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Title: Comparative review of pharmacological therapies in individuals with HER2 positive advanced breast cancer with focus on hormone receptor subgroup.

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Abstract:

Breast cancer is the fifth leading cause of cancer related deaths worldwide. Randomized controlled trials (RCTs) of targeted therapies in human epidermal receptor 2 (HER2) positive advanced breast cancer (ABC) have provided an evidence base for regulatory and reimbursement agencies to appraise the use of cancer therapies in clinical practice. However, a subset of these patients harbor additional biomarkers e.g. a positive hormone receptor status which may be more amenable to therapy, and improve overall survival. This review seeks to explore the reporting of evidence for treatment effects by hormone receptor status using the RCTs evidence of targeted therapies for HER2 positive ABC patients. PRISMA guidelines were followed to identify published RCTs. Extracted data were synthesized using network meta-analysis to obtain relative effects of HER2 positive targeted therapies. We identified a gap in the reporting of the effectiveness of therapies by hormone receptor status as only 15 out of 42 identified RCTs reported hormone receptor subgroup analyses; the majority of which reported progression free survival (PFS), but not overall survival (OS) or overall response rate (ORR). In conclusion, we recommend that future trials in ABC should report the effect of cancer therapies in hormone receptor subgroups for all outcomes.

1. Introduction

Breast cancer is the most commonly diagnosed cancer and the fifth leading cause of cancer-related deaths worldwide (1). Advances in breast cancer screening, radiological, and surgical techniques have helped to improve overall survival rates. Additionally, a deeper understanding of the underlying molecular drivers of breast cancer pathogenesis has led to the development of a range of targeted treatments; e.g. to hormone-receptors, human epidermal receptor 2 (HER2) receptors or programme death receptor ligand 1, allowing an era of personalized medicine to be realized (2). When considering HER2-positive breast cancer, examples of targeted therapies include, trastuzumab, lapatinib, trastuzumab emtansine, trastuzumab deruxtecan, and neratinib etc. (3). Efficacy of these therapies has been demonstrated in randomized controlled trials (RCTs) leading to their market access approval by regulatory agencies, such as European Medicines Agency (EMA) and Food and Drug Administration (FDA) in the US. These have been subsequently appraised by reimbursement agencies such as National Institute for Health and Care Excellence (NICE) in the UK for use in routine clinical practice. NICE determines clinical and cost-effectiveness (or value for money) for the population covered in the full market authorization. However, they may consider the use of subgroups (such as subgroups defined by hormone-receptor biomarker status) if evidence shows an unclear value for money within one of the groups or in subgroups where patients are known to have improved prognosis. For example, the NICE appraisal of lapatinib or trastuzumab in combination with an aromatase inhibitor (AI) is recommended as the first-line treatment of HER2-positive ABC, in hormone-receptor-positive population only (TA257 - https://www.nice.org.uk/guidance/ta257). This review was undertaken to ascertain if there is available RCTs evidence on hormone-receptor status in HER2-positive ABC, as to whether the hormone-receptor status have a bearing on the clinical outcomes of individuals being treated for HER2-positive ABC. Specifically, we investigated the level of reporting of RCTs results by hormone-receptor status and explore whether the effectiveness of therapies in HER2-positive

ABC patients varies according to the hormone-receptor status (i.e. estrogen and or progesterone biomarker status). Hormone-receptor subgroups were established as hormone-receptor-positive (HR+ve) subgroup, which includes patients with positive estrogen and/or progesterone receptor status, and hormone-receptor-negative (HR-ve) subgroup, which includes patients whose status for both estrogen and progesterone were negative. Evidence from the identified trials was synthesized to estimate the effect of treatments on progression free survival (PFS) in HR+ve or HR-ve subgroups. The next section in this paper discusses the methods used in this review, the results are discussed in section three, and section four concludes with a summary of the findings, recommendations, limitations, and further research.

2. Methodology

2.1. Literature Review

RCTs were identified following a systematic approach, with a review of reviews carried out first followed by a search of more recent RCTs. The first step identified all the trials used as evidence in technology appraisals by NICE for targeted therapies in HER2-positive ABC patients. This was followed by identifying reviews, systematic reviews, meta-analysis, and network meta-analysis published in peer-reviewed journals that included RCTs of women with HER2-positive ABC (4-29). This approach was employed to utilize comprehensive systematic reviews and network meta-analyses that included RCTs of targeted therapies for HER2-positive ABC patients. The final step was an additional search for more recent RCTs evaluating targeted therapies among HER2-positive ABC patients. The eligibility criteria for selection of RCTs, and search terms are listed below.

Eligible criteria of selecting RCTs

The eligibility of the RCTs for inclusion in this study was defined by the following criteria for the population, interventions, comparators and outcomes (PICOs):

- Phase 2 and 3 RCTs focusing primarily on female patients with HER2-positive ABC.

- All treatments (interventions and comparators) targeted at HER2-positive ABC.
- RCTs that reported at least one of the following outcomes: overall survival (OS), progression free survival (PFS), and overall response (ORR).

RCTs excluded were:

- Studies reporting only outcomes with adverse effect or patients.
- Studies focusing on treatment dose escalation and biosimilar studies of trastuzumab.
- Single-arm studies
- Studies involving only postmenopausal women, patients with brain metastasis, leptomeningeal meningitis or central nervous system (CNS) metastases to ensure homogeneity of the trial populations across treatments.

Search Strategies

The search of the systematic reviews covered NICE guidelines, PubMed, Cochrane Library, and Scopus, with the search covering the period from the inception of the databases through to 20 March, 2022. More recent RCTs were then searched for within Scopus and PubMed, published in the last six years (2016 – 2022) to ensure more recent RCTs were included. The PRISMA flow chart presenting all stages of study selection is shown in Figure 1. The search terms are included in the supplementary file 1.

Figure 1: PRISMA flowchart of RCTs included in the review

2.2. Statistical methods

Network meta-analyses (NMA) were carried out to assess the efficacy of treatments identified in the review. Firstly, NMA was conducted using all the identified RCTs that formed a connected network (i.e. the trial had at least one treatment arm in common with another trial in the network) irrespective of whether the trial reported subgroups analyses or not. Secondly, NMA was conducted using information reported for hormone receptor subgroups. The experimental

treatments and comparators of the identified RCTs included in the NMAs are different and thus, in order to make comparisons across treatments, a reference treatment comparator needed to be identified. The reference treatment comparator was selected as the most commonly evaluated treatment in the connected networks, or where there were multiple common treatment comparisons, then the most efficacious treatment was selected(30). The efficacy of the treatments in the network including all HER2-positive patients were assessed based on PFS, OS and overall response rate (ORR). Treatments effects on PFS and OS were measured using hazard ratios (HRs) and the effects on ORR were measured in using odds ratios (ORs). Comparative efficacy of cancer therapies by hormone-receptor subgroups were based on PFS, which was the most commonly reported outcome in the identified RCTs. A random effects(31, 32) NMA in a Bayesian framework was used to synthesize the evidence from the identified trials. The analyses were performed using the WinBUGS 1.4.3 software. The effectiveness estimates were reported as means and corresponding 95% credible intervals (Crls). Non-informative prior distributions were used with the full WinBUGS code provided in the Technical Support Document (TSD)(33).

Figure 2: Network plots of identified trials (reporting PFS), with colors in the circles representing the proportion of patients in each RCT that are HR+ve (orange), HR-ve (green), unknown (blue), not reported (grey), and the middle purple circle indicated RCTs reporting subgroup analyses.

Figure 3: Network plot of hormone receptors subgroup RCTs (reporting PFS)

3. Results

3.1. All RCTs network Results:

Forty-two published RCTs focusing on treatments administered to HER2 positive ABC patients were identified from 26 reviews and four NICE technology appraisals (TAs) (34-80). The eight RCTs identified from the TAs overlapped with the RCTs identified in the reviews. There were no additional RCTs identified from the additional search (of RCTs published between 2006 and 2022) that have not been included in the reviews (Figure 1). All RCTs meeting the eligibility criteria and included in the review were phase II and phase III.

A network diagram of all 42 trials (reporting PFS) is displayed in Figure 2, similarly as in Cope et al(81). Figure 2 included three networks of trials (with at least one arm common with another trial, thus forming a network) disconnected from each other due to a lack of a common comparator. In the plot (Figure 2), different colors in the circles indicate the proportion of patients in each RCT that are HR+ve (orange), HR-ve (green), unknown (blue), and not reported (grey). The trials reporting subgroup analyses by hormone-receptor status are highlighted with a purple circle in the middle of a colored circle. Six RCTs recruited HR+ve patients and of the 36 RCTs recruiting mixed populations of HR+ve and HR-ve patients, only 15 RCTs reported separate hormone receptor subgroup analyses. The identified RCTs do not all form a connected network for the broader population; hence, three connected networks were investigated. These connected networks are trastuzumab–taxane (HX) connected network (Figure 2A), AI connected network (Figure 2B), and the trastuzumab–chemotherapy (HChem) connected network (Figure 2C). Paclitaxel and docetaxel, which inhibit microtubule dynamics, were classified as a taxane. Letrozole and anastrozole, which are non-steroid third generational aromatase inhibitors that interferes with the production of estrogen, were classified as aromatase inhibitors (AI), (30, 82-85). NMAs were carried out to compare treatments that form each of the smaller connected networks. A list of all included RCTs is provided in the supplementary file 2.

For the network of treatment comparisons for the total population (Figure 2), HX was the most commonly evaluated intervention and thus was used as the reference treatment comparator.

168 The treatment effect estimates and corresponding 95% CrIs for PFS in this population for each
169 connected network are provided in Figure 4. In the overall NMA, taxane showed an important
170 increase in the risk of disease progression compared to HX with a hazard ratio of 2.21(95% CrI:
171 1.61, 2.91); pyrotinib + capecitabine (PYC) showed an important reduction in risk of progression
172 compared to HX with hazard ratio of 0.44 (0.20, 0.82); and capecitabine appeared to show a
173 meaningful increase in the risk of progression compared to HX with hazard ratio of 2.22 (1.00,
174 3.86). Other treatments evaluated using HX as the reference treatment did not show a
175 meaningful difference in effect as their 95% credible interval spans the point of no difference
176 (1). The relative treatment effects (for all treatment comparison in the network) for PFS, OS,
177 and ORR are reported in the supplementary file 3. For example, HER2 positive targeted
178 therapies combined with taxane –such as lapatinib with taxane (LX), neratinib with taxane (NX),
179 trastuzumab with taxane and bevacizumab (HXB), trastuzumab with taxane and carboplatin
180 (HXCb), trastuzumab with taxane and capecitabine (HC), trastuzumab with taxane and
181 pertuzumab (PHX), trastuzumab with everolimus and taxane (HXE), and trastuzumab with
182 taxane and non-pegylated liposomal doxorubicin (HXNPLD) – and some targeted therapies like
183 trastuzumab emtansine (TDM1), and neratinib with capecitabine, all had an important
184 decreased risk of disease progression compared to taxane alone. In addition, TDM1 (using the
185 points estimates) showed to prolong overall survival when compared to other HER2-positive
186 targeted therapies like HX, HC, LC, taxane, and LX (see supplementary file 3). Pertuzumab
187 with TDM1 (PTDM1) showed a meaningful decreased risk in disease progression compared to
188 LC, capecitabine, taxane, and neratinib. The relative treatment effects of all treatments
189 evaluated in the mixed and hormone receptor subgroup population are reported in the
190 supplementary file 3. PYC showed a meaningful decreased risk in disease progression
191 compared to some targeted therapies such as HX, TDM1, LX, and trastuzumab with
192 capecitabine. The meaningful treatment effects showed by PYC could be associated with the fact that
193 pyrotinib is an irreversible inhibitor of the ERBB family including HER1, HER2, and HER4; therefore,
194 potentially allowing wider HER2 inhibition compared to other anti HER2 therapies. In addition, PYC was

evaluated only as a second line of therapy, which may have had an impact on the results from the NMA as we discuss in more detail in the Discussion section. For the AI connected network (Figure 2B), only HR+ve patients were included as the AI therapies are only used in the HR+ve breast cancer setting (84).

Figure 4: Summary forest plots obtained from the NMA including all RCTs for PFS

3.2. Results of subgroup analyses:

Among the 15 RCTs that recruited mixed populations of hormone-receptors status patients and reported their subgroups analyses, 13 RCTs reported results for HR+ve patients and 14 RCTs reported results for HR-ve patients. The number of treatment regimens evaluated in the hormone-receptor subgroups (16) was smaller than the treatment regimens evaluated in the overall NMA (26). These do not include treatment regimens in the AI and HChem connected network, as RCTs in both connected networks have primarily HR+ve participants. Network plots of RCTs within the hormone receptor subgroups are displayed in Figure 3. The RCTs that reported results for the hormone-receptor subgroups formed two disconnected networks in the subgroup analysis; HX connected network, and capecitabine connected network. Figure 5 and Figure 6 show summary forest plots of treatments effects for PFS in the hormone-receptor subgroups respectively for the HX connected network, and the capecitabine connected network. The treatment effects from the HR+ve subgroup and HR-ve subgroup are depicted with red and blue bar plots respectively. The green bar plots shows the estimated treatment effects for the mixed patients using only RCTs that reported subgroup analysis, and the grey bar plots depict the treatments effects extracted from the overall NMA including all RCTs (Figure 4). In the subgroup analysis, PYC showed a meaningful reduction in the risk of disease progression compared to lapatinib with capecitabine (LC) in the HR-ve subgroup analysis with a hazard ratio of 0.31 (95%CrI: 0.12, 0.70). Other treatment regimens evaluated in the

capecitabine or HX connected network did not show a meaningful effect as the 95% credible intervals included the point of no difference (value of 1).

Figure 5: Comparative summary forest plots of treatment effects obtained from the HX connected network for PFS

Figure 6: Comparative summary forest plots of treatment effects obtained from capecitabine connected network for PFS

4. Discussion and conclusion

We have conducted the first review of RCTs involving HER2-positive ABC, specifically focusing on the reporting of treatment effects by hormone receptor status. . We found that the RCTs that reported subgroups analyses reported PFS, not OS or ORR. We would like to note that despite PFS being the primary endpoint of these RCTs, evidence of its surrogacy for OS in HER2-positive ABC is limited (86).

Our results show that, regardless of the hormone-receptor status of the patients, a taxane-only therapies were associated with an important increased risk of disease progression compared to HX as well as to other targeted therapies combined with a taxane (as shown in supplementary file 3). This supports the findings from the wider literatures (7, 45, 48, 59, 66). PYC showed a meaningful effect over HX with a hazard ratio of 0.44 (95% CrI: 0.20, 0.82). In the subgroups analyses, PYC showed a meaningful effect over LC in the HR-ve subgroup analysis with a hazard ratio of 0.31 (95% CrI: 0.12, 0.70) and the mixed patients' analysis with a hazard ratio of 0.40 (95% CrI: 0.18, 0.79).

In addition, our results indicate that the point estimates of HER2 treatments in combination with an AI show a meaningful effect over AI alone, which support the findings by Kawalec et al (13)

One of the limitations of the review, from the point of view of the clinical interpretation was the fact that our NMA for both the overall population and the hormone receptor subgroups included all RCTs that evaluated targeted therapies in HER2-positive patients irrespective of their line of treatments. We chose this approach to capture all relevant evidence available in the reporting of hormone receptor subgroup analysis in the RCTs, as the primary aim of this review was to assess the level of reporting of the effectiveness of therapies in the biomarker subgroups and the impact of under-reporting on the results of NMA. The non-homogeneity of the included RCTs in terms of treatment line could have played a significant role in the results obtained from the NMA. For example, as mentioned in the Results section, the three RCTs that evaluated PYC in comparison to either LC or capecitabine, recruited HER2-positive ABC patients whose disease have progressed after receiving HX, which could have resulted in a meaningful and relatively large treatment difference between PYC and HX. The conclusions drawn from these results are not specific to the line of therapy and therefore the clinical interpretation of these results is limited. Moreover, the sparse and almost star shape geometry of the network as well as the lack of direct evidence of PYC with other HER2 target therapies, such as TDM1, pertuzumab, or HX, mean that there are further limitations of the results in terms of their reliability for the clinical interpretation.

Our review did not identify important differences in treatment effectiveness across hormone-receptor subgroups. The treatment effects estimates for the subgroup analyses were estimated with increased uncertainty (compared to the mixed population), not only due to the reduced sample size in the subgroups, but also due to the limited reporting of subgroup analyses the RCTs. However, across treatments, the HR-ve subgroup often present with lower estimated hazard ratio than HR+ve patients for PFS. This may therefore warrant a further RCT, powered to investigate the efficacy of HER2 targeted therapies among hormone-receptor subgroups and extending the outcomes assessed by subgroup to include not only PFS but also OS, and ORR. This is because, while PFS may be an attractive primary endpoint as it is available earlier than

OS, and is not influenced by subsequent treatments, questions regarding whether PFS is a valid surrogate for OS remain (87-89). Alternatively, an RCT could also be complemented with an analysis of Electronic Health Records (EHR) to explore if these HER2 targeted therapies are more effective in HR+ve patients compared to HR-ve patients.

Our work serves as an example of exploring the support of a broad evidence base (across treatments) for subgroup effects. It illustrates the evidential and methodological challenges in formally considering subgroups effects using extended networks, which arise due to limited reporting of subgroup results; not only across trials but also across outcomes. This work is still important to inform the value and uncertainty over restricted use in decisions at national level, such as those facilitated by NICE in the UK. This is particularly important where clinical and economic value of a treatment in a particular subgroup is unclear, and therefore the value of wide adoption is also unclear. In this case, drawing on such an extended evidence base can inform further research recommendations, particularly in considering whether subgroup effects may be generalized across treatments. . Our review, could be further extended to include data that targets the wider HER2 treatment pathway, or to include outcomes such as adverse events, quality or life, or time to progression (TTP).

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Conceptualization and design: CMUC, SB

Data collection: CMUC, SB

Statistical analysis: CMUC

Clinical expertise: AO, SK

Manuscript: CMUC

Critical revision of the manuscript: CMUC, MOS, AO, RKO, SK, KRA, SB

Supervision: MOS, RKO, KRA, SB

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Competing Interest

SB is a member of the NICE Decision Support Unit. She served as a paid consultant, providing unrelated methodological advice to NICE, pharmaceutical industry and consultancy companies. She received payments for educational events from Roche and has received research funding from European Federation of Pharmaceutical Industries & Association (EFPAI) and Johnson and Johnson.

RKO is a member of the National Institute for health and Care Excellence (NICE) Technology Appraisal committee, member of the NICE Decision Support Unit (DSU), and associate member of the NICE Technical Support Unit (TSU). She has served as a paid consultant to the

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MOS is a member of a research funding panel for the National Institute for Health and Care Research (NIHR), and collaborates with the NICE Decision Support Unit (DSU). She has served as a paid consultant to the pharmaceutical and life sciences industry generally, as well as to DHSC/NICE, providing unrelated methodological advice.

CMUC has no conflicts of interest to declare.

AO has no conflicts of interest to declare

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Additional material

Supplementary file 1

Name: Searchterms.docx

Description: List of the search terms used in the review

Supplementary file 2

Name: IncludedRCTs.docx

Description: List of RCTs included in the review

Supplementary file 3

Name: PFS treatment effects.xls

Description: Relative treatment effects of the targeted therapies evaluated