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Randomized study of single-agent metronomic *versus* weekly oral vinorelbine (VNR) as first-line chemotherapy in patients with HR+/HER2- advanced breast cancer

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Abstract

Background

- Single-agent chemotherapy (CT) is a valuable option for patients with advanced breast cancer (ABC) and weekly oral VNR is one of the recommended agents. Metronomic VNR increases patient's exposure to the drug while improving safety. In early studies, minimal toxicity and promising efficacy were observed with metronomic VNR 50 mg thrice weekly (tw). We randomized patients with ABC to receive either metronomic or weekly oral first-line VNR.

Methods

- Open-label, multicentre, randomized phase II study evaluating Disease Control Rate (DCR) as primary endpoint in patients previously untreated with CT for HR+/HER2- ABC, pretreated with endocrine-therapy (ET) and no longer candidates to further ET. Arm A: Metronomic VNR 50 mg tw, Arm B: VNR 60 mg/m² weekly at cycle 1, increased to 80 mg/m² weekly for subsequent cycles in the absence of grade 3-4 neutropenia, until progression or intolerance.

Results

- 163 patients included (82 in arm A, 81 in arm B): 86% had ≥2 organs involved and 63% had previous 1-2 lines of ET. Relative dose intensity ≥ 90% per patient was 58.5% in arm A and 29% in arm B. Primary endpoint was reached in both arms with DCR of 63.4% [95%CI: 52.0 - 73.8] in arm A and 72.8% [95%CI: 61.8- 82.1] in arm B, respectively. Median PFS was 4.0 [95% CI: 2.8; 5.4] and 5.6 [95% CI: 4.4; 7.8] months in arm A and arm B, respectively. Median overall survival was 22.3 months [95% CI: 19.0; 27.3] in Arm A and 26.7 months [95%CI: 22.2; 37.8] in arm B. Grade 3-5 adverse events were 31% in arm A and 60% in arm B, including 24% versus 51% of neutropenia, and 0% versus 2.5 % of febrile neutropenia, respectively. We observed less gastrointestinal toxicity in arm A than in arm B: 46% versus 73%, any grade. Two toxic deaths were observed in each arm (2 sepsis, 1 enterocolitis, 1 cardiac failure).

Conclusions

- Although the study was not comparative, PFS and OS were numerically higher in the weekly arm, while tolerance and dose intensity were better in the metronomic arm, suggesting "peak effect". Awaiting the results of other ongoing randomized studies in combination or later lines, weekly single agent VNR should be preferred over metronomic single agent VNR in first line CT after progression on ET in HR+ ABC patients.

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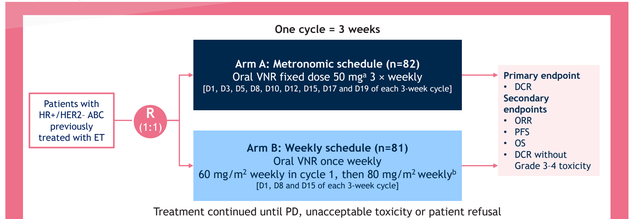
Background

- Single-agent chemotherapy (CT) is recommended as the preferred treatment option for patients with advanced breast cancer (ABC).[1]
- Vinorelbine (VNR) is one of the recommended agents available.[1]
- Oral VNR as a single agent, administered once weekly at 60-80 mg/m², is effective and well-tolerated, as demonstrated in several randomised studies.[2-4]
- Metronomic CT represents an interesting approach to the treatment of solid tumours, with the potential to expose patients to a significant amount of drug with an improved safety profile.
  - It comprises fractionated, frequent and long-term administration of a single drug without breaks until disease progression or unacceptable toxicity.[5,6]
  - It may have a complementary mechanism of action to classical cytotoxic CT, with addition of a tumour vasculature therapeutic target counteracting any tumour regrowth that may occur between CT cycles.[5,7]
- In phase I studies of patients with advanced cancer, metronomic VNR thrice weekly was associated with minimal toxicity and promising efficacy at a dose of 50 mg administered 3 × weekly.[8-10]
- The objectives of this open-label, multicentre, randomised, non-comparative phase II study were to:
  - Assess the efficacy and safety of a metronomic schedule of VNR delivered at fixed doses 3 × weekly as first-line treatment in patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) ABC previously treated with endocrine therapy (ET).
  - Evaluate whether the metronomic approach may offer the possibility of disease control coupled with a favourable safety profile in these patients.

Methods

- Primary endpoint:
  - To evaluate the disease control rate (DCR) with metronomic oral VNR and weekly oral VNR in patients with HR+/HER2- ABC previously untreated with CT.
  - DCR was defined as the proportion of patients with complete response [CR], partial response [PR] or stable disease [SD].
- Statistical methodology:
  - The two-stage design for phase II clinical trials (as described by Simon) was used.[11]
  - With a null hypothesis H0 for the true DCR of 50%, an alternative hypothesis H1 of 70%, two testings, a type I error α of <2.5% and a type II error ß of <10%, 73 evaluable patients per treatment arm had to be enrolled in this phase II study.
- Efficacy was determined by tumour assessments according to RECIST guidelines (version 1.1), conducted at baseline and every 6 weeks until disease progression, and adverse events (AEs) were graded according to National Cancer Institute Common Toxicity Criteria version 4.0.
- Randomisation (1:1) was stratified according to centre, prior taxane use (yes/no), prior everolimus (yes/no) and visceral metastases (yes/no).
- The efficacy analyses were performed in the intent-to-treat population (Arm A: n=82; Arm B: n=81), and the safety and exposure analyses were performed in the safety population (Arm A: n=82; Arm B: n=80).
- Inclusion criteria:
  - Age ≥18 years and provided written informed consent.
  - Histologically confirmed adenocarcinoma of the breast, with documented locally recurrent or metastatic disease previously untreated by CT and not amenable to curative surgery or radiotherapy.
  - HR+/HER2- disease.
  - Presence of ≥1 measurable lesion (RECIST version 1.1) not previously irradiated and completed staging within 4 weeks.
  - Should have received ≥1 previous ET for breast cancer at any disease stage and/or no longer a candidate for further ET.
  - Karnofsky performance status (KPS) ≥70%.
  - Adequate bone marrow, hepatic and renal function.
- Exclusion criteria:
  - Females with positive pregnancy test or who are pregnant or lactating.
  - Symptoms suggesting CNS involvement or leptomeningeal metastases.
  - Concomitant ET for ABC.
  - Malabsorption syndrome or disease significantly affecting gastrointestinal function or major resection of the stomach or proximal small bowel that could affect absorption of oral VNR.
  - Prior treatment with CT in the locally advanced or metastatic setting.
  - Dysphagia or an inability to swallow tablets.

Study design



[a] One 20-mg capsule + one 30-mg capsule.
[b] In the absence of Grade 3 or 4 neutropenia.
ABC, advanced breast cancer; D, day; DCR, disease control rate; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomisation; VNR, vinorelbine.

Results

- Patient clinical characteristics were generally balanced between the two arms, except for the mean time since diagnosis (**Table 1**).

Table 1. Patient characteristics

	Arm A: Metronomic Schedule (n=82)	Arm B: Weekly Schedule (n=81)
Mean (SD) age, years	64.2 (10.2)	65.5 (11.8)
Age category, n (%)		
18-64 years	42 (51.2)	34 (42.0)
65-84 years	37 (45.1)	46 (56.8)
≥85 years	3 (3.7)	1 (1.2)
Median KPS at baseline, %	90.0	90.0
Mean (SD) time since diagnosis, months	92.6 (76.1)	105.9 (83.5)
Disease extent at study entry, n (%)		
Locoregional	2 (2.4)	4 (4.9)
Metastatic	80 (97.6)	77 (95.1)
No. of organs involved, n (%)		
1	11 (13.4)	12 (14.8)
2	33 (40.2)	31 (38.3)
≥3	38 (46.3)	38 (46.9)

KPS, Karnofsky performance status; SD, standard deviation.

Table 2. Drug delivery

	Arm A: Metronomic Schedule (n=82)	Arm B: Weekly Schedule (n=81)
Mean (SD) no. of cycles	7.5 (7.6)	9.5 (9.2)
Mean (SD) cumulative dose, mg/m²	1755.6 (1750.1)	1827.5 (1958.4)
Mean (SD) relative dose intensity per patient, %	85.0 (17.7)	75.9 (19.0)
Mean (SD) dose intensity per patient, mg/m²/week	75.7 (16.9)	57.2 (14.7)
No. patients with ≥1 dose modification, n (%)	58 (70.7)	70 (87.5)
Reasons for dose modification, n (%)		
Adverse event	41 (50.0)	64 (80.0)

SD, standard deviation.

Table 3. Clinical activity

	Arm A: Metronomic Schedule (n=82)	Arm B: Weekly Schedule (n=81)
Patients with measurable disease at baseline, n (%)	80 (97.6)	81 (100.0)
DCR (CR + PR + SD), n (%) [95% CI]	52 (63.4) [52.0-73.8]	59 (72.8) [61.8-82.1]
DCR without Grade 3-4 toxicity [95% CI]	24 (29.3) [19.7-40.4]	18 (22.2) [13.7-32.8]
ORR (CR + PR), n (%) [95% CI]	14 (17.1) [9.7-27.0]	17 (21.0) [12.7-31.5]
Median PFS, months [95% CI]	4.0 [2.8-5.4]	5.6 [4.4-7.8]

CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 4. Overall survival

	Arm A: Metronomic Schedule (n=82)	Arm B: Weekly Schedule (n=81)
Patients with measurable disease at baseline, n (%)	80 (97.6)	81 (100.0)
Median OS, months [95% CI]	22.3 [19.0-27.3]	26.7 [22.2-37.8]
Estimated OS rate, % [95% CI]		
12 months	72.7 [61.5-81.1]	74.7 [63.6-82.9]
24 months	46.8 [35.5-57.4]	56.4 [44.7-66.6]
36 months	32.5 [20.5-45.1]	44.0 [31.1-56.2]

CI, confidence interval; OS, overall survival.

- Selected treatment-related AEs are summarised in **Table 5** and an overview of serious AEs (SAEs) and AEs leading to dose reduction or discontinuation is shown in **Table 6**.
- AEs of any grade occurred in 58 patients (70.7%) in Arm A and 75 (93.8%) in Arm B; the rate of grade 3-5 AEs was 31% and 60%, respectively.
- Two toxic deaths occurred in each arm (sepsis and enterocolitis in Arm A, sepsis and cardiac failure in Arm B).

Table 5. Selected treatment-related AEs

n (%)	Arm A: Metronomic Schedule (n=82)				Arm B: Weekly Schedule (n=80)			
	Any grade	Grade 3	Grade 4	Grade 5	Any grade	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders	27 (32.9)	9 (11.0)	11 (13.4)	0	57 (71.3)	24 (30.0)	18 (22.5)	0
Neutropenia	27 (32.9)	9 (11.0)	11 (13.4)	0	57 (71.3)	24 (30.0)	18 (22.5)	0
Anaemia	2 (2.4)	0	0	0	4 (5.0)	2 (2.5)	0	0
Febrile neutropenia	0	0	0	0	2 (2.5)	0	2 (2.5)	0
Gastrointestinal disorders	38 (46.3)	3 (3.7)	0	1 (1.2)	58 (72.5)	6 (7.5)	0	0
Nausea	24 (29.3)	2 (2.4)	0	0	43 (53.8)	2 (2.5)	0	0
Vomiting	7 (8.5)	0	0	0	29 (36.3)	1 (1.3)	0	0
Diarrhoea	19 (23.2)	0	0	0	25 (31.3)	1 (1.3)	0	0
Upper abdominal pain	4 (4.9)	0	0	0	6 (7.5)	0	0	0
Constipation	5 (6.1)	1 (1.2)	0	0	5 (6.3)	0	0	0
Dyspepsia	5 (6.1)	0	0	0	2 (2.5)	0	0	0
General disorders and administration site conditions	22 (26.8)	2 (2.4)	0	0	36 (45.0)	2 (2.5)	0	0
Asthenia	13 (15.9)	1 (1.2)	0	0	23 (28.8)	1 (1.3)	0	0
Fatigue	8 (9.8)	1 (1.2)	0	0	9 (11.3)	1 (1.3)	0	0
Infections and infestations	3 (3.7)	0	0	1 (1.2)	5 (6.3)	0	0	1 (1.3)
Neutropenic sepsis	0	0	0	0	1 (1.3)	0	0	1 (1.3)
Sepsis	1 (1.2)	0	0	1 (1.2)	0	0	0	0
Metabolism and nutrition disorders	4 (4.9)	1 (1.2)	0	0	11 (13.8)	0	0	0
Musculoskeletal and connective tissue disorders	2 (2.4)	0	0	0	5 (6.3)	0	0	0
Nervous system disorders	4 (4.9)	0	0	0	10 (12.5)	0	0	0
Paraesthesia	0	0	0	0	2 (2.5)	0	0	0
Skin and subcutaneous tissue disorders	3 (3.7)	0	0	0	10 (12.5)	1 (1.3)	0	0
Alopecia	3 (3.7)	0	0	0	8 (10.0)	1 (1.3)	0	0

Table 6. Overview of SAEs and AEs leading to dose reduction or discontinuation

n (%)	Arm A: Metronomic Schedule (n=82)		Arm B: Weekly Schedule (n=80)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
≥1 SAE, regardless of causality	22 (26.8)	20 (24.4)	13 (16.3)	12 (15.0)
≥1 treatment-related SAE	4 (4.9)	4 (4.9)	7 (8.8)	6 (7.5)
≥1 treatment-related AE leading to permanent discontinuation	4 (4.9)	4 (4.9)	8 (10.0)	6 (7.5)
≥1 AE requiring dose reduction, regardless of causality	15 (18.3)	14 (17.1)	31 (38.8)	25 (31.3)
≥1 related AE requiring dose reduction	15 (18.3)	14 (17.1)	30 (37.5)	25 (31.3)

AE, adverse event; SAE, serious adverse event.

Conclusion

- Although this study was not designed to confirm a statistical difference between metronomic and weekly VNR regimens (i.e. non-comparative), PFS and OS were numerically longer with weekly *versus* metronomic VNR.
- However, VNR dose intensity was higher and tolerability was improved among patients in the metronomic arm, with lower incidences of neutropenia, gastrointestinal disorders, asthenia, decreased appetite and alopecia.
- Such a paradox suggests a 'peak effect' with weekly VNR, since the dose per intake is higher with this schedule, which may explain the observed improvement in efficacy.
- Awaiting the results of other ongoing randomised studies in combination or later lines, weekly single-agent VNR should remain the preferred option over metronomic single-agent VNR as first-line CT in patients with HR+/HER2- ABC who have progressed on ET.

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MC has participated on an advisory board for Eli Lilly. NM-J has received consulting fees from AstraZeneca, Daiichi Sankyo, Pfizer, Novartis, Lilly, Pierre Fabre, Roche and GSK, and travel support from Roche, AstraZeneca, Pfizer and Novartis. MMM has received personal fees from Roche, Novartis and Eisai, and other financial support from Roche and Lilly. PM has received consulting fees from Astra Zeneca, Novartis, Pfizer, Eli Lilly and Amgen. EP has received consulting fees from AstraZeneca, Daiichi Sankyo, Pfizer, Novartis, Lilly, Pierre Fabre, Roche and GSK, research funding from Daiichi Sankyo, Pfizer, Lilly, Novartis, Seattle Genetics, AstraZeneca and Roche, and travel support from AstraZeneca, GSK, Pfizer, Lilly and GSK. JE has received consulting fees from AstraZeneca, Daiichi Sankyo, Pfizer, Novartis, Lilly, Pierre Fabre, Roche and Tesaro, research funding from Daiichi Sankyo, Pfizer, Lilly, Novartis, Seattle Genetics, AstraZeneca, Roche and Odonate, and travel support from AstraZeneca, Daiichi Sankyo, Celgene, Pfizer, Novartis, Lilly, and Tesaro. AR has participated on advisory boards for Boehringer, BMS and MSD, and internal training at Pfizer and AstraZeneca. LC has received honoraria from AstraZeneca, MSD and Pfizer, and has acting in a consulting or advisory role for Pfizer, Novartis, Tesaro and Clovis. CDA, RR, GV and CTTM are Pierre Fabre employees. BK-B, MU, HB, SM, JB, LC, TP and NC have no disclosures to declare. GF was the principal investigator of the study, participated in advisory boards, acted as a speaker, and conducted training sessions on behalf of Pierre Fabre.

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