Weekly paclitaxel (Ta) and capecitabine (Xel) in HER2 negative metastatic breast cancer (MBC): a multicentre GINECO randomised phase II study comparing two TaXel schedules

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ABSTRACT - N°1114

BACKGROUND: Ta and Xel are synergistic *in vitro*. Compared to a continuous weekly Tax combined with a classical 14 days (d)/21 Xel administration *(Elza-Brown et al ASCO 2000)*, we have explored the combination of Xel 5d/week (wk) and weekly Ta 3 wk out of 4 with the objective of increasing the efficacy/toxicity ratio of the TaXel combination.

METHODS: Patients (pts) in 1st or 2nd line of MBC, previously treated with anthracycline ± docetaxel were randomised either to A: Ta (60 mg/m²/w) + Xel (2000 mg/m²/d x 14 d/21) or to B: Ta (80 mg/m²/w) + Xel (2000 mg/m²/d x 5 d/wk) 3wk out of 4.

RESULTS: From 01/2006 to 01/2008, 130 pts were accrued (A 66, B 64). Pt characteristics were well balanced between the two arms including median age (58 yrs), histologic type and grade, hormone receptor-positive tumour (80%), previous treatment, visceral disease (72%), number of sites (>1; 63%), ECOG PS (0; 42%, 1; 58%). Pts received a median of 6 cycles (1-23) with a received/planned mean dose of 89.3% for Ta in both arms and of 74 and 76% for Xel respectively in arm A and B. Haematological toxicity (Tox) was low in both arms with neutropenia Gr 3 in only 8% of cycles, G-CSF support in 2% of cycles and infection G3 in 5 pts. Alopecia G2 was less frequent in arm A (29 *vs* 60%). Other Tox were similar in both arms: [G2/3 (%) cutaneous (35/17), pain (36/9), fatigue (26/13), neuropathy (20/3), diarrhoea (15/6), mucositis (8/2), vomiting (9/1)] but treatment interruption due to Tox was more frequent in A (A 19, B 7 pts) (p=0.02). Response rate was 52% (B) *vs* 44% (A). A progression-free survival advantage was seen for B over A (366 *vs* 272 days, p=0.15) including in the triple negative pt subset (n = 26 pts) (197 *vs* 150 days, p=0.07).

CONCLUSION: The intermittent schedule (3 wk out of 4) of weekly paclitaxel and capecitabine 5d/week is a well accepted, safe and effective TaXel regimen and might be a chemotherapy regimen of choice in MBC including triple negative patients.

BACKGROUND

- The combination of a Taxane and Capecitabine has demonstrated a synergic effect and significant antitumour activity in patients with advanced breast cancer.[1,2]
- Paclitaxel (175 mg/m² q3w) combined with a classical 14 days/21 Xel administration (standard schedule) showed excellent efficacy (Objective Response Rate: 52%; Time To Progression: 8.1 months) in a phase II study in metastatic breast cancer.[2]
- However, this schedule of Ta in combination with Xel was associated with significant toxicities (particularly hand-foot syndrome 42%).[2]
- Xel given as 1000mg/m² bid 5d/wk was associated with an excellent efficacy/safety ratio in phase I.[3]
- The purpose of this study was to explore the efficacy/toxicity safety of the combination of Xel 5d/week (wk) and weekly Ta 3 wk out of 4 compared to a continuous weekly Tax combined with a classical 14 days (d)/21 Xel administration (standard schedule) in patients with MBC.

PATIENTS AND METHODS

STUDY DESIGN

- This is a phase II, open label, multicentre, prospective, randomised study. All patients provided written informed consent.
  The study was conducted in compliance with Good Clinical Practice Guidelines.

TREATMENT

Median dose-intensity of Taxol (mg/m²/week) was identical in both arms

Patients

- Women ≥ 18 years with HER2-negative MBC
- First or second line of MBC
- ECOG 0-2

Number of patients: n=130

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Arm A (n=66)
(standard schedule - every 21 days)
TAXOL IV: 60mg/m² D1, D8 and D15
XELODA per os: 1000mg/m² bid D1-D14

Arm B (n=64)
(experimental schedule - every 28 days)
TAXOL IV: 80mg/m² D1, D8 and D15
XELODA per os: 1000mg/m² bid D1-D5, D8-D12 and D15-D19

STUDY OBJECTIVES

Main objective

- Assessment of the proportion of patients who needed a dose reduction in the first 6 months of the treatment related to a grade 3-4 toxicity.

Secondary objectives

- Complete response (CR), partial response (PR) according to RECIST criteria, and response duration.
- Safety.
- Time to progression (TTP).
- Overall survival.

STATISTICAL ANALYSIS

- The primary endpoint of this study was to determine the proportion of patients who needed a dose reduction in the first 6 months of the treatment or a delay more than 1 week in one cycle related to a grade 3-4 toxicity according to CTCAE.
- The sample size of this study was based on estimates of dose reduction rate of about 75%. On the basis of a predicted attrition rate of 15%, α risk = 0.05 (type I error) and β = 0.20 (type II error), a total of 130 patients were needed (65 per arm) for the study.

RESULTS

PATIENT DEMOGRAPHICS

- From 01/2006 to 01/2008, 130 patients were accrued (66 in Arm A and 64 in Arm B). Patient (Pt) characteristics were well balanced between the two arms.

Patient and disease characteristics

Characteristics (%)		Arm A (n=66)	Arm B (n=64)
Age, years	• Median	58	59
	• Range	34-82	39-78
PS	• 0	47	38
	• 1/2	53	62
Histology	• Ductal	83	86
	• Lobular	11	9
	• Other	6	5
Histologic tumour evaluation	• Well differentiated	9	6
	• Moderately differentiated	30	34
	• Poorly or undifferentiated	44	38
	• Unknown	17	22
ER, PR status	• Positive (ER+, and/or PR+)	83	77
	• Negative (RH-)	17	23
HER2 status	• Negative	98	94
	• Unknown	2	6
Metastatic sites	• Bone	59	56
	• Hepatic	47	50
	• Lung/mediastin	44	31
	• Lymph nodes	32	38
	• Other	19	22
No. of metastatic sites	• 1	33	41
	• >1	67	59
Prior adjuvant therapy	• Chemotherapy	70	59
	• Hormonotherapy	61	45
Prior palliative therapy	• Chemotherapy	8	9
	• Hormonotherapy	26	16
	• Chemotherapy + hormonotherapy	33	39
	• No treatment	33	36

Abbreviations: ER, oestrogen receptor, PR, progesterone receptor, RH, receptor hormone

TREATMENT EXPOSURE

- A total of 414 and 402 cycles of paclitaxel and capecitabine were administered to 66 patients in arm A and 64 in arm B, respectively.
- Patients received a median of 6 cycles (range 1 to 23 cycles) with a received/planned mean dose of 89% for Ta in both arms and 75% for Xel in both arms in patients who were on treatment.

DOSE REDUCTIONS AND TREATMENT DELAYS

The PRIMARY OBJECTIVE of the study was met:

- There is significantly less dose reduction throughout the first 6 cycles in patients treated in arm B (67%) compared to arm A (82%).

Dose reductions

Dose reductions (%) (throughout the first 6 months)	Arm A (n=66)	Arm B (n=64)
• Taxol	48	45
• Xeloda	70	59
• Taxol and Xeloda*	82	67

*p=0.05

- Delayed cycles rates were similarly reported in arm A (58%) compared to arm B (50%), p=0.386

SAFETY

- Treatment discontinuations due to toxicity were significantly more frequent in arm A (29%) than in arm B (8%) (p=0.02). The difference between the 2 arms is mainly due to non-haematological toxicity (A=26% of the pts, B = 8%), including hand-foot syndrome (A = 12%, B = 2%).
- Hospitalisation for toxicity was required for 14% and 3% of the patients in arm A and B, respectively.

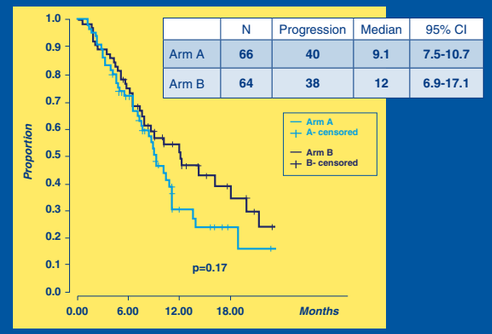
Treatment-related grade 3/4 - Adverse Events and supportive treatments

Grade 3/4 - Adverse events (%)		Arm A (n=66)	Arm B (n=64)
Haematological toxicities	• Leukopaenia	5	16
	• Neutropaenia	12	23
	• Thrombocytopaenia	-	-
	• Anaemia	6	32
Supportive treatments	• G-CSF	8	8
	• Antibiotics	29	22
Non haemato-logical toxicities	• Hand-foot syndrome	20	16
	• Pain	9	9
	• Vomiting	2	2
	• Diarrhoea	12	-
	• Fatigue	11	16
	• Infection	5	3
	• Febrile neutropaenia	2	-
	• Sensory neuropathy	2	5
	• Oedema	5	-
	• Hypersensitivity reaction	-	2
	• Alopecia *(grade 2)*	29	60

EFFICACY

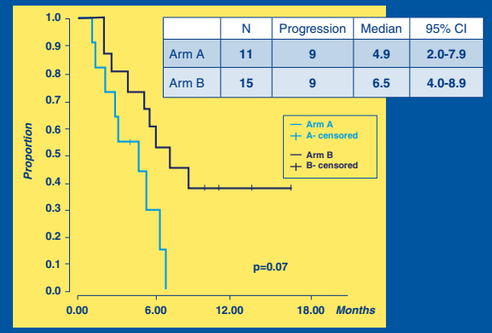
- Objective response rate was not significantly different between the two arms (44% in arm A *vs* 52% in arm B, p=0.524).
- A progression-free survival advantage was seen in arm B over A (12 *vs* 9 months, p=0.172), including in the triple negative patient subset (n=26 patients) (6.5 *vs* 4.9 months, p=0.07) (FIGURES 1 & 2).

Fig.1: ***Progression free survival of the whole population (Kaplan-Meier)***



	N	Progression	Median	95% CI
Arm A	66	40	9.1	7.5-10.7
Arm B	64	38	12	6.9-17.1

Fig.2: ***Progression free survival of the triple negative subset population (Kaplan-Meier)***



	N	Progression	Median	95% CI
Arm A	11	9	4.9	2.0-7.9
Arm B	15	9	6.5	4.0-8.9

CONCLUSION

The intermittent TaXel schedule (weekly taxol 3/4 weeks and Xeloda 5d/wk concomitant with Taxol administration) was found to have a more favorable benefit/risk ratio than the standard TaXel schedule (continuous weekly Taxol and d1-14 Xeloda):

- ***A better tolerance (less dose reduction & early treatment stopping)***
- ***And a trend for better efficacy in term of progression-free survival***

These encouraging results in favor of the intermittent TaXel schedule were also found in the triple negative population warranting further studies in this subset of MBC patients.

REFERENCES

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