Il tumore della mammella nei pazienti anziani

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Chemotherapy in older patients with metastatic breast cancer

- Some general concepts
- Focus on nab-paclitaxel

Challenges in treating older patients with ABC: 1. heterogeneity of the population

Ernestine Shepherd

Functional Status

Comorbidities

Organ Function

Polypharmacy

Old frail woman

Cognition

Social Support

Culture

Psychological status

Spirituality

Finances

Challenges in treating older patients with ABC: 2. underrepresentation in clinical trials

Few older adults included in registration studies!
Breast cancer as an example

Agent Name	Approval	N	Age ≥ 65	N	Age ≥ 75
Palbociclib	2/2015	37	44%	8	10%
		86	25%		--
Everolimus	7/2012	290	40%	109	15%
Pertuzumab	6/2012	60	15%	5	1%
Eribulin mesylate	11/2010	121	15%	17	2%
Lapatinib	1/2010	34	17%	2	1%
		282	44%	77	12%
Ixabepilone	10/2007	45	10%	3	<1%
		32	13%	6	2.5%

Package Insert, "Geriatric Usage" section

Courtesy of Arti Hurria & Etienne Brain

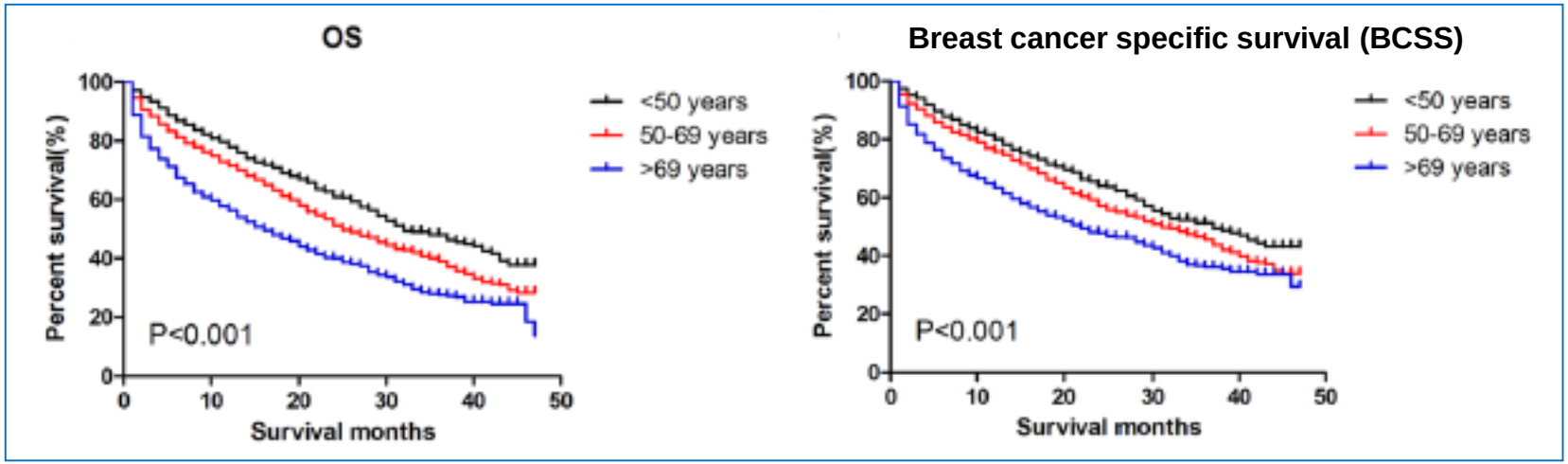
Challenges in treating older patients with ABC: 3. underrepresentation of unfit pts in elderly-focused trials

Impact of geriatric risk factors on pegylated liposomal doxorubicin tolerance and efficacy in elderly metastatic breast cancer patients: Final results of the DOGMES multicentre GINECO trial ☆

Patient's characteristics	$N = 60$
Age (years)	
Median (range)	77 (71–89)
<75	19 (31.7)
75–79	21 (35.0)
⩾80 (*n*; %)	20 (33.3)
Performance status (*n*; %)	
0	11 (18.3)
1	40 (66.7)
2	8 (13.3)
3	1 (1.7)

Falandry et al. Eur J Cancer 2013

Survival according to age in M+ BC: a SEER population based analysis



Chen et al. Scientific Reports 2017

Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA)

Chemotherapy is indicated in older patients with ER-disease, hormone-refractory disease, or rapidly progressing disease

- Elderly patients with metastatic breast cancer are expected to derive similar benefits from chemotherapy as younger patients
- Preference should be given to chemotherapy agents with better safety profiles (such as weekly taxanes, pegylated liposomal doxorubicin, capecitabine, and vinorelbine) that have been studied in older patients

Biganzoli et al. Lancet Oncol 2012

New agents

- Nab-paclitaxel
- Eribulin

Weekly *nab*-paclitaxel is safe and effective in ≥65 years old patients with metastatic breast cancer: A post-hoc analysis

Pooled data from 2 studies

ABC
≥65 years

n=33 → **nab-paclitaxel *vs.* docetaxel**

Phase II
First-line chemotherapy

n=30 → **nab-paclitaxel *vs.* solvent based paclitaxel**

Phase III
≥ first-line chemotherapy

Frequent treatment-related grade 3 and 4 adverse events in patients ≥65 years old

Adverse Events, *n* (%)	Phase 3		Phase 2			
	q3w	q3w	q3w	q3w	weekly	weekly
	Sb-PAC 175 mg/m^2 (n = 32)	*nab*-PAC 260 mg/m^2 (n = 30)	Sb-DOC 100 mg/m^2 (n = 19)	*nab*- PAC 300 mg/m^2 (n = 9)	*nab*- PAC 100 mg/m^2 (n = 14)	*nab*- PAC 150 mg/m^2 (n = 10)
Neutropenia						
Grade 3	10 (31)	8 (28)	2 (11)	4 (44)	4 (29)	4 (40)
Grade 4	11 (34)	2 (7)	14 (74)[a]	2 (22)	1 (7)	1 (10)
Leukopenia						
Grade 3	7 (22)	0	11(58)	4 (44)	1 (7)	2 (20)
Grade 4	0	0	2 (11)	0	0	0
Neuropathy – Sensory						
Grade 3	0	5 (17)	3 (16)	1 (11)	3 (21)	2 (20)
Grade 4	0	0	0	0	0	0
Fatigue						
Grade 3	1 (3)	3 (10)	6 (32)	0	2 (14)	1 (10)
Grade 4	1 (3)	0	0	0	0	0
Myalgia						
Grade 3	1 (3)	4 (13)	0	0	0	0
Grade 4	0	0	0	0	0	0
Arthralgia						
Grade 3	2 (6)	2 (7)	0	1 (11)	0	0
Grade 4	0	0	0	0	0	0
Diarrhea						
Grade 3	0	1 (3)	2 (11)	1 (11)	0	0
Grade 4	0	0	0	0	0	0

Aapro et al. Breast 2011

Final Effectiveness and Safety Results of NABUCCO: Real-World Data From a Noninterventional, Prospective, Multicenter Study in 697 Patients With Metastatic Breast Cancer Treated With nab-Paclitaxel.

Prospective multicenter study on the routine treatment in Germany with nab-paclitaxel (different dose/schedules) after failure of 1st- line treatment and when anthracyclines are not indicated (2012-2015); 697 patients; n=291 ≥ 65 years

Dosing by age	Total (N = 697)	Age < 65 Years (N = 406)	Age ≥ 65 Years (N = 291)
Duration (weeks), median (25-75% quartile)	18.3 (12.0-25.6)	18.1 (12.0-25.1)	18.4 (12.0-26.1)
Dose intensity (mg/m^2 per week), median (25-75% quartile)	76.8 (64.1-85.8)	79.1 (65.9-86.8)	71.8 (59.7-84.7)

Events of particular interest	Grade 3/4		
	Total (N = 697)	Age < 65 Years (N = 406)	Age ≥ 65 Years (N = 291)
Peripheral sensory neuropathy	30 (4.3)	20 (4.9)	10 (3.4)
Fatigue	13 (1.9)	7 (1.7)	6 (2.1)

Different applied treatment schemes of nab-paclitaxel

- q3w (260 mg/m²): according to SmPC; starting dose 260 mg/m² ± 15%
- q3w-reduced (220 mg/m²): starting dose ≤ 220mg/m²
- qw3/4 (150 mg/m²): qw3/4 (d1,d8,d15 of a 28 day cycle); starting dose 150 mg/m² ± 15%
- qw3/4 (125 mg/m²): qw3/4 (d1,d8,d15 of a 28 day cycle); starting dose ≤ 125 mg/m²
- qw3/3 (78-153 mg/m²): qw3/3 (d1,d8,d15 of a 21 day cycle); no limitation of starting dose, actual range: 78-153 mg/m²

Treatment selection bias ?

Marschner et al. Clin Breast Cancer 2018

EFFECT: A randomized phase II study to evaluate the EFficacy and impact on Function of two different doses of nab-paclitaxEl in elderly patients with advanCed breasT cancer

- Nab-paclitaxel 100mg/m2 (arm A) vs 125 mg/m2 (arm B) on day 1,8, 15 q 28
- Primary end-point: Event-free survival (EFS) where an event is either disease progression or death or decline in functional status
- 15 Italian centers

Baseline patient & tumor characteristics

Characteristic	Arm A n=79	Arm B n=79
Median age, y (range)	72 (65-84)	73 (65-88)
Median ECOG PS (range)	0 (0-2)	0 (0-2)
IADL impairment, n (%)	20 (25)	20 (25)
Grade 3-4 CIRSG, n (%)	8 (10)	10 (13)
HR +/HER2+, n (%)	68 (86)/ 2 (2.5)	67 (84)/ -
Visceral disease, n (%)	56 (71)	55 (70)
Prior exposure to T, n (%)	11 (14)	10 (13)

Treatment exposure

- More dose reductions (56% cycle vs 39%) and Rx discontinuation due to AEs (28% pts vs 14%) in arm B

Biganzoli et al. manuscript in preparation

Outcomes

- Similar efficacy in the two Rx arms

Event	Arm A 100mg/m2 (n=79)	Arm B 125mg/m2 (n=79)
Median EFS, mos (90% CI)	8.2 (5.9-8.9) 6.2 (5.8-8.4)#	8.3 (6.2-9.7) 6.4 (5.8-7.7)#
Median PFS, mos (95% CI)	8.3 (5.9-10.5)	8.8 (7.4-10.3)
Median OS, mos (95% CI)	22.4 (17.0-35.6)	20.7 (16.8-28.6)
Best OR, n (%)	n=60	n=65
CR	4 (7)	1 (2)
PR	20 (33)	26 (40)
SD	24 (40)	18 (28)
PD	9 (15)	14 (21.5)
NE	3 (5)	6 (9)

#Based on central review

Adverse Events

- Less neurotoxicity in Arm A

AEs, % incidence of ≥ 20% for G 2 or any G 3-4 in either arm	Arm A G 2/3/4	Arm B G 2/3/4
Anemia	33/3/-	37/-/-
Leucopenia	25/9/-	29/19/1
Neutropenia	23/18/1	16/32/4
Febrile neutropenia	-/1/-	-/3/-
Infection	10/3/1	4/-/-
Fever	3/-/-	-/1/-
Fatigue	32/11/-	46/5/-
Peripheral neuropathy (NTX)	15/4/-	28/10/-
Arthralgia/Myalgia	14/1/-	11/-/-
Nausea/vomiting	10/1/-	15/3/-
Diarrhea	4/5/-	6/-/-
Dyspnea	5/-/-	1/1/-
Hepatotoxicity	6/3/-	1/1/-
Alopecia	30/-/-	27/-/-

- Due to similar efficacy, lower rates of treatment discontinuation due to AEs and reduced neurotoxicity, WNP 100 is the suggested dose to be used in older pts with ABC

A Phase II Trial of Older Adults with Metastatic Breast Cancer Receiving nab-Paclitaxel: Melding the Fields of Geriatrics and Oncology

- nab-paclitaxel 100mg/m^2 day 1, 8, 15 q 28

Characteristic	Total (N=40)	
Age, years		
65-69	15	(38%)
70-74	9	(23%)
≥ 75	16	(40%)
Instrumental Activities of Daily Living (IADL)		
Median (range)	13	(6-14)
Dependence in at least one IADL	24	(60%)
Activities of Daily Living (ADL) (0-100)		
Mean (SD)	53.7	(27.94)
Dependence in ADL	26	(65%)
≥ 1 fall in the previous 6 months	9	(22.5%)
≥ 6% weight loss in the previous 6 months	10	(25%)
Comorbidities		
Median (range)	3	(0-6)

High % of pts with markers of vulnerability

- RR and PFS similar to those reported in a phase II trial utilizing a similar dosage of weekly nab-paclitaxel
- 30% pts were hospitalized and 28% stopped treatment due to Rx-related AEs
- The risk score (CARG) can identify patients who are at a high risk of experiencing severe toxicity or hospitalization, as well as those less likely to complete the planned treatment → "this could help clinicians and their older patients weigh the risks and benefits of treatment, ultimately personalizing cancer care"

Hurria et al. Clin Breast Cancer 2018

Conclusions

- Nab-paclitaxel is active in older breast cancer patients
- 100mg/m2 on days 1,8,14 q 28 is the recommended dose to be used
- Fatigue and neurotoxicity are the most frequently reported AEs
- Monitoring of patients' function is recommended
- Tools are available to predict feasibility in unfit patients
- Implementation of geriatric tests /consultations may results in improved quality of care

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CONVEGNO

Terzo incontro nazionale sul trattamento della paziente anziana affetta da carcinoma mammario

9 crediti formativi

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