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Systematic or Meta-analysis Studies

Mechanism of drug resistance in relation to site of metastasis: Meta-analyses of randomized controlled trials in advanced breast cancer according to anticancer strategy

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ABSTRACT

Background: Breast cancer is heterogeneous at different levels: biologic subtypes, intratumoral areas, and sites of metastases. Randomized controlled trials (RCTs) classify metastatic sites as visceral or non-visceral, but this has little influence in treatment decisions, particularly in the absence of clinical urgency. Indeed, it is unclear if response to treatments differs among sites of metastases.

Patients and methods: RCTs investigating 3 different anticancer strategies in metastatic breast cancer were identified: (1) new hormonal therapy, (2) new targeted therapies in hormone receptor positive tumours (everolimus or palbociclib), and (3) new anti-HER2 therapies. RCTs reporting hazard ratios (HR) for Progression Free Survival (PFS) and Overall Survival (OS) for sub-groups based on sites of metastases were weighted using generic inverse variance approach, and pooled in meta-analyses using Revman 5.3. Subgroup difference was tested with Chi^2 statistics.

Results: Eleven RCTs (6701 pts.) qualified. There was a significant difference in PFS between women with visceral versus non-visceral metastases when two endocrine strategies were compared, with benefits limited to women with visceral metastases [Pooled HR 0.85; 95% CI, 0.77–0.95 versus 1.02 (0.88–1.18) for non-visceral; p(difference) = 0.05]. However, combination of an endocrine therapy and a targeted therapy was associated with better PFS compared to endocrine therapy alone for both groups [HR 0.51 (0.43–0.60) versus 0.45 (0.36–0.56) for non-visceral; p(difference) = 0. 36]. Novel HER-2 targeted therapies were associated with significantly better PFS and OS only in visceral metastases [HR 0.59 (0.52–0.66) versus 0.71(0.44–1.13) for non-visceral, p(difference) = 0.45, for PFS; and 0.64 (0.56–0.73) versus 0.82 (0.57 = 1.19) for non-visceral, p(difference) = 0.20, for OS].

Conclusion: Combination of targeted agents and endocrine therapy results in concordant, superior PFS suggesting targetable endocrine resistance across metastatic sites. Discordant responses with endocrine strategy alone support use of targeted therapy, rather than change in endocrine agent at disease progression. HER2 targeted therapies may be less effective in areas of poor vascularization.

Introduction

Breast cancer has been classified in several subtypes by its transcriptomic profile, and from a clinical perspective, some of these subtypes can be grouped by using immunohistochemical techniques [1,2]. In this context, such classifications have permitted the evaluation of new agents, and the stratification of tumors according to therapeutic strategies [3].

In HER2 overexpressing tumors, anti-HER2 therapies like trastuzumab and lapatinib have demonstrated clinical benefit [3]. Recently, the addition of pertuzumab to trastuzumab-based combinations has improved overall survival, which suggests that such strategies rescue resistant clones of tumor [4]. Similarly, for progressive disease administration of the antibody drug conjugate TDM1 also produces a survival gain, acting on population of cells that exhibit resistance to conventional anti-HER2 therapies [5]. For hormone receptor (HR) positive tumors, the addition of everolimus, an agent targeted against the mammalian target of rapamycin (mTOR) and palbociclib, a CDK4/6 inhibitor, augment the

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efficacy of hormonal therapy alone [6,7]. Demonstrated superiority of these noble endocrine manipulations are likely due to their increased activity against population of cells that possess primary or secondary resistance to hormonal inhibition alone.

Breast cancer is a heterogeneous disease at different levels – among biologic subtypes, among different areas within the same primary tumor, and among different metastatic sites resulting from evolution of clonal subpopulations in different sites [8,9]. Finally, the selective pressure produced by a given treatment leads to the development of resistance by specific clones although it is unclear if these clones differ between tumor locations [10].

Clinical trials classify study population based on involvement of visceral and non-visceral organs although it is unknown whether the efficacy of new treatments differs among sites of metastases. Indeed, in daily clinical practice locations of metastases are not taken into consideration to guide treatment decisions particularly if the disease is relatively stable and there is no medical urgency. American society of clinical oncology guidelines recommend sequential hormone therapy as preferential treatment for most women with hormone receptor positive disease except in immediate life-threatening disease thereby emphasizing extent of disease and rate of disease progression as a factor to consider while choosing therapy [11].

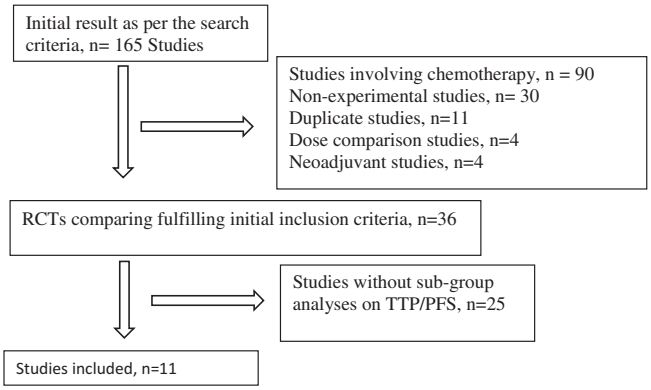

Fig. 1. PRISMA search result.

In this meta-analysis we evaluate the efficacies of different strategies for treatment of advanced breast cancer including endocrine agents, targeted therapies, and HER2 directed therapies by the location of the metastatic site.

Methods

Search criteria

A comprehensive search of MEDLINE, EMBASE, and COCHRANE databases from the inception to June 2016 was performed. Key words included POPULATION: exp breast neoplasms/or (exp Carcinoma/and exp breast/). EXPOSURE: tamoxifen/or arimidex/or anastrozole/or femara/or letrozole/or aromasine/or exemestane/ fulvestrant/or faslodex/or everolimus/or affinitor/or palbociclib/or CDK 4/6 inhibitor/or trastuzumab/or herceptin/or pertuzumab/or T-DM1/or kadcyla. STUDY TYPES: Randomized control trials/or double-blind method/or clinical trials/or prospective studies. OUTCOMES: prognosis/or disease-free survival/or treatment outcome/ or treatment failure/or disease progression/or survival rate/or survival analysis/or disease-free survival/or proportional hazards model/or exp risk. We searched manually the reference lists of all pertinent reviews. Presentations made at American Society of Clinical Oncology (ASCO) Annual Meetings, ASCO Breast Cancer Symposium, and San Antonio Breast Cancer Symposium in the last 5 years was also searched. We included studies reporting results of RCTs that compared an experimental arm (defined below) to an endocrine therapy (and/or a HER-2 targeted therapy) in the control arm for treatment of women with inoperable locally advanced or metastatic breast cancer. Studies evaluating chemotherapy were excluded. Studies reporting Hazard Ratios (HR) for progression-free survival (PFS), time-to-progression (TTP) or overall survival (OS) based on visceral and non-visceral metastasis were included. These studies were divided into three sub-groups based on the anticancer agent(s) used in the experimental arm as follows: group 1 – comparison of 2 endocrine strategies; group 2 – Combination of an endocrine strategy and a targeted therapy compared with an endocrine therapy alone; and group 3 – new HER-2 targeted strategy compared with an existing HER-2 targeted strategy.

Table 1
Characteristics of the included studies.

Study	Treatment Group	Control group	N (Experimental)	N (Control)	Efficacy endpoint	Line of therapy	Age range (years)
Group 1 – New hormonal therapies (comparison of two endocrine strategies)							
Chia et al. [21]	Fulvestrant	Exemestane	351	342	TTP	Front + later line	32–91
Johnston et al. [22]	Fulvestrant	Exemestane	231	249	PFS	Front + later line	57–75
Bergh et al. [23]	Fulvestrant + anastrozole	Anastrozole	258	256	TTP	Front line	33–90
Mehta et al. [24]	Fulvestrant + anastrozole	Anastrozole	350	345	PFS	Front line	27–92
Group 2 – New targeted therapies for hormone receptor positive tumors (combination of an endocrine strategy and a targeted therapy compared with an endocrine therapy alone)							
BOLERO2 Baselga et al. [25]	Everolimus + exemestane	Exemestane	485	239	PFS	Later line	28–90
PALOMA1 Finn et al.[26]	Palbociclib + letrozole	Letrozole	84	81	PFS	Front line	54–72
PALOMA2 Finn et al.[27]	Palbociclib + letrozole	Letrozole	444	222	PFS	Front line	30–89
PALOMA3 Cristofanilli et al.[28]	Palbociclib + fulvestrant	Fulvestrant	521	347	PFS	Later line	29–88
Group 3 – New HER2 therapies (new HER-2 targeted strategy compared with an existing HER-2 targeted strategy)							
CLEOPATRA Swain et al. [4]	Pertuzumab + trastuzumab + docetaxel	Trastuzumab + docetaxel	406	402	PFS, OS	Front line	22–82
EMILIA Verma et al.[29]	T-DM1	Lapatinib + Capecitabine	496	495	PFS, OS	Later line	25–84
TH3RESA Krop et al.[30]	T-DM-1	Treatment of physician's choice	404	198	PFS, OS	Later line	27–89