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Citation for final published version:

Battist, Nicolo Matteo Luca, Reed, Malcolm W. R., Herbert, Esther, Morgan, Jenna L., Collins, Karen A., Ward, Sue E., Holmes, Geoffrey R., Bradburn, Michael, Walters, Stephen J., Burton, Maria, Lifford, Kate, Edwards, Adrian, Robinson, Thompson G., Martin, Charlene, Chater, Tim, Pemberton, Kirsty J., Shrestha, Anne, Brennan, Alan, Cheung, Kwok Leung, Todd, Annaliza, Audisio, Riccardo A., Wright, Juliet, Simcock, Richard, Green, Tracey, Revell, Deirdre, Gath, Jacqui, Horgan, Kieran, Holcombe, Chris, Winter, Matthew C., Naik, Jay, Parmeshwar, Rishi, Gosney, Margot A., Hatton, Matthew Q., Thompson, Alastair M., Wyld, Lynda and Ring, Alistair 2021. Bridging the age gap in breast cancer: Impact of chemotherapy on quality of life in older women with early breast cancer. *European Journal Of Cancer* 144, pp. 269-280. 10.1016/j.ejca.2020.11.022

Publishers page: <http://dx.doi.org/10.1016/j.ejca.2020.11.022>

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ARTICLE TYPE: Original article**TITLE: Bridging The Age Gap in breast cancer: impact of chemotherapy on quality of life in older women with early breast cancer.****AUTHORS**

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HIGHLIGHTS

- Multicentre, cohort study of 3416 women (aged >70 years) with breast cancer
- In older women with high-risk, early breast cancer, chemotherapy reduces quality of life.
- Relevant affected domains include cognition, fatigue, physical, role and social functioning.
- Chemotherapy QoL impacts are transient and largely resolve completely by 18-24 months.

ABSTRACT

Introduction

Older patients with early breast cancer (EBC) derive modest survival benefit from chemotherapy but have increased toxicity risk. Data on the impact of chemotherapy for EBC on quality-of-life in older patients are limited, but this is a key determinant of treatment acceptance. We aimed to investigate its effect on quality-of-life in older patients enrolled in the Bridging the Age Gap study.

Materials and methods

A prospective, multicentre, observational study of EBC patients ≥ 70 years old was conducted in 2013-2018 at 56 UK hospitals. Demographics, patient, tumour characteristics, treatments and adverse events were recorded. Quality-of-life was assessed using the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaires [EORTC-QLQ] C30, BR23 and ELD 15 plus the Euroqol-5D [EQ5D] over 24 months and analysed at each time point using baseline adjusted linear regression analysis and propensity score-matching.

Results

3416 patients were enrolled in the study; 1520 patients undergoing surgery and who had high-risk EBC were included in this analysis. 376/1520 (24.7%) received chemotherapy. At 6 months, chemotherapy had a significant negative impact in several EORTC-QLQ-C30 domains, including global health score, physical, role, social functioning, cognition, fatigue, nausea/vomiting, dyspnoea, appetite loss, diarrhoea and constipation. Similar trends were documented on other scales (EORTC-QLQ-BR23, EORTC-QLQ-ELD15 and EQ-5D-5L). Its impact was no longer significant at 18-24 months in unmatched and matched cohorts.

Conclusions

The negative impact of chemotherapy on quality-of-life is clinically and statistically significant at 6 months but resolves by 18 months, which is crucial to inform decision-making for older patients contemplating chemotherapy.

Keywords: Breast cancer, older patients, adjuvant chemotherapy, quality of life

ACKNOWLEDGEMENTS

This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (grant reference number RP-PG-1209-10071). In addition, NB and AR would like to acknowledge the support of the Cridlan Ross Smith Charitable Trust and the NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London.

The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health.

Sponsorship

The study was sponsored by Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust. Clinical Research Office, First Floor 'C' Block, Doncaster Royal Infirmary, Armthorpe Road, Doncaster, DN2 5LT, UK.

Disclaimer

This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference Number RP-PG-1209-10071). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Disclosure

The authors declare no conflict of interest. Professors Stephen Walters and Thompson Robinson are National Institute for Health Research (NIHR) Senior Investigators, Jenna Morgan is a NIHR Clinical Lecturer and Kate Lifford is funded by the NIHR as part of this project. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care.

Trial registration number ISRCTN: 46099296

INTRODUCTION

Almost half of all breast cancer cases are diagnosed in patients aged ≥ 65 years.[1] Nonetheless, older adults are under-represented in clinical trials.[2] Moreover, standard trial endpoints may not be appropriate for older individuals and quality of life (QoL), functional status and cognition may be as important as chance of cure.[3] These knowledge gaps contribute to considerable variation in treatment in this age group.[4]

Curative chemotherapy is associated with a survival benefit only in patients with node-positive and oestrogen receptor (ER)-negative disease.[5, 6] Older adults have higher risk of treatment toxicities due to comorbidities and reduced organ function, while benefits are mitigated by competing risks.[7] The impact of chemotherapy on QoL may influence clinicians' and patients' perspectives.[8]

Therefore, the effect of anticancer treatments on QoL is essential to inform treatment decisions in this cohort. The CALGB 49907 study documented better QoL for patients aged ≥ 65 receiving capecitabine versus standard regimens but no QoL differences persisted at 1 year.[9] Patients receiving chemotherapy within clinical trials had better QoL improvements compared with those treated off study.[10] Nonetheless, prospective data on QoL for older patients with early breast cancer (EBC) receiving standard chemotherapy are lacking.

Comorbidities, literacy, symptoms and compliance may influence patient-reported outcomes,[11] but the European Organisation for Research and Treatment of Cancer (EORTC) questionnaires have been validated to evaluate QoL generically in cancer patients,[12] and specifically in older individuals[13] and in those diagnosed with breast cancer.[14]

We aimed to investigate the impact of chemotherapy on QoL in real-world EBC patients aged ≥ 70 recruited to the Bridging the Age Gap study.[15] Matching survival outcomes for the cohort are reported separately.

METHODS

Regulatory approval

Ethics approval (IRAS: 12 LO 1808) and research governance approval were obtained. All patients (or their proxies, if cognitively impaired) gave written informed consent.

Study design

Bridging the Age Gap is a prospective multicentre, observational cohort study. Patients were recruited from 56 UK centres in England and Wales (Table S1). Eligible patients were women ≥ 70 years at diagnosis of operable invasive breast cancer (TNM stages: T1-3, plus some operable T4b, N0-1, M0). Those unsuitable for surgery or with previous EBC within five years were not eligible.

Baseline data collection

Patients were recruited at the time of diagnosis and could participate at three levels: full, partial (no requirement to complete QoL assessments) or proxy (simple third-party data collection for those with cognitive impairment).

Primary tumour characteristics were collected at baseline. Staging was performed if indicated. Surgery, radiotherapy and systemic treatment data were also collected.

Baseline geriatric assessments included comorbidities (Charlson comorbidity index [CCI])[16], nutrition (Abridged Patient Generated Subjective Global Assessment [aPG-SGA])[17-19], functional status (Eastern Cooperative Oncology Group Performance status (ECOG PS), Activities of Daily Living [ADL],[20] Instrumental Activities of Daily Living [IADL])[21], cognition (Mini Mental State Examination [MMSE])[22], and medications. Patients were classified as high-risk based on ≥ 1 of the following criteria: 1) HER2-positive status; 2) ER-negative status; 3) grade 3; 4) ≥ 1 malignant lymph node; 5) Recurrence Score (RS) ≥ 30 (Table S2).

QoL was evaluated using four questionnaires. The EORTC QLQ-C30 includes five functions (physical, role, emotional, cognitive and social), nine symptoms (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) and global health status.[12] The EORTC-QLQ-BR23 comprises 23 questions evaluating body image, sexual functioning and enjoyment, future perspective, systemic therapy side effects, breast symptoms, arm symptoms and

frustration with hair loss.[14] The EORTC-QLQ-ELD15 contains five scales (functional independence, relationships with family and friends, worries about the future, autonomy and burden of illness).[13] The EQ-5D-5L was used in this analysis to assess overall QoL[23] and individual questions were scored separately from 1-5.

Patients were followed up at 6 weeks, 6, 12, 18 and 24 months and QoL and side-effects, based on the Common Terminology Criteria for Adverse Events (CTCAE v4.0), were assessed at each visit.

Statistical analyses

Analyses were performed in IBM SPSS statistics version 24 and R version 3.6.3.[24, 25] A $p < 0.05$ was considered statistically significant.

The questionnaires were scored according to the EORTC Scoring Manual (3rd Edition).[13] Missing data were managed accordingly. The analysis included high-risk EBC patients where QoL questionnaires were available. The mean difference (95% CI) of the domain scores at each time point, adjusted for baseline scores, was calculated with linear regression models for high-risk participants. Effect sizes after analyses of the EORTC-QLQ-C30 will be categorised as either trivial, small, medium or large according to pre-specified thresholds for each domain.[26]

The chemotherapy effect on the global health score over time for high-risk patients was estimated using a mixed-effect linear model. The model allowed for time, treatment, treatment-time interaction, and baseline global health status. Differences between the chemotherapy and non-chemotherapy groups were derived at each timepoint using linear contrasts. The model was fitted to high-risk patients and to the propensity score-matched patients only. For the unmatched analysis the model also adjusted for age and baseline functionality scores.

We also performed propensity score-matching to compare the EORTC-QLQ-C30 global health score and the EQ-5D-5L usual activities score in a matched cohort receiving chemotherapy versus patients not receiving it. Logistic regression was used to calculate propensity scores for treatment allocation in high-risk patients. These were used to match chemotherapy patients to those who did not receive chemotherapy based on ADL, IADL, MMSE, ECOG, aPG-SGA, CCI, number of medications, and age. The ratio and calliper widths of the propensity scores were chosen based on examination of propensity score overlaps for several combinations of ratios and callipers. A 1:3 ratio for chemotherapy to no chemotherapy and a calliper of 0.25 times the propensity scores standard deviation was used to

optimally match quality and numbers. Participants were matched on Nottingham Prognostic Index (NPI) category (good ≤ 3.4 , moderate 3.5-5.4, poor > 5.4) and HER2 status.

RESULTS

Between January 2013 and June 2018, 3456 women were recruited from 56 hospitals in England and Wales and 3416 included in the analysis. 2811/3416 (82.3%) underwent surgery within 6 months of diagnosis, 1520/2811 (54.1%) had high-risk EBC and 376/1520 (24.7%) received chemotherapy. (Figure 1)[27]. The time frames for treatments received in each cohort are shown in Figure S1 wherein the slight offset in timing of endocrine therapy and RT between the chemotherapy and no chemotherapy groups can be seen and should be considered when interpreting the findings.

Patients had a median age of 76.9 years, CCI of 1 (range 0-9) and took a median of 4 medications (0-18); 1063 (69.9%) were independent in their ADLs and 1091 (71.8%) in their IADLs, 1346 (88.6%) had normal MMSE, 1168 (76.8%) had a low aPG-SGA score and 1379 (90.7%) had ECOG PS 0-1 (Table 1).

Chemotherapy data were available for 360 patients: 124 (34.4%) received anthracycline and taxanes, 119 (33.1%) a taxane alone, and 116 (32.2%) an anthracycline alone; one patient received cyclophosphamide, methotrexate, fluorouracil (CMF). 332 patients (21.8%) had HER2-positive disease: 150 (45.2%) received chemotherapy plus trastuzumab, 13 (3.9%) received trastuzumab alone, and 9 (2.7%) chemotherapy alone. EBC was ER-positive in 1134 patients (75.3%), with 1079 (95.1%) receiving endocrine therapy (Figure S1).

Of these high-risk patients, 1120 (73.7%) enrolled with full participation in the protocol (necessary for completion of QoL questionnaires) and 304/1120 (27.1%) had chemotherapy. Figures S2-S4 and Tables S3-5 show completion rates of QoL questionnaires.

Impact on QoL domains (EORTC QLQ-C30)

1049/1120 patients (93.7%) completed the global health status questions included in the EORTC QLQ-C30 questionnaire at baseline (Table S6a; Figure 2). Following adjustment for baseline scores, at 6 weeks the differences in the mean scores on some EORTC QLQ-C30 domains were statistically significant between patients undergoing chemotherapy compared to those not receiving it, including global health (adjusted mean difference -2.81, 95% CI -5.17 to -0.44, $p=0.020$), social functioning (-3.57, CI -6.71 to -0.43, $p=0.026$) and constipation (3.43, CI 0.23 to 6.62, $p=0.035$). The impact of chemotherapy remained significant on most domains at 6 months, including global health which was both statistically and clinically significant but small (-9.20, CI -11.95 to -6.44, $p < 0.001$), physical functioning (medium difference: -8.05, CI -10.21 to -5.89, $p < 0.001$), role functioning (small difference: -17.59, CI -21.24 to -13.95, $p < 0.001$), cognitive functioning (small difference: -5.55, CI -7.97 to -3.13, $p < 0.001$), social functioning (large difference: -18.72, CI -22.17 to -15.27, $p < 0.001$), and financial

problems (small difference: 3.28, CI 1.16 to 5.39, $p=0.002$). At 12 months statistically significant differences persisted in physical functioning (trivial difference: -2.76, CI -4.95 to -0.57, $p=0.014$), role functioning (trivial difference: -4.41, CI -8.17 to -0.64, $p=0.022$), social functioning (trivial difference: -3.78, CI -7.00 to -0.56, $p=0.022$), diarrhoea (small difference: 4.15, CI 1.62 to 6.68, $p=0.001$) and financial problems (trivial difference: 2.50, CI 0.27 to 4.73, $p=0.028$). Chemotherapy was no longer impactful in any of these domains at 18 and 24 months.

The analyses were repeated on a propensity score-matched subgroup of 410 patients (150 chemotherapy, 260 no chemotherapy) with similar findings (Figure S5-7; Table S6b).

Impact on breast cancer-specific QoL domains (EORTC QLQ-BR23)

1054/1120 patients (94.1%) completed some or all of the EORTC QLQ-BR23 questionnaire at baseline (Figure 3; Table S7). After adjustment for baseline measurements patients given chemotherapy experienced a significant decline of some EORTC QLQ-BR23 mean scores at 6 weeks compared with those not receiving it in future perspective (adjusted mean difference -7.20, 95% CI -10.72 to -3.68, $p<0.001$) and systemic therapy side-effects (3.04, CI 1.47 to 4.61, $p<0.001$). At 6 months, mean scores were significantly different in future perspectives (-7.54, CI -11.28 to -3.80, $p<0.001$) and systemic therapy side-effects (16.97, CI 15.00 to 18.94, $p<0.001$). At 12 months, the mean scores between the two groups differed in future perspectives (-4.96, CI -8.89 to -1.03, $p=0.013$), systemic therapy side-effects (3.32, CI 1.41 to 5.22, $p=0.001$) and the effect of chemotherapy became significant in arm symptoms (4.94, CI 2.18 to 7.69, $p<0.001$). At 18 months, the differences remained significant in future perspective (-4.97, CI -9.37 to -0.57, $p=0.027$) and arm symptoms (3.27, CI 0.01 to 6.54, $p=0.049$), and at 24 months only in arm symptoms (4.02, CI 0.13 to 7.90, $p=0.043$).

Impact on older adults-specific QoL domains (EORTC QLQ-ELD15)

Some or all of the EORTC QLQ-ELD15 questionnaire was completed at baseline by 1048/1120 (Table S8; Figure 4). At 6 weeks scores were significantly different between patients given chemotherapy and those not treated in worries about others (adjusted mean difference 5.31, 95% CI 1.55 to 9.07, $p=0.006$), worries (4.09, CI 0.92 to 7.27, $p=0.011$) and burden of illness (4.68, CI 1.25 to 8.11, $p=0.007$). These differences persisted at 6 months (worries about others [6.19, CI 2.44 to 9.95, $p=0.001$]; worries [4.18, CI 0.89 to 7.46, $p=0.013$]; burden of illness [21.60, CI 17.82 to 25.39, $p<0.001$]); the impact on mobility also became significant (9.82, CI 6.87 to 12.78, $p<0.001$). At 12 months, changes remained

significant regarding worries about others (4.47, CI 0.42 to 8.52, $p=0.031$) and burden of illness (15.21, CI 11.30 to 19.12, $p<0.001$), which was the only domain significantly influenced also at 18 months (12.99, CI 8.81 to 17.17, $p<0.001$) and 24 months (8.80, CI 3.93 to 13.66, $p<0.001$).

Maintaining purpose did not differ throughout the follow-up period, whereas chemotherapy had a positive impact on family support mean scores at 6 weeks (6.21, CI 2.26 to 10.17, $p=0.002$), at 6 months (4.91, CI 0.26 to 9.56, $p=0.038$) and at 12 months (5.43, CI 0.39 to 10.46, $p=0.035$).

Impact on EQ-5D-5L score and questions

Among the high-risk patients, an EQ-5D-5L score was calculated in 1315 patients (86.5%) at baseline. Health utilities were similar with estimated mean differences less than 0.02 units ($p>0.1$), whereas the visual analogue scale (VAS) measures were significantly worse at 6 months in patients receiving chemotherapy versus not (adjusted mean difference -6.57, 95% CI -8.74 to -4.40, $p<0.001$). Changes were subsequently no longer significant (Table S9; Figure 5).

A similar pattern on EQ-5D-5L usual activities score was seen in 520 (118 chemotherapy, 332 no chemotherapy) propensity score-matched patients (Figure S8).

DISCUSSION

This study demonstrates that chemotherapy has a both a clinically and statistically significantly negative impact at 6-12 months on several QoL domains (physical, role, cognitive and social functioning, financial problems), symptoms (fatigue, nausea, dyspnoea, appetite loss, constipation, diarrhoea), and perceived global health. These changes are clinically meaningful and involve key domains for this population[28] for whom even low-grade toxicities may be challenging.[29]

Reassuringly, this effect resolves for most items over 18-24 months, which is consistent with previous QoL data reported in younger cohorts: for example, in 280 EBC patients many domains improved within 12 months after diagnosis, with the exception of cognitive function and financial problems[30] and similar improvements in role functioning were seen in a study of 817 EBC patients.[31] A registry-based analysis documented better physical functioning, role-physical, role-emotional and fatigue scales at 15 years in EBC patients including 46.9% aged ≥ 65 .[32] Similarly, 588 EBC patients enrolled in the Moving Beyond Cancer study had improved physical and psychosocial functioning after radical treatment regardless of chemotherapy use.[31] Neuropsychological analyses also confirmed improving cognitive function during the first four years after radical therapy for EBC,[33, 34] although data on financial impact are limited.[30] The CANTO study confirmed the transient nature of the impact of chemotherapy on QoL in a large population.[35] Nonetheless, these analyses have either focused on younger patients, where the risk/benefit is different, or addressed the impact of breast cancer treatments (and not specifically of chemotherapy) on QoL in this age group. Our findings are consistent with a previous study in 109 patients aged 70 or older, of whom 57 received adjuvant docetaxel/cyclophosphamide chemotherapy.[36]

To our knowledge, this is the largest study to evaluate the impact of contemporary chemotherapy regimens in older adults with EBC in real-world patients. QoL is a meaningful endpoint for older patients, who typically derive less survival benefit and increased toxicities on systemic anticancer treatments.[37, 38] These benefits need to be carefully balanced with the detrimental impact on QoL and treatment side-effects.[39]

Our analysis included baseline geriatric assessments characterizing patients in relevant health domains for this age group, such as functional status, comorbidity, cognition, nutrition and concurrent medications which may impact QoL. A comprehensive geriatric assessment can help achieve the required balance between treatment benefits and side-effects and is recommended by guidelines from the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and the International Society for Geriatric Oncology.[28, 40] In a randomized study, integrated oncogeriatric care has recently been shown to improve QoL in older patients with cancer being considered for

systemic anticancer therapy.[41] Of particular interest was our finding that in patients ≥ 80 the negative impact on QoL does not resolve, which suggests a lack of resilience in this cohort.

The study has several limitations. Selection bias may have influenced our findings despite its inclusive entry criteria and the different levels of participation. The recruited population was slightly skewed towards younger individuals compared with the general UK EBC patient population.[42] Moreover, we did not include socio-economic factors that might influence frailty nor the effect of endocrine therapy or radiotherapy on QoL, owing to multiple confounders to such an analysis. We did not capture the impact of chemotherapy on QoL outcomes beyond 24 months and missing data on longitudinal QoL assessments may have influenced findings. Other factors not measured by our analysis may also impact on chemotherapy decisions; therefore, the propensity score matching does not adjust for all differences between the groups. Furthermore, some effects of chemotherapy on QoL documented in our analysis might be statistically significant but not clinically relevant, although for the majority of domains clinically meaningful changes are seen at the six-month timepoint, which represents the time when most women would have been on chemotherapy. Finally, it was not possible to categorise chemotherapy effects on QoL measured on BR23, ELD15 and EQ-5D-5L domains as thresholds have not been established for these specific tools and the latter is a utility scale.

In conclusion, our analysis shows that chemotherapy has an impact on several QoL domains in older EBC patients compared to a matched cohort who did not receive cytotoxics. Nonetheless, these effects are temporary and largely resolve within two years. This is essential information for older women to use in decision-making, since individualised decisions on treatment options should be based on their values.

FIGURE CAPTIONS

- Figure 1 – STROBE flow diagram for the chemotherapy versus no chemotherapy analyses.
- Figure 2 – Mean (95% CI) scores over time points for the chemotherapy versus no chemotherapy population measured on the EORTC-QLQ-C30 scale.
- Figure 3 – Mean (95% CI) scores over time points for the chemotherapy versus no chemotherapy population measured on the EORTC-QLQ-B23 scale.
- Figure 4 – Mean (95% CI) scores over time points for the chemotherapy versus no chemotherapy population measured on the EORTC-QLQ-ELD15 scale.
- Figure 5 – Mean (95% CI) scores over time points for the chemotherapy versus no chemotherapy population measured on the EQ-5D-5L scale.

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