

Permanent scalp alopecia related to breast cancer chemotherapy by sequential fluorouracil/epirubicin/cyclophosphamide (FEC) and docetaxel: a prospective study of 20 patients

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Background: To analyze the clinical and histological features of permanent alopecia following a sequential fluorouracil/epirubicin/cyclophosphamide (FEC) and docetaxel regimen for adjuvant breast cancer treatment.

Patients and methods: Women treated for breast cancer by a sequential adjuvant FEC and docetaxel regimen who developed permanent alopecia diagnosed between 2007 and 2011 were identified from the Department of Dermatology (Saint-Eloi Hospital, Montpellier, France) and the Department of Medical Oncology (CRLC Val d'Aurelle, Montpellier, France). Data were collected regarding demographics, type of cancer, delay of onset after chemotherapy, Dermatology Life Quality Index® (DLQI), clinical description of the lesions, scalp biopsies, laboratory explorations investigating steroid hormonal, iron, zinc and thyroid status, therapy and outcome.

Results: Twenty white Caucasian females were included. Hair loss presented with a moderate or intense androgenetic-like pattern of scalp alopecia. Biopsy specimen examinations were normal or displayed the androgenetic-like pattern. Laboratory explorations ruled out iron or zinc deficiency and thyroid disorders and confirmed hormonal menopause without hyperandrogenism. The overall mean DLQI score reflected the distressing psychological consequences in the patients' lives. No spontaneous regrowth of the scalp hair was noted. Treatment including vitamins, minoxidil, psoralen and ultraviolet A therapy and spironolactone proved to be ineffective.

Conclusion: Permanent and severe alopecia is a newly reported complication of the FEC 100–docetaxel breast cancer regimen.

Key words: breast cancer, chemotherapy, FEC–docetaxel, permanent alopecia

Introduction

Alopecia is a common and distressing side-effect of systemic chemotherapy. Scalp, pubic and axillary hair may be lost, as well as eyebrows and eyelashes, but in most cases, the hair loss is temporary and usually reversible, with complete hair regrowth within the 3–6 months following the chemotherapy cycles [1, 2]. However, in the past few years, dramatic case reports of permanent irreversible post-chemotherapy alopecia have been described [3–12]. Its true incidence remains unknown. Most observations have been reported with high-dose busulfan regimens in bone marrow transplant patients [4–6, 9]. De Jonge [7] reported 8 cases of permanent alopecia in a series of 24 patients treated with cyclophosphamide,

thiotepa and carboplatin (CTC regimen) for conditioning before autologous transplant. More recently, cases of permanent alopecia after chemotherapy protocols applied for breast cancers have been described, including taxanes alone, docetaxel or paclitaxel [10, 12], or a regimen of docetaxel, carboplatin and trastuzumab [11]. We report herein a case series of 20 women treated for breast cancer by a sequential fluorouracil/epirubicin/cyclophosphamide (FEC) and docetaxel regimen who developed severe and permanent alopecia.

patients and methods

patients and disease characteristics

From 1 January 2007 to 1 January 2011, we carried out a prospective dermatological study on all the patients followed after a breast cancer diagnosis in the Department of Medical Oncology (CRLC Val d'Aurelle, Montpellier, France). Patients were referred by two oncologists (GR, WJ)

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for severe permanent alopecia that occurred after a FEC–docetaxel protocol for chemotherapy to manage breast cancer [13]. Permanent alopecia was defined as absent or incomplete hair regrowth at ≥ 6 months post-chemotherapy.

Data were collected regarding demographics (age, sex, ethnicity), type of cancer, menopausal status, chemotherapy regimen, delay of onset after chemotherapy and the clinical description of the lesions and their localization: scalp, eyebrows, eyelashes, axillary and pubic areas and upper/lower limbs. For scalp alopecia, we used Ludwig's classification in an attempt to evaluate the stages of severity in our patients, using a simple and quick validated method. Briefly, Ludwig's classification defines three patterns representing stages or progressive types of female androgenetic alopecia: grade 1 (minimal) with perceptible thinning of the hair on the crown, limited by a line situated 1–3 cm behind the frontal hair line; grade 2 (moderate) with pronounced rarefaction of the hair on the crown within the area seen in type 1; and grade 3 (intense) characterized by full baldness (total denudation) within the area seen in grades 1 and 2 (frontal hairline maintained) [14]. Although this classification was not developed for post-chemotherapy hair loss, it appeared to be useful and simple. Standard pictures from the lateral side and the vertex were taken, and two dermatologists (NK, DB) carried out a blind classification of the patients. Menopausal status was determined by questioning about the presence or absence of menstrual cycles. Menopause was defined as the cessation of menstrual periods for at least 1 year [15]. Therapy and outcome issues were collected.

histological and biological analysis

Punch skin biopsies of 3–4 mm were carried out for histological analysis. They were fixed in 10% formalin solutions and sections were stained for hematoxylin and eosin. Laboratory explorations included hemograms, liver and kidney functions, serum electrophoresis, serum iron (normal 8.8–27 $\mu\text{mol/l}$) and ferritin (11–307 ng/ml), thyroid-stimulating hormone (TSH) (0.2–3.6 mUI/ml), total testosterone (0.1–0.6 ng/ml), free testosterone (0.5–2.5 pg/ml), dehydroepiandrosterone sulfate (DHEA-S) (0.5–2.5 mg/ml), delta-4 androstenedione ($\delta 4$ -ASD) (0.5–2 ng/ml), 17-OH progesterone (17OH-P) (0.1–1 ng/ml) with the synacthen test and follicle-stimulating hormone (FSH) (3–8 mUI/ml), luteinizing hormone (LH) (1.5–6 mUI/ml) and estradiol (20–150 pg/ml) levels.

health-related quality of life analysis

Impairment of health-related quality of life (QoL) was assessed by a self-administered questionnaire, the Dermatology Life Quality Index® (DLQI) [16] and by whether or not the patient permanently wore a medical hair prosthesis. Briefly, the DLQI is a validated, rapid and highly sensitive test used in routine clinical practice to evaluate the QoL for various skin diseases. DLQI is composed of the following 10 items to evaluate patients' perceptions of the impact of skin disease on different aspects of their QoL over the past week: (i) symptoms, (ii) embarrassment, (iii) shopping and daily activities, (iv) clothes, (v) leisure, (vi) sport, (vii) work or study, (viii) relationships, (ix) sexual difficulties, and (x) treatment. Each response is scored from 0 to 3 with a maximum score of 30, and higher scores indicate greater impairment of the patient's QoL.

results

patients

A total of 20 white Caucasian females were included, with a mean age at presentation of 54 years (range, 38–69). The main patient characteristics are summarized in Table 1. Briefly, all but one patient had no history of acute or chronic hair loss.

Only one patient (patient 18) reported chronic but stable mild hair loss on the vertex treated with long-term application of minoxidil for several years before chemotherapy. Patient 1's mother had a familial history of alopecia areata. All the patients had a history of invasive ductal or lobular carcinoma of the breast diagnosed between 1999 and 2009. Patient 3 had a history of two metachronous breast carcinomas (1999 and 2005). Patient 16 was affected by two synchronous bilateral carcinomas. Two other patients were treated for relapsing disease (patients 6 and 18). Oncologic management for all the patients included breast surgery, lymph node sentinel procedure with or without lymph node dissection, radiotherapy, chemotherapy without scalp cooling and hormonal therapy according to age and the hormonal status of the tumor. Surgery was carried out either before (adjuvant setting, $n = 12$) or after (neoadjuvant setting, $n = 7$) chemotherapy. The chemotherapy protocols included in most cases (19/20) a combination of epirubicin 100 mg/m^2 , cyclophosphamide 500 mg/m^2 , and 5-fluorouracil 500 mg/m^2 , for three cycles every 3 weeks (FEC 100 protocol), followed by docetaxel 100 mg/m^2 every 3 weeks for either three cycles as adjuvant therapy after surgery ($n = 12$) [13] or four cycles as neoadjuvant therapy before surgery ($n = 7$). Patient 12 received epirubicin 100 mg/m^2 and docetaxel 75 mg/m^2 for six cycles. Patient 3, who had two metachronous breast cancers, first received mitoxantrone–cyclophosphamide–5-fluorouracil for three cycles, docetaxel for three cycles and then tamoxifen for three cycles, in 2005, she received the protocol mentioned above: FEC 100–docetaxel 100 mg/m^2 for three cycles every 3 weeks. Patient 6 received three cycles of FEC 100 and four cycles of docetaxel 100 mg/m^2 in 2005, followed by surgery, anastrozole and radiotherapy. After surgery for a lymph relapse in 2007, she was given paclitaxel 90 mg/m^2 for six cycles associated with bevacizumab [17] (first-line metastatic setting due to lung metastases) then tamoxifen. Patient 18 first received FEC 100 for four cycles and 2 years later, FEC 100–docetaxel 100 mg/m^2 for three cycles each after surgery for an ipsilateral lymph node relapse. HER-2 overexpression was confirmed in three patients who elected to receive trastuzumab according to a standardized weekly dose of 4 mg/kg for cycles 2–5 and then 6 mg/kg every 3 weeks to complete 6–12 months of treatment [18]. Hormone receptors expression of the breast tumor was confirmed in 14 patients, who received hormonal treatment after chemotherapy: exemestane ($n = 3$), tamoxifen ($n = 8$), anastrozole ($n = 3$) or letrozole ($n = 6$) according to medical status and standard of care.

alopecia characteristics

The main relevant characteristics are summarized in Table 1. Hair loss occurred within 2 weeks of the first cycle of FEC and affected the scalp but also the eyebrows, eyelids, axillary and pubic/lower limbs areas in most of the cases. None of the patients experienced any regrowth during the entire six to seven cycles of FEC–docetaxel. After completion, incomplete hair regrowth within 4–6 months, characterized by diffuse loss and thinning hair predominating over the crown, was reported by both patients and oncologists. Interestingly, patient 18, who in 2005 had received four cycles of FEC 100, recalled having

Table 1. Patient's clinicopathologic characteristics

N	Age (years)	Ludwig grading	Duration	Histology	DLQI/30	Hair prosthesis	Follow-up (months)/Regrowth
1	38	3	4	Reduced number of terminal hairs; Increased number of miniaturized follicles; Mild interstitial and perifollicular lymphocytic infiltrate	NP	Yes	21/—
2	49	2	5	Reduced number of terminal hairs; Mild lymphocytic perifollicular infiltrate	14	Yes	22/minim ^a
3	49	2	5	Normal	NP	No	20/—
4	42	2	4	Normal	17	Yes	45/—
5	51	3	2	Reduced number of terminal hairs	10	Yes	21/—
6	67	2	5	Normal	7	No	19/—
7	65	2	2	Reduced number of terminal hairs; Mild perifollicular deposition of mucin	10	No	19/minim ^a
8	49	2	3	Reduced number of terminal hairs; Mild lymphocytic perifollicular infiltrate	7	Yes	19/—
9	58	3	4	NP	1	No	18/minim ^a
10	50	3	3	Reduced number of terminal hairs; Mild lymphocytic perivascular infiltrate	14	Yes	14/—
11	56	3	3	Reduced number of terminal hairs; Mild dermohypodermic lymphocytic infiltrate	0	Yes	17/minim ^a
12	60	2	8	NP	1	Yes	1/—
13	62	2	2	Mild lymphocytic perivascular infiltrate	7	Yes	15/minim ^a
14	56	2	3	Mild lymphocytic perifollicular infiltrate	14	Yes	14/minim ^a
15	44	1	2	Mild lymphocytic perivascular infiltrate	6	Yes	9/minim ^a
16	65	2	2	Mild lymphocytic perifollicular infiltrate	5	No	10/—
17	58	2	3	NP	13	Yes	8/minim ^a
18	46	NP	1	NP	13	Scarf	7/minim ^a
19	69	2	4	NP	0	No	12/minim ^a
20	45	3	1	Reduced number of terminal hairs; Mild lymphocytic perifollicular infiltrate	19	Yes	1/—

Duration, alopecia duration (years); Ludwig grading, scalp Ludwig grading score.

minim, minimal regrowth of the pubic hairs.

DLQI, Dermatology Life Quality Index[®]; NP, not carried out.

had full regrowth after completion of the cycles, whereas permanent alopecia occurred after completion of the 3 FEC 100–3 docetaxel 100 protocol. Similarly, patient 6 acknowledged the start of regrowth after the 3 FEC 100–4 docetaxel 100 protocol, but this regrowth was blocked by the initiation of paclitaxel therapy. The frequency and grade of other well-known taxane-induced side-effects were grossly similar to previously reported toxic effects in this setting, and we did not identify any excessive or unexpected toxicity in this cohort of patients outside of permanent alopecia.

Physical examination revealed diffuse hair loss always prominent over the crown and the frontal scalp, with thinning and widening of the central parting of the scalp in an oval form composed of hair uniform in quality and fine in texture, surrounded by a circular band of hair of variable dimensions on the frontal, temporoparietal and occipital regions that appeared with normal density (supplemental Figures S1 and S2, available at *Annals of Oncology* online). No inflammation, desquamation or scarring was noted. Using Ludwig's classification, 12 women (63%) showed a type II degree (moderate) of alopecia, 6 (32%) a type III degree (intense) of alopecia and 1 patient (5%) a type I degree (minimal). One

patient (patient 18) declined clinical photography. Hair loss also affected the eyebrows (20/20 cases), eyelashes (19/20 cases, supplemental Figure S3, available at *Annals of Oncology* online), axillary (16/20 cases) and pubic/lower limbs (18/20 cases) areas in most of the cases. No hirsutism on the face or the trunk was present and the nails appeared almost normal.

alopecia treatments and outcomes

All the oral treatments prescribed during this study, including dexpantenol and biotin, methionine cysteine, and cystin-vitamin B6, and all those chosen by the patient herself, like brewer's yeast or phytotherapy, proved to have no efficacy. Treatment by topical minoxidil 2% or 5% was always unsuccessful after >3 months (14 patients, 70%). Two patients underwent psoralen and ultraviolet A therapy (30 regimens) without any hair regrowth after >3 months of follow-up. One patient was treated by spironolactone (150 mg/day, 3 months), a potassium-sparing diuretic used off-label as an antiandrogen in the treatment of female androgenetic alopecia, without any efficacy. With a median dermatological follow-up of 15.6 months (range 1–45 months), most patients had the feeling

that hair was not growing, yet without any more loss. Ten patients (50%) reported minimal improvement in hair density, especially in the pubic area. However, such assessments were difficult to confirm, and no significant regrowth on the scalp was observed.

histology

Punch skin biopsy specimens were available for 15 patients. Examination was normal in three cases (20%). Reduced hair follicle density and/or an increased amount of vellus hair in favor of androgenetic alopecia were noted in eight cases (53%). Besides, in 10 cases (67%), a mild lymphocytic infiltrate was present, mostly with a perifollicular (6/15) and/or perivascular (3/15) distribution (Figure 1). Neither fibrosis nor destruction of the hair follicle, evocative of scarring alopecia, was reported. None of the patients presented with scalp localization of metastatic breast carcinoma (*alopecia neoplastica*).

biology

White and red blood cell counts, serum electrophoresis and kidney and liver functions were normal in all available patients (17/17). Laboratory analysis including antinuclear antibodies, zinc and iron status and cortisol levels were always in the normal range. TSH levels were mildly elevated in three patients and considered nonsignificant, as T3 and T4 levels were normal or slightly increased. Elevated levels of FSH and LH were constant (14/14). Low and normal estradiol levels were respectively found in 93% (14/15) and 7% (1/15) of the cases. No androgen excess was noted: total testosterone (15/15) and free testosterone (10/10) were always normal, while DHEA-S, δ 4-ASD and 17OH-P (synacthen test) were normal or decreased.

health-related QoL

The DLQI was self-administered by 18 patients. The overall mean DLQI score was 8.66 (range 0–19), reflecting significant impairment when compared with the mean DLQI score of the healthy population (0.5) [10]. Severe impairment of the DLQI

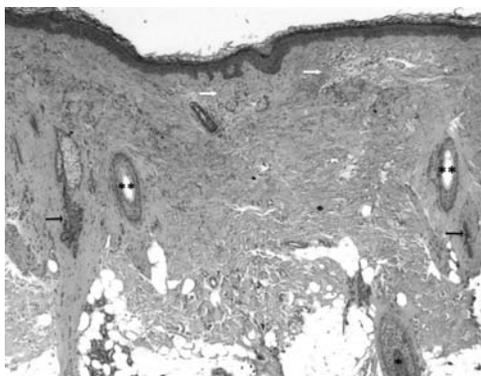


Figure 1. Vertical section of a punch biopsy specimen showing diminished pilosebaceous units (*) with reduced anagen hair follicles (**), two telogen hair follicles (black arrows) and a slight lymphocytic infiltrate of the upper reticular dermis (white arrows); hematoxylin and eosin, original magnification, $\times 50$.

was reported by seven patients (38.8%, score 11–20). The regular wearing of a hair prosthesis or scarf (1 case) to hide the alopecia was reported by 70% (14/20).

discussion

We report the first comprehensive series of patients with permanent diffuse and irreversible scalp alopecia and body hair loss following a sequential regimen of FEC and docetaxel chemotherapy for invasive breast carcinoma. Ninety-five percent of our patients (19/20) received a standardized regimen including three FEC cycles followed by three to four cycles of docetaxel 100 mg/m². All the patients showed a strikingly similar clinical presentation, with hair loss within 2 weeks of the first FEC cycle and maintained until the end of docetaxel cycles. Hair regrowth occurred within 4–6 months but was clearly incomplete. It was marked by thinning hairs and absence of fibrosis leaving a characteristic aspect of scalp alopecia predominating over the crown with an ‘androgenetic hair loss pattern’, almost always associated with eyebrow and eyelash hair loss.

Since 2009, nine cases of permanent scalp alopecia after systemic chemotherapy related to taxanes used to treat breast cancer have been reported [10–12]. Docetaxel was almost always involved, alone in seven cases (75 mg/m² in one case, dose not indicated in six cases) or in association with carboplatin (650 mg) and trastuzumab (4 mg/kg) [10]. One observation of paclitaxel alone inducing alopecia (175 mg/m²) was reported. Details of the clinical features with illustrations are limited to two reports [10, 11] and the presentation of scalp alopecia seems strikingly similar to that of our patients with severe androgenetic-like alopecia without fibrosis. An alopecia areata pattern was reported in one case (without illustration) associated with hair loss of the eyebrows, eyelashes and the axillary and pubic regions [10]. In this latter case, although there was an absence of exclamation mark hairs, nail changes or positive hair pull test, one could not formally exclude authentic alopecia areata, which might have been merely coincidental [10].

Our histological analyses were consistent with androgenetic alopecia: reduced hair follicle density and/or increased amount of vellus hair (53%), mild dermal lymphocytic infiltrate (67%) and a constant non-scarring pattern. These histological results were in accordance with the previous findings of three observations [10, 11] and a recent histological series of 10 patients who developed severe permanent alopecia after systemic chemotherapy [12], using not only taxanes (9/13) but also busulfan (3/13) and cisplatin/etoposide (1/13). Twenty percent of our patients had normal biopsies. However, we carried out only one biopsy per patient, and we thus cannot rule out the possibility that we missed minimal histological abnormality in some of our patients.

The pathophysiology of this permanent alopecia remains unknown, with hypotheses involving toxic damage to stem cells/hair matrix cells of the hair bulb or disturbance of the signaling pathways to the secondary hair germ [10, 11]. Endocrine dysfunctions have also been suggested [8]. In our study, the laboratory findings were normal and ruled out iron or zinc deficiency as well as significant thyroid disorders. All

the patients displayed biological menopause, either due to age or to the chemotherapeutic treatment, without hyperandrogenism. However, rarefaction of eyebrows, eyelashes and pubic and axillary hair, as well as the absence of clinical or biochemical evidence of androgen excess, suggests that mechanisms other than direct androgen action contribute to this form of hair loss. Therefore, extensive and systematic hormonal screening (androgens and gonadotrophins) seems useless.

Chemotherapy-induced alopecia is one of the most distressing/troublesome side-effects of chemotherapy, along with nausea, vomiting and fatigue. It may significantly impact an individual's self-image with poorer body image, and recent studies indicate that patients with both clinically apparent and clinically imperceptible hair loss may have significantly decreased QoL [19, 20]. In our series, distressing psychological consequences were common and severe as reflected by the wearing of a scalp hair prosthesis or scarf in two-thirds of the population, the mean DLQI score (8.66) and the elevated DLQI results (score 11–20) in 38.8% of our patient population. These DLQI results are in accordance with the only large study to date on the effect of chronic hair loss on QoL as assessed by DLQI [21]. However, as stressed by some authors, the degree of hair loss does not necessarily predict impact on QoL [19, 20]. Our patients had had high expectations of receiving efficient treatment of alopecia. One patient even acknowledged, "she would have preferred not to receive any chemotherapy for her breast cancer" rather than being affected by such a distressing and permanent side-effect. In addition to the elevated DLQI scores in almost 40% of our patients, our other results also emphasized the powerful impact that alopecia has on the daily lives of patients cured of cancer. To our knowledge, there are no reported data evaluating the preventive effect of scalp cooling with regard to permanent alopecia. As scalp cooling is rarely used in our institution, and considering the estimated 2% incidence of this side-effect, the putative preventive effect of such intervention remains to be evaluated.

As already suspected by Prevezas et al. [10] and Tallon et al. [11], taxanes seem to be responsible for this side-effect. Indeed, all our patients received taxanes during the course of their treatment, while not all of them received antiestrogen or aromatase inhibitor treatment. One of our patients (patient 18) received a first series of four cycles of FEC alone for breast cancer and recalled transient but clearly reversible alopecia shortly afterward. Because of a relapse, she received an FEC 100–docetaxel regimen with permanent alopecia as a consequence. The relatively recent description of this side-effect could be linked to the fairly recent validation of taxane-based adjuvant breast cancer therapy, which was introduced in France in 2005. The conjunction of taxane-based treatment with a population having a good prognosis, thereby allowing for a long follow-up without chemotherapy, could perhaps explain this new cutaneous side-effect. In addition, the relatively low incidence of this side-effect may have delayed its description. Approximately 1000 patients affected by early breast cancer were treated with this type of sequential, anthracycline- and taxane-based adjuvant or neoadjuvant chemotherapy in our institution during the accrual period. It could thus be roughly estimated that the incidence of this side-

effect in this patient population is ~2%. However, biases like losses to follow-up or underreporting of the side-effect are possible. During the same accrual period, from 1 January 2007 to 1 January 2011, WJ and GR carried out a systematic prospective screening of all breast cancer patients treated in our institution in order to detect mild to severe alopecia. During this period of time, no breast cancer patients treated using anthracycline-based regimens without concomitant or sequential taxanes in our institution was affected by such severe permanent scalp alopecia.

The main limitations of our study include a small sample size, the lack of a control group having received another chemotherapeutic regimen or having another cancer and the bias related to memory recollection by the patient to determine whether spontaneous regrowth occurred.

In conclusion, severe and permanent female hair loss, especially scalp alopecia, is a new and rare cutaneous side-effect of the sequential FEC–docetaxel regimen used for early breast cancer adjuvant treatment. This alopecia is clinically and histologically consistent with female androgenetic alopecia and is probably related to taxane use. Considering the increasing role of taxane-based therapies in adjuvant treatment, physicians and patients should be aware of this new distressing side-effect.

disclosure

The authors have declared no conflicts of interest.

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Outcome and clinical–biological characteristics of patients with advanced breast cancer undergoing removal of ovarian/pelvic metastases

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Background: Patients with metastatic breast cancer to the ovary, without tumor debulking and after systemic therapy, have a 5-year survival rate < 10%.

Patients and methods: We analyzed a series of 37 patients, operated in one institution over 10 years, for both the primary tumor (PT) and ovarian/pelvic metastases (OPM). Estrogen receptors (ER), progesterone receptors (PgR), HER-2 and Ki-67 were determined.

Results: Patients were predominantly young: 27 (73%) patients were < 50 years. Average ER/PgR expression did not change significantly between PT (mean ER = 66%, PgR = 35%) and OPM (mean ER = 67%, PgR = 28%). Median time to OPM was 42 months (range 0–176); 5-year OS after OPM was 51% (95% confidence interval 32% to 67%). When combining ER and PgR status, patients with ER > 50% on both PT and OPM and with PgR > 50% on PT and/or OPM (good prognosis, 11 patients) had a better outcome versus 0 patients with ER and PgR ≤ 50% on both PT and OPM (bad prognosis, eight patients) and also versus the remaining patients (intermediate prognosis, 18 patients), *P* value = 0.010.

Conclusion: Patients with OPM from breast cancer show a favorable prognosis after tumor debulking, whether it was radical or not, especially when a high expression of ER and PgR is present in both PT and OPM.

Key words: breast cancer, ER status, HER-2 overexpression, ovarian metastases, PgR status, prognosis

introduction

Breast cancer is the most common cancer in European women accounting for an incidence of 28.9% [1]. Approximately 6%–10% of patients with breast cancer have evidence of distant

metastases at diagnosis, and 20–85% of patients will develop metastatic disease within 5 years of the initial diagnosis [2].

The most common metastatic sites are bones, liver and lungs. Ovarian metastases (OMs) have a lower incidence and still bring many open questions as regards the diagnosis, treatment and prognosis. Metastases and micrometastases in the ovaries have been reported in different series with a prevalence ranging from 3% to 30%, including autopsies, prophylactic or therapeutic ovariectomies, and incidental

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