the somatostatin analogue SMS 201-995 pa LAR (octreotide pamoate) plus tamoxifen versus tamoxifen plus placebo as first-line therapy in women with locally recurrent or metastatic oestrogen- and/or progesterone receptor-positive breast cancer. Both groups received tamoxifen 20 mg once daily and either octreotide pamoate given as a 160-mg intramuscular injection every 2 weeks for the first 6 weeks and thereafter every 4 weeks or placebo injections at the same time-points. The study was approved by the Ethical Committee at each institution, and each patient provided written informed consent. While the protocol planned for 416 patients to be enrolled, recruitment was terminated prematurely at a protocol-planned interim analysis for futility (<5% chance of a significant difference at the final analysis given the interim results). Of 263 patients randomised and actually treated, fasting blood samples obtained prior to treatment and on day 43 were available from 150 patients (octreotide: $n = 69$, placebo: $n = 81$). There was a reduction in the number of patients in the two groups compared to randomisation, as patients had to have at least 1 blood sample collected during therapy to compare values with baseline. Demographics and tumour characteristics of these patients are included in Table 1.

2.2. Blood sampling

Patient had fasting (8 h) blood samples obtained before study, at day 43 and every 16 weeks during the first year on treatment, and subsequently every 26 weeks. Serum was separated by centrifugation and stored at −20 °C until analysis.

2.3. Materials

Human recombinant IGF-I and IGF-II were purchased from GroPep (Adelaide, Australia). IGF-I and IGF -II were iodinated using the chloramine-T method. Labelled peptide was separated from non-incorporated ^{125}I by AcA 202 columns (BioSepra, Villeneuve, France) using 1×40 cm columns.

2.4. Assays

Serum levels of IGF-I, IGF-II, Western ligand blotting for insulin-like growth factor binding protein (IGFBP) profile and immunoblots for IGFBP-3 were measured according to methods reported elsewhere in Ref. [15]. Free IGF-I and IGFBP1-3 were measured by commercial kits immunoradiometric assay/radioimmunoassay (IRMA/RIA) from Diagnostic System Laboratories (Webster, TX) according to the manufacturer's instruction. IGFBP-3 protease activity was measured indirectly as "IGFBP-3 fragmentation", defined as the ratio of the major IGFBP-3 fragment (30 kDa) to total IGFBP-3 evaluated by densitometric scanning on

Table 1
Demographics and tumour characteristics for the 150 patients included in the study

	Oncolar + tamoxifen ($n = 69$)	Tamoxifen + placebo ($n = 81$)
Age in years median (range)	65 (33–84)	60 (30–82)
Menopausal status		
Pre-(age < 50 years)	7 (10%)	19 (24%)
Post-(age > 50 years)	62 (90%)	62 (77%)
Baseline Karnofsky performance status		
60–70	8 (12%)	10 (12%)
80–100	61 (88%)	71 (88%)
Dominant disease site		
Visceral	26 (38%)	38 (47%)
Bone	27 (39%)	24 (30%)
Soft tissue	16 (23%)	19 (24%)
Prior adjuvant tamoxifen		
Yes	10 (15%)	17 (21%)
No	59 (86%)	64 (79%)

immunoblots [15]. Treatment arm allocation and clinical outcome for each patient was unknown to the analysts.

2.5. Statistical analysis

All IGF-parameters were previously found to fit well to a log-normal distribution [16]. Thus, parameters are given as their geometric mean value with 95% Confidence Intervals of the mean. Potential differences with respect to the effects of the two treatment arms on the IGF-parameters were evaluated using analysis of variance. The Bonferroni–Holm sequential test procedure was used to adjust for multiple comparisons on Day 43 [17]. Due to the reduced sample size at later timepoints, no inferential testing was performed beyond Day 43. We used a stratified (for adjuvant tamoxifen treatment, dominant disease site, menopausal status, Karnofsky performance status, and measurability of disease) Cox proportional hazards model to identify a set of baseline prognostic factors at the 10% level using backward elimination. We then added the IGF variables at baseline and at day 43 and computed the statistical significance of the added IGF covariates using the likelihood ratio test. If any IGF covariates were significant at the 5% level, potential treatment × covariate interaction was tested at the 10% level of significance. Since the parameter estimates for the two log ligand IGFBP-2 variables were similar in magnitude, but different in sign (1.0494 at day 43 and −0.8236 at baseline), an analysis based on percentage change from the baseline should approximate the analysis based on the Cox model, but may facilitate clinical interpretation.

The cut-off points for IGFBP-2 for the percentage change from baseline analysis were chosen arbitrarily, as there are limited data to support any specific limits. However, as a 25% decrease of IGFBP-2 approximated the median change from baseline, this criterion was used to define one category. By symmetry, a 25% or greater increase from baseline was used to define another category and less than a 25% change from baseline defined a third category.

3. Results

3.1. Clinical data

No significant differences were recorded in the response rate (26% for tamoxifen + OP-LAR versus 31% for tamoxifen + placebo) or median progression-free survival (PFS): 6.9 months for OP-LAR + tamoxifen versus 6.7 months for tamoxifen + placebo) for the 150 patients with measured IGF-parameters. The small difference in PFS between the total group of patients in the clinical study (median PFS: 6.2 months for the placebo group vs. 5.6 months for the OP-LAR group) and the patients available for analysis of IGF-parameters is due to exclusion of patients for whom on-treatment samples were lacking, mainly due to termination of therapy before Day 43 (15).

3.2. Effects on IGF-parameters

Alterations in the different IGF-parameters at Day 43 are given in Table 2 and later intervals are included in Figs. 1(a) and (b)). A significant decrease in the serum levels of IGF-I, free IGF-I and an increase in IGFBP-1 were observed among the patients in both treatment groups. However, we observed significantly lower levels of IGF-I, free IGF-I, IGF-II and IGFBP-3 and higher IGFBP-1 levels ($P < 0.05$ for all) during treatment with OP-LAR + tamoxifen compared with tamoxifen and placebo. There was also a significant decrease in IGFBP-3 evaluated by Western ligand blot in the

Table 2
Measured levels (with 95% Confidence Intervals of the mean) of IGF-parameters at baseline and percentage of pretreatment values (with 95% Confidence Intervals of the mean) at various treatment intervals for both treatment arms

	Baseline (measures values)		Day 43 (% of baseline)	
	TAM + placebo, $n = 81$	TAM + octreotide, $n = 69$	TAM + placebo, $n = 81$	TAM + octreotide, $n = 69$
IGF-I[a]	14.9 (13.1–16.3)	13.3 (12.0–14.8)	74 (70–79)[d]	47 (45–51)[c,d]
Free-IGF-I[a]	0.26(0.21–0.32)	0.29(0.23–0.36)	61(55–68)[d]	29(25–34)[c,d]
IGF-II[a]	80.2 (76.0–84.6)	75.1 (69.5–81.1)	102 (98–107)	88 (83–93)[c,d]
IGFBP-1[a]	1.13 (0.95–1.35)	1.32 (1.08–1.62)	154 (130–181)[d]	216 (184–254)[c,d]
IGFBP-2[a]	22.4 (20.2–24.8)	23.8 (21.3–26.7)	77 (71–83)[d]	98 (90–107)[c]
IGFBP-3[a]	167 (153–182)	167 (153–182)	98 (92–103)	83 (77–89)[c,d]
IGFBP-3[b] Protease	0.52 (0.49–0.55)	0.53 (0.49–0.58)	99 (94–104)	101 (97–106)
IGFBP-2 WLB[e]	9.3 (7.6–11.3)	11.7 (9.2–15.0)	68 (63–75)[d]	83 (73–94)[d]
IGFBP-3 WLB[e]	83.8 (67.7–103.8)	94.3 (76.6–116.0)	105 (92–120)	92 (82–103)

n = number of observations.
[a] nmol/L.
[b] Fragmented to total IGFBP-3 on immunoblots.
[c] Significant difference between treatment arms ($P < 0.01$ for all except IGFBP-2. $P < 0.05$) analysis of variance adjusted for multiple comparison by Bonferroni–Holms sequential test.
[d] Significant difference compared with pretreatment levels.
[e] Densitometric scanning, arbitrary units.

OP-LAR treatment group ($P < 0.05$), which paralleled the changes in immunoreactive IGFBP-3. No correlation between individual suppression of IGF-I or free IGF-I and tumour response was recorded within the groups. IGFBP-2 (immunoreactive and Western ligand blot – IGFBP-2WLB) was significantly reduced during treatment with tamoxifen, but not during combined therapy. There was significantly less suppression of immunoreactive IGFBP-2 in the OP-LAR group compared to tamoxifen + placebo ($P < 0.05$).

3.3. The IGF-system and prognosis

Cox's proportional hazards model indicated that baseline as well as Day 43 levels of IGFBP-2WLB were significant prognostic factors for PFS, even after adjusting for stratification factors ($P < 0.0001$) (Table 3). Noteworthy, an increase in IGFBP-2 (measured by WLB) $\geqslant 25\%$ was associated with a shorter time to progression in the OP-LAR group ($P < 0.025$) and the total patient population ($P < 0.005$) (Fig. 2), but not in the tamoxifen + placebo group. This may be due to the low number of patients in the tamoxifen + placebo group who had $\geqslant 25\%$ increase in IGFBP-2 ($n = 4$).

4. Discussion

Somatostatin analogues and tamoxifen are both known to influence the IGF-system *in vivo*. Somatostatin suppresses growth hormone [18], causing a drop in circulating IGF-I, an increase in IGFBP-1 and a slight reduction in immunoreactive IGFBP-3 [7]. Tamoxifen has been shown to suppress plasma IGF-I and to increase circulating IGFBP-1 [19]. Thus, an additive effect on the IGF-system by combining these drugs has been postulated.

To our knowledge, this is the first study reporting the effects of a long-acting somatostatin analogue in concert with tamoxifen versus tamoxifen monotherapy on free IGF-I and IGF-binding protein status in breast cancer patients. The study reveals significantly better suppression of free and total IGF-I, IGF-II, and IGFBP-3 and a larger increase in IGFBP-1 by combined treatment versus monotherapy. Others have found a similar effect on total IGF-I following administration of octreotide as a non-depot formulation in concert with tamoxifen [11]. Interestingly, the magnitude of the alterations in the IGF-parameters is not much different from what was previously reported during treatment with OP-LAR monotherapy in patients with advanced pancreatic and gastrointestinal tumours [7]. The decrease in IGF-II and IGFBP-3 in patients receiving combined therapy in this study, but also in studies administering OP-LAR monotherapy [7], contrasts the findings in patients treated with tamoxifen monotherapy in this study as well as others [20], and suggests that these effects could be due to somatostatin-induced suppression of growth hormone [18].

The finding of no difference in clinical outcome between the treatment arms, despite a difference in suppression of serum total and free IGF-I, is of interest. In addition, the lack of any correlation between the degree of IGF-I suppression and time to progression or survival within any of the treatment arms supports the hypothesis that suppression of serum IGF-I and alterations in IGF-binding proteins within the range reported in this study has little effect on outcome in women suffering from advanced breast cancer. This finding does not exclude an effect of serum IGF-I on the growth of sub-

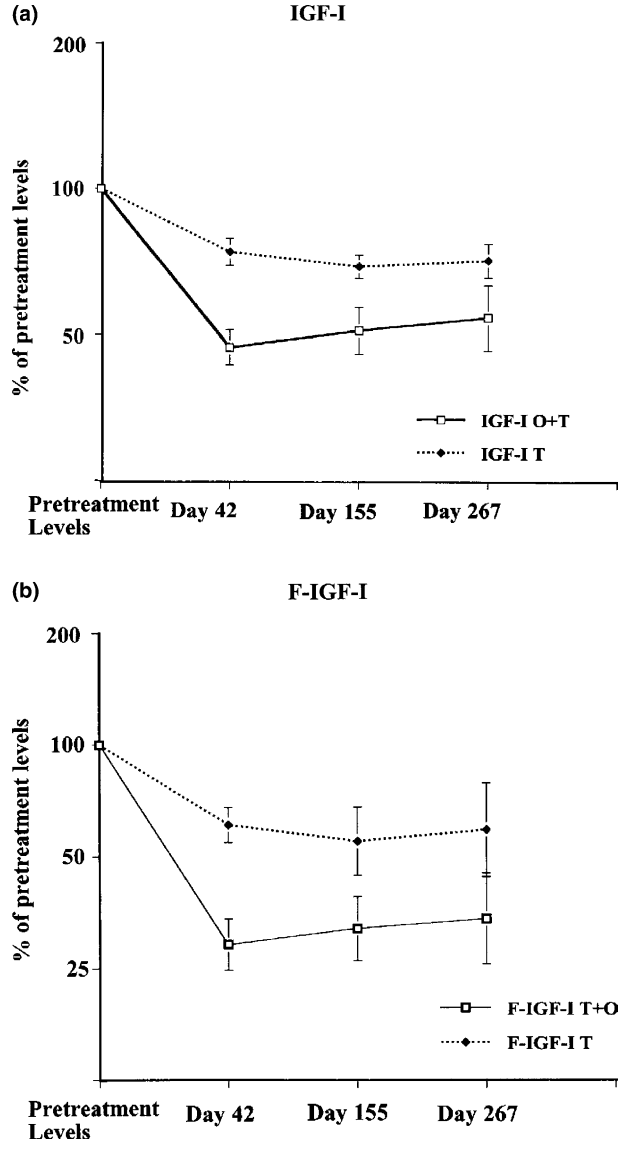

Fig. 1. Total IGF-I (a) and free IGF-I (b) shown as precentage of pretreatment levels for both treatment groups (T + O = tamoxifen + octreotide, T = tamoxifen + placebo). Error bar shows 95% Confidence Intervals of the mean.

clinical cancers in the process of carcinogenesis. Thus, high serum levels of IGF-I were found to be a risk factor for development of breast cancer in premenopausal women [3]. This apparent paradox resembles observations in relation to endogenous oestrogens and breast cancer risk. Thus, several studies have reported a significant association between high oestrogen levels and the risk of postmenopausal breast cancer within the physiological range [21]. By contrast, studies with second- and third-generation aromatase inhibitors have revealed the need for profound aromatase inhibition (>90%) and oestrogen suppression to achieve antitumour effects in metastatic breast cancer [22]. It is possible that a more pronounced suppression of IGF-I levels than what was achieved by combined OP-LAR and tamoxifen treatment with compounds inhibiting the function of the IGF-I receptor may result in clinical responses.

Interestingly, an increase in the plasma levels of IGFBP-2 was associated with a poor prognosis in patients receiving combined treatment with tamoxifen and OncoLAR, but not among patients receiving tamoxifen monotherapy. While this may suggest an interaction with drug treatment ($P = 0.07$), the possibility exists that this may be related to a general increase in tumour burden. Other observations provide indirect evidence supporting the first theory. Thus, elevated serum levels of IGFBP-2 have been found in patients suffering from other types of cancer [23–25], but also among patients suffering from acquired immuno deficiency syndrome (AIDS) or diabetes [26,27]. In a previous study, we observed a drop in plasma levels of IGFBP-2 as well as IGFBP-3 protease activity in AIDS patients responding to therapy [26]. IGFBP-2 may possibly be a non-specific marker which reflects an increase in tumour burden and clinical deterioration, but a lack of specificity may hamper its clinical use as a parameter for tumour response or growth during therapy.

In conclusion, our data suggest that the effects on the IGF-system achieved by combining OP-LAR and tamoxifen do not improve clinical outcome compared with tamoxifen monotherapy. While an increase in plasma levels of IGFBP-2 was associated with a poor outcome among patients treated with OncoLAR and tamoxifen in concert, a similar association was not recorded among patients treated with tamoxifen monotherapy. Thus, future studies are needed to assess the

Table 3
Cox proportional hazard model estimates for progression-free survival (PFS), background prognostic factors and log ligand IGFBP2 measured at baseline and Day 43 ($n = 150$)

Variable	Group 1	Group 2	Parameter estimate	Wald χ^2	Wald P-value	Hazard ratio[a]
Baseline Karnofsky Performance status	60–70	80–100	0.9944	10.3622	0.0013	2.703
Menopausal status	Pre- (<50)	Post- (⩾50)	0.8690	8.7771	0.0031	2.385
Disease measurability	Non-measurable	Measurable	0.5137	3.9318	0.0474	1.671
Log baseline IGFBP-2 WLB	1	0	−0.8236	9.0079	0.0027	0.439
Log Day 43 IGFBP-2 WLB	1	0	1.0494	15.8295	0.0001	2.856

[a] Estimated multiple of hazard for a patient with covariate value at Group 1 relative to a patient at Group 2 assuming the remaining four covariates are the same for both patients. In the case of the IGFBP-2 WLB covariates, the Group 1 covariate value is one log (base e) greater than the corresponding Group 2 patient.

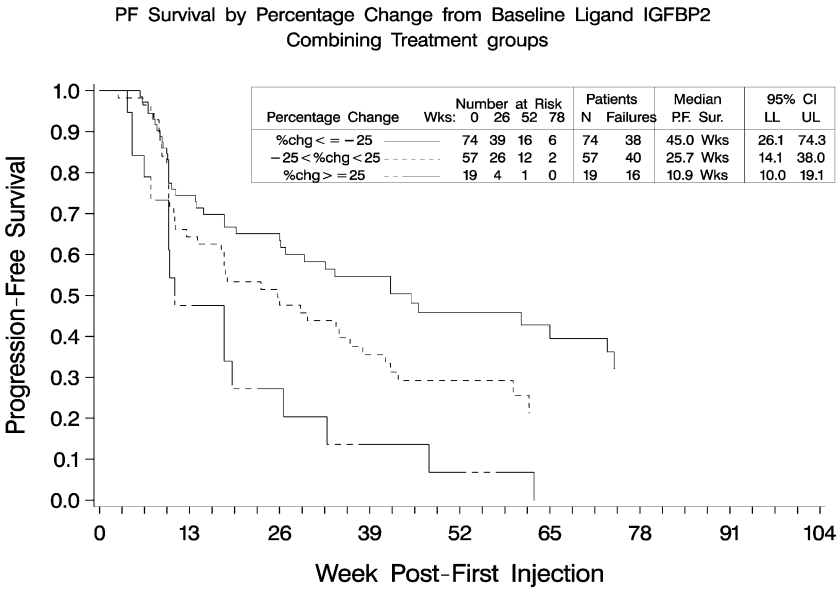

Fig. 2. Progession-free survival (PFS) in relation to alterations in IGFBP-2 evaluated by Western ligand blot in all patients. Significant differences between the three categories were obtained ($P < 0.005$). chg, change; wks, weeks; 95% CI, 95% Confidence Interval; LL, lower limit; UL, upper limit; O, observed; N, number.

specificity of this parameter with respect to the tumour type as well as treatment regimen before implementing it as a prognostic factor. Our results do not support a therapeutic role of manipulating serum IGF-I levels within the range outlined here as a therapeutic strategy in breast cancer.

Participating centres

S. Helle, P. Lønning, Department of Oncology Haukeland University Hospital, Bergen, Norway; E. Bajetta, Instituto Nazionale Tumori, Milan, Italy; H. Sommer, Universitats-Frauenklinik, Munich, Germany; J. Guastalla, Centre Leon Bernard, Lyon, France; I. Szakolczai, National Institute of Oncology, Budapest, Hungary; E. Baltali, Hacettepe University Medical School, Oncology Institute, Ankara, Turkey; T. Pinter, Petz Aladar County Hospital; Gyor Hungary, M. Csepreghy Uzoki Hospital, Budapest, Hungary; L. Ottestad, Oslo, Norway; C. Boni, Arcispedale S. Maria Nuova Reggio-Emilia, Italy; C. Bryce, Vancouver Cancer Centre, Vancouver, Canada; J. Klijn, Daniel Den Hoed Klinick & Academic Hosptal, Rotterdam, Netherlands. G. Cocconi, Medical Oncology Division, Azienda Ospedaliera Universitaria, Parma, Italy; JP. Janssens, European Cancer Prevention Organization, Limburgs Universitair Centrum, Universitaire Campus, Diepenbeek, Belgium; P. Chollet, Centre Jean Perrin and INSERM U 71, Clermont-Ferrand, France; JP. Bergerat, Departement d'Oncologie, Hopitaux Universitaires de Strasbourg, France; J. Bergh, Department of Oncology, Uppsala University Hospital, Uppsala, Sweden; I. Schindler, University Hospital Benjamin Franklin, Free University of Berlin, Germany; P. Dombernowsky, Department of Oncology, Herlev University Hospital, University of Copenhagen, Denmark; R. Hultborn, Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden; P. Fargeot, Department d'Oncologie Medicale, Centre Rene Gauducheau, Nantes, France; J. Krook, Duluth Clinic, Duluth, Minnesota, USA; NO Bengstsson, Department of Oncology, Umea University Hospital, Umea, Sweden; JTM Burghouts, Bosch Medicentrum, locatie Groot Ziekengasthuis, Netherlands; M. Mallarino, Hodges Cancer Center, Methodist Hospital, Lubbock, Texas, USA; H. Roche, Groupe de Pharmacologie Clinique et Experimentale des Medicaments anticancereux, Centre Claudius-Regaud, Toulouse, France; A. Lluch, Servicio De Oncologia Medica, Hospital Madrid, Spain; C. Mendiola, Division of Medical Oncology, Hospital Universitario, Madrid, Spain; K. Possinger, Medizinische Klinik II der Charite, Berlin, Germany; A. Moyano, Medical Oncology Service, Alcala de Henares University, Madrid, Spain; A. Zori Comba, Hospital Zubizarreta, Argentina; N. Wilking, Department of Oncology, Radiumhemmet, Karolinska Hospital, Stockholm, Sweden; M. Tubiana-Hulin, Department of Pharmacology, Centre Rene Huguenin, Saint-Cloud, France; RM. Bremnes, Department of Oncology, University Hospital of Tromso, Norway; P. Clingan, UNSW Department of Surgery, St. George Hospital, Sydney, Australia; D. Charpentier, Toronto Hospital, Canada; J. Hamm, Alliante Health Care Systems, Louisville, Kentucky, USA; F. Icli, Department of Medical Oncology, Ibni Sina Hospital, Faculty of Medicine, Ankara University,

Sihhiye-Ankara, Turkey; JR. Germa Lluch, Oncology Department, Hospital de la Santa Creu I Sant Pau, Universitat Autonoma, Barcelona, Spain; A. Berra, Hospital Provincial, Rosario, Argentina; J. Brunet, Department of Oncology, Hospital de La Santa Creu I Sant Pau, Barcelona, Spain; G. King, Hematology & Oncology Associates, Greenville, South Carolina, USA; R. Michaelson, Cancer Center of St Barnabas, Livingston, New Jersey, USA; L. Baez, VA Medical Center, San Juan, Puerto Rico; J. Zalcberg, Division of Haematology and Medical Oncology, Peter MacCallum Cancer Institute, Melbourne, Australia; S. Sergengecti, Istanbul University, Cerrahpasa Medical Faculty, Medical Oncology Department, Istanbul, Turkey; J. Gralow, University of Washington Medical School, Division of Oncology, Seattle, USA; B. Norris, Fraser Valley cancer Centre, British Columbia Cancer Agency, Surrey, Canada; Szanto, M. Chipman, Austin & Repatriation Medical Centre, Melbourne, Australia; R. Heikkila, Rogaland Central Hospital, Stavanger, Norway; J. Bonneterre, Centre Oscar Lambret, Lille, France; MR. Di Noto, Hospital San Roque, Cordoba, Argentina; R.D. Chacon, Alexander Fleming Institute, Buenos Aires, Argentina; E. Woltering, Louisiana University Medical Center, New Orleans, Louisiana, USA; P. Warnier, Saint-Lu Hospital, Brussels, Belgium; T. Vandenberg, Fraser Valley Cancer Centre, British Columbia Cancer Agency, Surrey, Canada; C. Lewis, Department of Medical Oncology, Prince of Wales Hospital, Sydney, Australia; T. Bauknecht, University of Bonn Medical School, Bonn, Germany; V. Goel, Toronto Sunnybrook Regional Cancer Centre, Canada; P. De Souza, Prince of Wales Hospital, Sydney, Australia.

Conflict of interest statement

None declared.

Acknowledgement

The technical assistance of Mr. Dagfinn Ekse is highly appreciated.

References

1. Mendelsohn J, Baselga J. Status of epidermal growth factor receptor antagonists in the biology and treatment of cancer. *J Clin Oncol* 2003, **21**, 2787–2799.
2. Karey KP, Sirbasku DA. Differential responsiveness of human breast cancer cell lines MCF-7 and T47D to growth factors and 17 beta-estradiol. *Cancer Res* 1988, **48**, 4083–4092.
3. Hankinson SE, Willett WC, Colditz GA, *et al*. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet* 1998, **351**, 1393–1396.
4. Weckbecker G, Tolcsvai L, Stolz B, *et al*. Somatotatin analogue octreotide enhances the antineoplastic effects of tamoxifen and ovariectomy on 7,12-dimethylbenz(a)anthracene-induced rat mammary carcinomas. *Cancer Res* 1994, **54**, 6334–6337.
5. Setyono-Han B, Henkelman MS, Foekens JA, *et al*. Direct inhibitory effects of somatostatin (analogues) on the growth of human breast cancer cells. *Cancer Res* 1987, **47**, 1566–1570.
6. Colletti RB, Roberts JD, Devlin JT, *et al*. Effect of tamoxifen on plasma insulin-like growth factor I in patients with breast cancer. *Cancer Res* 1989, **49**, 1882–1884.
7. Helle SI, Geisler J, Poulsen JP, *et al*. Microencapsulated octreotide pamoate in advanced gastrointestinal and pancreatic cancer: a phase I study. *Br J Cancer* 1998, **78**, 14–20.
8. Parisot JP, Leeding KS, Hu XF, *et al*. Induction of insulin-like growth factor binding protein expression by ICI 182,780 in a tamoxifen-resistant human breast cancer cell line. *Breast Cancer Res Treat* 1999, **55**, 231–242.
9. Stewart AJ, Johnson MD, May FE, *et al*. Role of insulin-like growth factors and the type I insulin-like growth factor receptor in the estrogen-stimulated proliferation of human breast cancer cells. *J Biol Chem* 1990, **265**, 21172–21178.
10. Pollak M. Enhancement of the anti-neoplastic effects of tamoxifen by somatostatin analogues. *Digestion* 1996, **57**(Suppl.), 29–33.
11. Ingle JN, Suman VJ, Kardinal CG, *et al*. A randomized trial of tamoxifen alone or combined with octreotide in the treatment of women with metastatic breast carcinoma. *Cancer* 1999, **85**, 1284–1292.
12. Bontenbal M, Foekens JA, Lamberts SW, *et al*. Feasibility, endocrine and anti-tumour effects of a triple endocrine therapy with tamoxifen, a somatostatin analogue and an antiprolactin in post-menopausal metastatic breast cancer: a randomized study with long-term follow-up. *Br J Cancer* 1998, **77**, 115–122.
13. Kutz K, Nuesch E, Rosenthaler J. Pharmacokinetics of SMS 201-995 in healthy subjects. *Scand J Gastroenterol Suppl* 1986, **119**, 65–72.
14. Bajetta E, Procopio G, Ferrari L, *et al*. A randomized, multicenter prospective trial assessing long-acting release octreotide pamoate plus tamoxifen as a first line therapy for advanced breast carcinoma. *Cancer* 2002, **94**, 299–304.
15. Frost VJ, Helle SI, Lonning PE, *et al*. Effects of treatment with megestrol acetate, aminoglutethimide, or formestane on insulin-like growth factor (IGF) I and II, IGF-binding proteins (IGFBPs), and IGFBP-3 protease status in patients with advanced breast cancer. *J Clin Endocrinol Metab* 1996, **81**, 2216–2221.
16. Helle SI, Ekse D, Holly JM, *et al*. The IGF-system in healthy pre- and postmenopausal women: relations to demographic variables and sex-steroids. *J Steroid Biochem Mol Biol* 2002, **81**, 95–102.
17. Holm ST. A simple sequentially rejective multiple test procedure. *Scand J Stat* 1979, **6**, 65–70.
18. del Pozo E, Neufeld M, Schluter K, *et al*. Endocrine profile of a long-acting somatostatin derivative SMS 201-995. Study in normal volunteers following subcutaneous administration. *Acta Endocrinol (Copenh)* 1986, **111**, 433–439.
19. Lonning PE, Hall K, Aakvaag A, *et al*. Influence of tamoxifen on plasma levels of insulin-like growth factor I and insulin-like growth factor binding protein I in breast cancer patients. *Cancer Res* 1992, **52**, 4719–4723.
20. Lahti EI, Knip M, Laatikainen TJ. Plasma insulin-like growth factor I and its binding proteins 1 and 3 in postmenopausal patients with breast cancer receiving long term tamoxifen. *Cancer* 1994, **74**, 618–624.
21. Dorgan JF, Longcope C, Franz C, *et al*. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst* 2002, **94**, 606–616.
22. Lonning PE. Aromatase inhibitors and inactivators for breast cancer therapy. *Drugs Aging* 2002, **19**, 277–298.

23. Cohen P, Peehl DM, Stamey TA, *et al*. Elevated levels of insulin-like growth factor-binding protein-2 in the serum of prostate cancer patients. *J Clin Endocrinol Metab* 1993, **76**, 1031–1035.
24. Muller HL, Oh Y, Lehrnbecher T, *et al*. Insulin-like growth factor-binding protein-2 concentrations in cerebrospinal fluid and serum of children with malignant solid tumors or acute leukemia. *J Clin Endocrinol Metab* 1994, **79**, 428–434.
25. Renehan AG, Jones J, Potten CS, *et al*. Elevated serum insulin-like growth factor (IGF)-II and IGF binding protein-2 in patients with colorectal cancer. *Br J Cancer* 2000, **83**, 1344–1350.
26. Helle SI, Ueland T, Ekse D, *et al*. The insulin-like growth factor system in human immunodeficiency virus infection: relations to immunological parameters, disease progression, and antiretroviral therapy. *J Clin Endocrinol Metab* 2001, **86**, 227–233.
27. Bereket A, Lang CH, Blethen SL, *et al*. Insulin-like growth factor-binding protein-2 and insulin: studies in children with type 1 diabetes mellitus and maturity-onset diabetes of the young. *J Clin Endocrinol Metab* 1995, **80**, 3647–3652.