Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

SAFETY AND EFFICACY OF CONCOMITANT RADIATION AND CDK4/6 INHIBITORS IN METASTATIC BREAST CANCER

Autori: B. Bettazzi1,2, N. Bertini1,2, I. Bonaparte1,2, L. Visani1, C. Becherini1, E. Scoccimarro1, V. Salvestrini1, M. Valzano1,2, I. Desideri1, V. Scotti1, C. Saieva3, I. Meattini1,2, L. Livi1,2

Affiliazioni: 1, Radiation Oncology Unit, Azienda Ospedaliera-Universitaria Careggi, Florence, Italy; 2, Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", University of Florence, Florence, Italy; 3, Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy;

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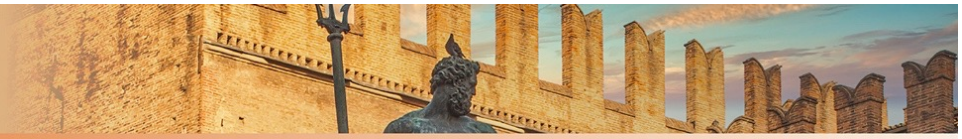

DICHIARAZIONE

Dr.ssa Beatrice Bettazzi

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
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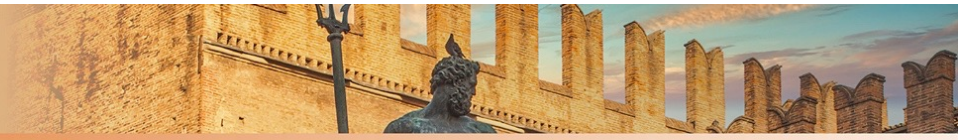


BACKGROUND

Cyclin-dependent kinase 4/6 inhibitors (**CDK4/6i**), palbociclib, ribociclib and abemaciclib, in combination with endocrine therapy (ET), currently represent the **standard of care** for I-II line **metastatic hormonal receptor (HR)-positive HER2-negative breast cancer**, demonstrating **improved efficacy** in comparison to ET alone.

In the metastatic setting, radiation therapy (**RT**) is often indicated for patients with either **palliative** or **ablative intent**.

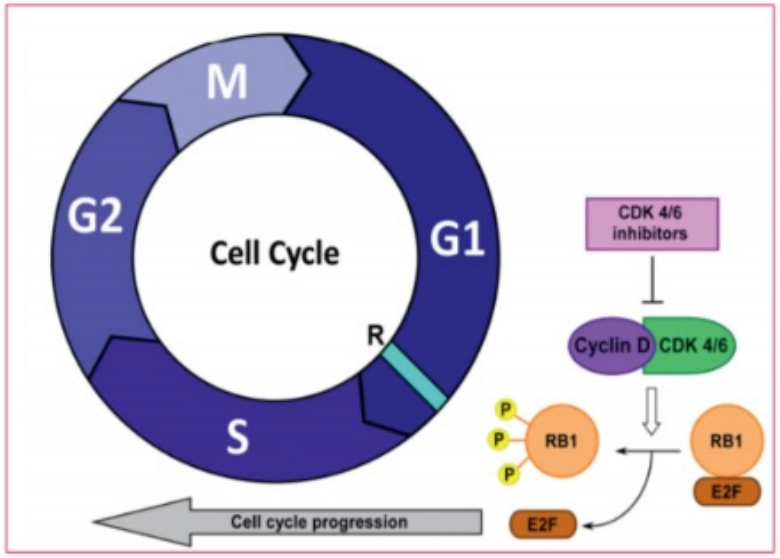
Cristofanilli M et al, Lancet Oncol 2016
Finn RS et al, N Engl J Med 2016
Slamon DJ et al, J Clin Oncol 2018
Hortobagyi GN et al, N Engl J Med 2016
Tripathy D et al, Lancet Oncol 2018
Im S et al, N Engl J Med 2019
Slamon DJ et al, N Engl J Med 2019
Sledge GW Jr et al, J Clin Oncol 2017
Goetz MP et al, J Clin Oncol. 2017

BACKGROUND

In preclinical model, CDK4/6i have demonstrated to potentially **improve the therapeutic efficiency of ionizing radiation**, even if this role is still debated

This approach is based on the rationale that:

- *The **cytotoxicity of ionizing radiation is cell cycle dependent** and cancer cells more sensitive in G1/S and G2/M transitions*
- *The **genetic knockdown of CDK4 and CDK6 confers radiosensitivity** in breast cancer cells by activating an apoptotic program and arresting tumor growth*
- *CDK4/6i cause **quiescence in non-cancerous tissues** and protect against common side effects associated with radiation exposure, such as hematologic and intestinal injury*



Pawlik, et al. IJRBP 2004
Hagen, et al. Cell Div. 2013
Whiteway, et al J Neurooncol. 2013
Johnson, et al. J Clin Invest. 2010
Wei, et al. J Clin Invest. 2016

BACKGROUND

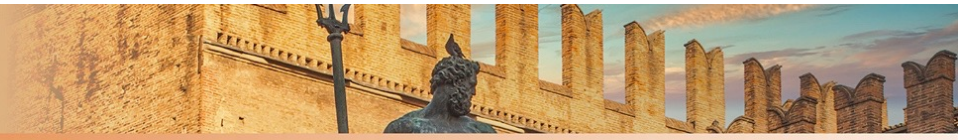
However, data available regarding the efficacy and toxicity of concurrent RT and CDK4/6i come from **small retrospective series** with **heterogeneity of administered RT**

Consequently, in clinical practice, RT is often avoided or typically more frequently delivered during the "off cycle week", or the CDK4/6i are withheld 1–3 days before and 1–3 days after treatment

Anyway, data suggest that concurrent administration is **well tolerated**, with generally a **modest increase of grade 3 or higher AEs**, with hematological toxicity being the most common

OBJECTIVE

The aim of our study is to evaluate the **safety** and **efficacy** of **concomitant RT and CDK4/6i** in metastatic HR+/HER2- breast cancer patients, comparing with patients treated with CDK4/6i alone



METHODS

We analysed data of **132 patients** consecutively treated at *Azienda Ospedaliero-Universitaria Careggi*, Florence, Italy and *Institute of Oncology*, Ljubljana, Slovenia with CDK4/6i with or without RT from September 2017 to February 2020

Primary outcome: association between RT and any adverse events (AEs)≥G3.
Secondary outcomes: association between RT and any AEs (any grade), CDK4/6i dose reduction rate and CDK4/6i treatment discontinuation rate.

Both **hematologic and non-hematologic acute toxicity** have been evaluated and scored according to CTCAE v.5.0

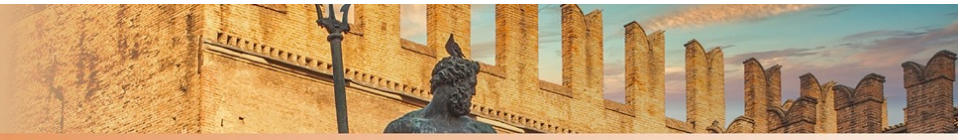
RESULTS

We performed an analysis by simple cross-tables with **chi-square test**, and **logistic analysis** to confirm emerged **associations between outcomes and several parameters**

Median age was **52.1 years** (range 32.3-78.2)

57 patients received **concomitant RT** with palliative (79.7%) or ablative intent (20.3%) during the course of CDK4/6i, while 75 patients did not

Features	N (%)
Distribution of metastases (all patients)	132 (100)
Only Bone	31 (23.5)
Only Visceral	23 (17.4)
Both	78 (59.1)
Number of sites of metastases (all patients)	132 (100)
1-2	58 (43.9)
>2	74 (56.1)
Sites of RT treated metastases	57 (100)
	70 treated sites
Bone	44 (77.2)
Spinal Bone	*26*
Non-spinal bone	*28*
Visceral	13 (22.8)
Brain	*4*
Breast	*2*
Nodal	*2*
Lung	*3*
Liver	*3*
Other	*2*
RT intent and fractionations	57 (100)
	70 treated sites
Ablative	13 (22.8)
45-54 Gy in 3 fractions	*3*
30-55 Gy in 5 fractions	*6*
21-24 Gy in 3 fractions	*2*
Other schedules	*3*
Palliative	44 (77.2)
30 Gy in 10 fractions	*7*
20 Gy in 5 fractions	*42*
8 Gy in 1 fraction	*2*
Other schedules	*5*
RT technique (per patient)	57 (100)
2D/3D	42 (73.7)
IMRT/CK	15 (26.3)



RESULTS

Outcome	Whole series (n=132) N (%)	RT group (n=57) N (%)	No RT group (n=75) N (%)	P-value*	OR (95% CI)°
Adverse events, any grade	127 (96.2)	55 (96.5)	72 (96.0)	1.0	1.15 (0.19-7.10)
Adverse events ≥ grade 3	90 (68.2)	35 (61.4)	55 (73.3)	0.19	0.58 (0.28-1.21)
CDK4/6i dose reduction	67 (50.8)	31 (54.4)	36 (48.0)	0.49	1.29 (0.65-2.58)
CDK4/6i discontinuation	8 (6.1)	1 (1.8)	7 (9.3)	0.14	0.17 (0.02-1.45)

* p-value from chi-square test.

° Hazard Ratio of specific outcome related to RT, from logistic regression analysis.

⇨ RT was **not significantly associated** with **≥G2 and any grade toxicity**

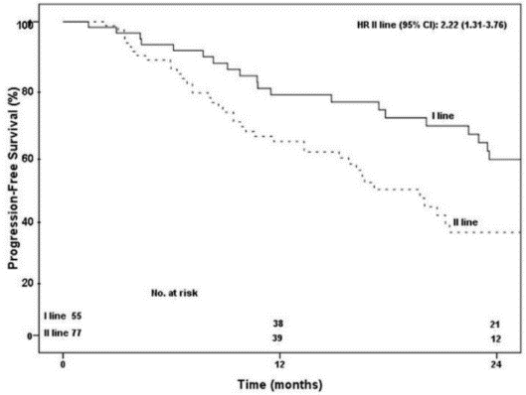
⇨ There was **no association** between RT and CDK4/6i **dose reductions and discontinuation**

Overall, the use of CDK4/6i plus ET in first or second line did **not show** an **impact** on **≥G2 toxicity** development (p=0.71), **dose reductions** (p=0.39) and **treatment discontinuation** (p=0.66)

Postmenopausal status was the only factor associated with a **significantly increased risk of ≥G2 toxicity** (p=0.005)

RESULTS

Parameter	P-values
Site of RT (bone vs visceral site)	
Any grade ≥2 toxicity	*0.73*
Any grade toxicity	*1.0*
CDK4/6i dose reductions	*1.0*
CDK4/6 discontinuations	*-*
RT technique (3D-CRT vs IMRT/CK)	
Any grade ≥2 toxicity	*0.041*
Any grade toxicity	*1.0*
CDK4/6i dose reductions	*0.76*
CDK4/6 discontinuations	*-*
Intent of RT	
Any grade ≥2 toxicity	*0.18*
Any grade toxicity	*1.0*
CDK4/6i dose reductions	*0.76*
CDK4/6 discontinuations	*-*



At a median follow up of **18.8 months**, overall **PFS rate** was **35%**

Among patients who received RT, **no significant associations** were found regarding **RT intent, technique and bone or visceral RT site**

CONCLUSION

- Our study showed that concomitant administration of RT with either palliative or ablative intent during CDK4/6i is **safe and effective**, without increased toxicity and significant impact on systemic treatment conduction

- To date, this is **one of the largest retrospective series** in which the concomitant administration of RT and CDK4/6i has been evaluated and compared to a group of patients who did not receive RT

- Data from **ongoing prospective trials** are awaited to confirm the safety and efficacy of the combination

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THANKS FOR YOUR ATTENTION

INSTITUTE OF ONCOLOGY LJUBLJANA