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Original Article

Tamoxifen *vs* Tamoxifen plus 13-cis-retinoic acid *vs* Tamoxifen plus Interferon α-2a as first-line endocrine treatments in advanced breast cancer: updated results of a phase II, prospective, randomised multicentre trial

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Abstract. *Aims and background:* To demonstrate the efficacy of 13-cis-retinoic acid (RA) or Interferon α-2a (IFN α-2a) with Tamoxifen (TAM) in the treatment of advanced breast cancer. *Methods:* Ninety-nine postmenopausal patients with advanced breast cancer, and a positive or unknown estrogen (ER) or progesterone (PgR) receptor status, were randomised to receive TAM 20 mg/m^2/day orally (arm A), or TAM plus RA 1 mg/kg/day orally (arm B), or TAM plus IFN α-2a 3 MU thrice a week intramuscular (arm C). The three treatment groups were well balanced in terms of the main prognostic factors. *Results:* Response was evaluable in 32 of the patients in arm A, 32 in arm B, and 30 in arm C. Intention-to-treat analysis showed no significant difference of response rate in the three arms (44% *vs* 38% *vs* 42%). After an eight years median follow-up, there was no significant between-group difference in median overall survival: 47.4 *vs* 38.2 *vs* 45.1 months. Side effects were negligible in arm A, but cutaneous (39%) and mucosal (62%) toxicities were frequent in arm B, and flu-like syndrome and/or myalgia (46%) in arm C. *Conclusions:* The administration of RA or IFN α-2a does not add anything to the therapeutic effects of TAM. (www.actabiomedica.it)

Key words: Tamoxifen, 13-cis-retinoic acid, interferon α-2a, advanced breast cancer

Introduction

In vitro studies have shown that retinoids inhibit the proliferation of neoplastic cells, particularly breast cancer cells (1), and it has been also observed that the combination of retinoids and tamoxifen (TAM) can have positive effects on the inhibition of cell growth (2). These effects are partially due to the ability of both drugs to stimulate the expression of the negative growth factor TGF-β (3). However, clinical studies on the use of retinoids in the treatment of advanced breast cancer have led to essentially negative results (4), although these involved patients who were refractory to conventional treatments.

It has been long known that, in addition to its antiviral effects, Interferon-α (IFN-α) shows antineoplastic activity due to immunomodulatory mechanisms, antiproliferative and/or differentiating effects, the inhibition of angiogenesis, interactions with growth factors, and the modulation of gene expression. As a single agent, despite reports that it has a certain degree of activity (5-10), it shows little or no

therapeutic effect in advanced breast cancer (11, 12), but more interesting results have been obtained when it is combined with TAM (13, 14).

The aim of this study was to investigate the efficacy of 13-cis-retinoic acid (RA) or IFN-α2a when used together with TAM in the treatment of advanced breast cancer.

In a previous work we reported the preliminary results of this trial (15).

Now we present the update with a longer follow-up.

Patients and methods

The entry criteria of this study of postmenopausal patients with metastatic breast cancer included a histological diagnosis of breast cancer, and age of <75 years, an unknown or positive estrogen and/or progesterone receptor status, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, a life expectancy of ≥3 months, leukocyte and platelet counts of respectively ≥3.500/mm^3 and ≥100.000/mm^3, and creatininemia and bilirubinemia levels of ≥1.5 mg/dl.

Post-menopause is defined as a period of amenorrhea of at least 12 months in patients aged ≥53 years or who had undergone ovariectomy; younger patients had to have a period of amenorrhea of at least 12 months and plasma FSH and LH levels of >40 MU/ml.

The patients could have received one or more lines of chemotherapy for advanced disease provided that they showed disease progression and all manifestations of acute toxicity had disappeared. Previous adjuvant endocrine therapy was allowed provided that at least 24 months had passed since its discontinuation; previous adjuvant chemotherapy was allowed regardless of the time since its discontinuation.

Patients who had received previous endocrine therapy for advanced disease were excluded, as were those in whom the only disease manifestation was osteoblastic bone metastasis or pleural/peritoneal effusion. The other exclusion criteria were massive liver metastases or central nervous system metastases; other previous or concomitant malignancies (excluding adequately treated skin carcinoma or *in situ* carcinoma of the uterine neck); heart failure and/or severe symptomatic ischemic heart disease and/or severe arterial hypertension and/or previous thromboembolic episodes; psychic disorders considered as making it difficult or impossible to apply the therapeutic programme.

The study was approved by our Ethics Committee and all of the patients gave their written informed consent.

Upon entry, a medical history was taken, and all of the patients underwent a physical examination, blood chemistry tests, a chest X-ray, bone scintigraphy, skeletal X-ray (except in the case of negative bone scintigraphy results), and liver echography or computed tomography. The patients subsequently underwent a physical examination and laboratory tests every month for the first three months, and then every three months; instrumental evaluations of the lesions present at study entry after three months, and then every three months; and chest X-ray, bone scintigraphy and hepatic echography (if normal at baseline) after six months, and then every six months.

Estrogen and progesterone receptors were measured using the carboxydextrane method in accordance with the guidelines of the European Organisation for Research and Treatment of Cancer (EORTC), or immunohistochemical methods.

Since the study was carried out before the adoption of the Response Evaluation Criteria In Solid Tumors (RECIST) criteria, therapeutic response was evaluated on the basis of the World Health Organisation (WHO) criteria (16).

Three treatment arms were analysed: arm A received conventional treatment with TAM 20 mg/m^2/day orally in two daily administrations until progression or disease relapse; arm B received the same TAM treatment plus RA 1 mg/kg/day orally in a single daily administration until progression or disease relapse; and arm C received TAM + IFN-α2a 3 MU intramuscular thrice weekly until progression or disease relapse.

Any dose adjustment due to early side effects could only be made after at least one week of treatment. Dose reductions or the temporary or permanent discontinuation of RA or IFN-α2a were foreseen on the basis of the degree of toxicity: grade I = no dose reduction; grade II = 50% reduction in RA or 33% reduction in IFN-α2a; grade III = 75% reduction in RA or temporary discontinuation of IFN-α2a (with sub-

sequent resumption at 33% of the starting dose); grade IV = permanent discontinuation of either drug.

Statistical analysis

The design of this 3-arm phase II randomised trial was based on the assumption that the response rate to first-line endocrine treatment would be approximately 40% with a median time to progression of about seven months. It was planned to enrol approximately 90 evaluable patients (about 30 patients per arm).

The χ^2 test was used to examine whether the types of response and toxicities were different in the three treatment groups; Kaplan-Meier curves were used to describe the time to progression and overall survival.

Three post-study hypotheses were postulated: the activation of a phase III randomised study comparing TAM and TAM + RA if the latter proved to be better than TAM, with no grade 3-4 toxicity; the activation of a phase III randomised study comparing TAM and TAM + IFN- α2a if the latter proved to be better than TAM, with no grade 3-4 toxicity; the discontinuation of the study without the activation of subsequent studies in the case of treatment equality, grade 3-4 toxicity.

Results

This study involved 99 patients (32 in arm A, 34 in arm B and 33 in arm C), 94 of whom were evaluable for response (32 in arm A, 32 in arm B and 30 in arm C); five patients were unevaluable because of insufficient treatment (2 in arm B and 3 in arm C).

Table 1 shows that the three groups were well ba-

Table 1. Patient characteristics

	TAM	TAM + RA	TAM + IFN-α2a
Eligible	32	34	33
Performance status (ECOG)			
0-1	30	27	32
2-3	2	7	1
Menopause			
Postmenopause ≤60 years	20	16	16
Postmenopause >60 years	12	18	17
Disease-free interval			
None	1	5	9
≤2 years	4	5	5
>2 years	27	24	19
Dominant site			
Soft tissue	11	10	11
Bone	11	13	12
Viscera	10	11	10
Estrogen receptors			
Positive	10	15	15
Unknown	24	19	18
PRogesterone receptors			
Positive	10	11	13
Unknown	24	23	20
Previous adjuvant therapy			
Yes	19	19	18
No	13	15	15
Previous chemotherapy for advanced disease			
Yes	4	6	1
No	28	28	32

Table 2. Response (intention-to-treat analysis)

	TAM	TAM + RA	TAM + IFN-α2a
Patients	32	34	33
Insufficient treatment	0	2	3
Progression	10	12	8
Stable disease	8	7	8
Partial response	9 (28%)	11 (32%)	10 (30%)
Complete response	5 (16%)	2 (6%)	4 (12%)
Complete + partial response	14 (44%)	13 (38%)	14 (42%)

lanced. Overall, the dominant site of metastasis was soft tissue in 32%, bone in 36% and viscera in 32%. Fifty-seven percent of the patients had received previous adjuvant treatments and only 11% previous chemotherapy for advanced disease; none had received endocrine therapy for advanced disease.

The overall response rate (CR + PR) at intention-to-treat analysis was 44% (95% CI: 26.8-61.2) in arm A, 38% (95% CI: 21.7-54.3) in arm B, and 42% (95% CI: 25.2-58.8) in arm C, with no significant difference among the groups; the CR rates were respectively 16% (95% CI: 3.3-28.7), 6% (95% CI: 0-13.9) and 12% (95% CI: 0.9-23.1) (Table 2).

Survival

After a median follow-up of eight years, there was no significant between-group difference in the overall median survival: 47.4 months (95% CI: 26.8-68.0) in arm A, 38.2 months (95% CI: 18.9-57.4) in arm B, and 45.1 months (95% CI: 30.5-59.7) in arm C (Fig. 1).

The median time to progression was 13 months in arm A, 12.5 months in arm B, and 10 months in arm C.

Toxicity

Side effects were negligible in arm A; cutaneous (39%) and mucosal toxicity (62%) were frequent in arm B; and flu-like syndrome and/or myalgia (46%) in arm C.

Most of these toxicities were grade 1-2 (Table 3).

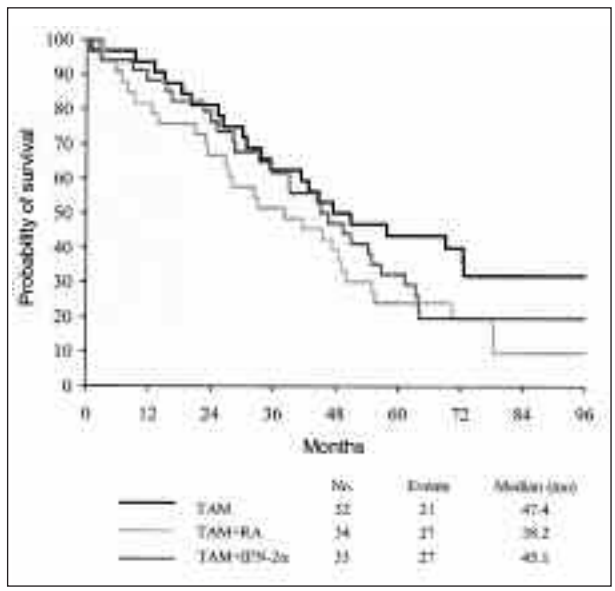

Figure 1. Overall suvival by treatment arm.

Discussion

This study was started in the 1990s, when tamoxifen represented the standard endocrine treatment for patients with metastatic breast cancer. However, although third-generation aromatase inhibitors are currently the most widely used drugs in the first-line endocrine treatment of advanced breast cancer (17-22), tamoxifen still plays a fundamental role in the disease management.

The rationale for TAM + RA or IFN-α2a combinations is based on the results of preclinical studies and preliminary clinical experiences indicating that

Table 3. Toxicity

	TAM	TAM + RA	TAM + IFN-α2a
Patients	32	34	33
Leukopenia			
Grade 1-2	3 (9%)	1 (3%)	6 (18%)
Grade 3-4	-	-	-
Anemia			
Grade 1-2	2 (6%)	1 (3%)	3 (9%)
Grade 3-4	-	-	-
Vomiting			
Grade 1-2	3 (9%)	1 (3%)	8 (24%)
Grade 3-4	-	-	1 (3%)
Flu-like syndrome			
Grade 1-2	2 (6%)	-	13 (39%)
Grade 3-4	-	-	-
Mucositis			
Grade 1-2	-	20 (59%)	1 (3%)
Grade 3-4	-	2 (6%)	-
Myalgia			
Grade 1-2	-	5 (15%)	1 (3%)
Grade 3-4	-	-	1 (3%)
Skin toxicity			
Grade 1-2	-	15 (44%)	1 (3%)
Grade 3-4	-	6 (18%)	-
Alopecia	-	1 (3%)	-
Metrorrhagia	1 (3%)	1 (3%)	-
Hot flushes	3 (9%)	-	1 (3%)

they might be more effective than TAM alone (1-14). In particular, Pozzolt et al. (13) treated three patients with TAM 30 mg/day combined with subcutaneous IFN-α 3 MU/day (the IFN-α dose was reduced to 3 MU twice a week because of the onset of leukopenia in two patients), and one experienced an extremely long partial remission lasting 59 months. In another study, Recchia et al. treated 20 patients with metastatic breast cancer refractory to conventional therapy with a combination of TAM plus intravenous retinol palmitate and subcutaneous INF-β 1 MU/day thrice weekly, and observed seven complete and five partial responses (14).

However, our results show that the two experimental treatments are not superior to conventional TAM therapy; furthermore, the patients in the two combined treatment arms experienced more side effects.

From the patients' characteristics, the lack of knowledge of receptor status can be noted; this can be explained by the fact that this procedure was not routinely performed in the 90's; however the three groups were well balanced.

On the basis of our findings, the combination of TAM with RA and/or IFN cannot be recommended in women with metastatic breast cancer.

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