Landin J, Vetter M. Recent Developments in Treatment of Older Patients with Breast Cancer. *healthbook TIMES Onco Hema.* 2024;19(1):62-69.
doi:10.36000/HBT.OH.2024.19.142

REVIEW

Recent Developments in Treatment of Older Patients with Breast Cancer

Julia Landin[1,2], Marcus Vetter[1,2a]

[1] Cancer Center Baselland, Cantonal Hospital Baselland, Liestal, Switzerland, [2] Center of Oncology and Hematology, Cantonal Hospital Baselland, Liestal, Switzerland

Keywords: breast cancer, older patients, geriatric oncology

https://doi.org/10.36000/HBT.OH.2024.19.142

healthbook TIMES Oncology Hematology

Vol. 19, Issue 1, 2024

Breast cancer is the most frequently diagnosed malignancy in women. Aging is an independent predictor of adverse treatment outcomes, including an increase in multimorbidity, which is associated with higher mortality, functional impairment, poor quality of life (QoL) and elevated healthcare utilization and costs. Geriatric screening tools and assessments that evaluate a patient's fitness and frailty status are becoming increasingly important in providing a comprehensive patient profile and developing an optimized treatment plan. However, older patients are currently underrepresented in clinical trials, resulting in a lack of published data. This article examines the results from recent clinical trials in breast cancer, with a focus on older patient populations.

PEER REVIEWED ARTICLE

Peer reviewers:
Dr Ute Gick, Onko-Netz KLG, Thun, Switzerland
Dr Andreas Hochstrasser, Hospital Thun, Thun, Switzerland
Dr Alexandru Eniu, Hospital Riviera-Chablais, Rennaz, Switzerland
One anonymous peer reviewer

Received on February 08, 2024; accepted after peer review on March 19, 2024: published online on March 26, 2024.

Introduction

Breast cancer is the most commonly diagnosed malignancy among women, with >30% of all patients being aged >70 years at the time of diagnosis.[1] Due to the aging population worldwide, the number of geriatric patients with breast cancer is expected to increase. Aging is an independent predictor of treatment-associated adverse outcomes and leads to increases in

a Corresponding author:
PD Dr Marcus Vetter
Cancer Center Baselland
Medical University Clinic
Cantonal Hospital Baselland
Rheinstrasse 26
4410 Liestal
Switzerland
Email: marcus.vetter@ksbl.ch

multimorbidity, mortality, functional impairment, poor quality of life (QoL) and high healthcare utilization and costs.[1-5] As a result, there is a growing need for geriatric screening tools and assessments that evaluate a patient's fitness and frailty status, providing a comprehensive portrait of a patient and helping in the development of an optimized treatment plan.[6-14] Unfortunately, older patients (aged ≥65 years) are currently underrepresented in clinical trials, leading to a gap in the published data and the lack of clinical guidelines specifically tailored to this patient population. This disparity is particularly pronounced in the very elderly population (aged ≥75 years), where the proportion of patients participating in clinical trials may be as low as 0–2%.[15] The older patients who are enrolled in these trials are highly selected and tend to have fewer comorbidities and organ dysfunctions compared to their real-life, age-matched counterparts. Furthermore, older patients are often undertreated due to concerns about their age and accompanying health issues. While many chemotherapy regimens and targeted therapies can be safely administered in older patients, more research is needed on dose adjustments and potential adverse events.[15] Addressing these concerns, the joint session organized by the European Society for Medical Oncology (ESMO) and the SIOG at the annual ESMO 2023 congress focused on the recent developments in the treatment of older patients with malignancies, including breast cancer.[12] This paper summarizes the data from selected recent studies, including those discussed at the ESMO/SIOG joint session, with a focus on the efficacy and safety of breast cancer therapies in the older patient population.

PALOMAGE: High frailty among patients with metastatic breast cancer

The prospective, observational, longitudinal real-life PALOMAGE study (EUPAS23012) assessed the feasibility of endocrine therapy (ET) in combination with palbociclib in women aged ≥70 years with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer.[16] The PALOMAGE study enrolled two cohorts of patients: those with first-line ET-sensitive disease (no prior treatment and no relapse within 1 year after adjuvant ET [Cohort A]) and those with ET-resistant disease after ≥2 lines of therapy (relapse on adjuvant ET within <1 year after completion, or prior treatment [Cohort B]). The following data were collected at baseline and then every 3 months: sociodemographic, clinical and biological characteristics, disease- and treatment-related response, QoL (the European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Core 30 [EORTC QLQ-C30] and ELD14), geriatric score (G8 and Geriatric-COre DatasEt [G-CODE]) and safety. The primary endpoint was the rate of palbociclib discontinuation at 18 months for any reason in Cohort A, while the secondary endpoints included time-to-treatment failure (TTF), progression-free survival (PFS), QoL and safety.

With a median follow-up of 20.7 months, the 18-month discontinuation rate for palbociclib was 41.9%, due to disease progression (20.8%), toxicity (7.7%), patient's choice (6.7%), death (4.6%) or other reason (2.1%). The median TTF and PFS were 22.7 months and 28.1 months, respectively. The results from this study show that a high proportion of patients from the all-comer population were frail, with 68.2% having a G8 score of ≤14.[16] These data are rarely collected in current clinical trials, although they are associated with changes in various aspects of QoL, including functionality, mobility, nutrition, cognition, mood and social environment. A G8 score ≤14 is also associated with patients being initiated at a lower dose of palbociclib versus younger, less frail patients (6.7% vs 2.9% at 75 mg palbociclib and 21.6% vs 11.9% at 100 mg palbociclib, respectively). Notably, data showed that palbociclib dose reductions were not associated with poorer overall survival (OS), including older patients treated in clinical practice.[17,18]

SONIA: CDK4/6 inhibitors in post-menopausal women with HR+, HER2- advanced breast cancer

This randomized, investigator-initiated phase III SONIA trial (NCT03425838) aimed to evaluate the efficacy, safety and cost-effectiveness of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (physician's choice of abemaciclib, palbociclib or ribociclib) plus ET in 1,050 treatment-naïve patients with HR+, HER2- advanced breast cancer in either first-line (Cohort A) or second-line (Cohort B) setting.[19] The vast majority of the study participants were post-menopausal women (n=905; 87%). The primary endpoint was the time from randomization to the second disease progression or death (PFS2), while secondary endpoints included OS, safety, QoL and cost-effectiveness.

After a median follow-up of 37.3 months, there was no significant difference in median PFS2 between patients in Cohort A and Cohort B (31.0 months vs 26.8 months; HR: 0.87 [95% CI: 0.74–1.03]; p=0.10).[19] Similarly, no significant OS difference was found between the two cohorts (median, 45.9 months vs 53.7 months; HR: 0.98 [95% CI: 0.80–1.20]; p=0.83). The safety profile was consistent with that previously reported with a combination of ET and CDK4/6 inhibitor. In Cohort A, patients received CDK4/6 inhibitors for a more extended period than those in Cohort B (24.64 months vs 8.08 months), resulting in a higher rate of grade ≥3 adverse events (AEs) (42% increase). These data suggest that first-line use of CDK4/6 inhibitors plus ET does not confer significant benefit to patients while increasing both toxicity and costs due to the extended treatment with CDK4/6 inhibitors (increased drug expenditure of $200,000 per patient). However, 91% of patients were treated with palbociclib, which demonstrated no significant OS benefit compared with placebo in the PALOMA-2 study.[20] Other CDK4/6 inhibitors used in SONIA included ribociclib (8%) and abemaciclib (1%),

which demonstrated statistically significant (MONALEESA-2)[21] and clinically meaningful (MONARCH-3)[22] OS benefit, respectively, in clinical trials.

ASCENT: Sacituzumab govitecan in older patients with metastatic triple-negative breast cancer

In the phase III ASCENT trial (NCT03425838), the efficacy of sacituzumab govitecan (SG) was assessed versus single-agent chemotherapy (treatment of physician's choice [TPC] of eribulin, vinorelbine, capecitabine or gemcitabine) in patients with relapsed or refractory metastatic triple-negative breast cancer.[23] The primary endpoint was PFS per blinded independent central review among patients without brain metastases.

Patients receiving SG displayed a significant improvement in median PFS versus those receiving TPC (5.6 months vs 1.7 months; HR: 0.41 [95% CI: 0.32–0.52]; p<0.001), as well as improvements in OS (median, 12.1 months vs 6.7 months, HR: 0.48 [95% CI: 0.38–0.59]; p<0.001).[23] The objective response rate (ORR) was higher in patients receiving SG versus TPC (35% vs 5%). The use of SG was associated with higher incidences of key treatment-related grade ≥3 AEs, such as neutropenia (51% vs 33%), leukopenia (10% vs 5%), diarrhea (10% vs <1%), anemia (8% vs 5%) and febrile neutropenia (6% vs 2%).

A prespecified subgroup analysis assessed the the efficacy and safety of SG (n=44) versus TPC (n=46) in patients aged ≥65 versus <65 years.[24] The percentage of patients aged ≥65 years was comparable between the SG arm and the TPC arm (19% vs 20%). Data from this subgroup analysis suggest that the benefit with SG is even more pronounced in the aged population (≥65 years) versus the younger population (<65 years). More specifically, in patients aged ≥65 years, SG treatment led to improvements versus TPC in median PFS (7.1 months vs 2.4 months, HR: 0.22 [95% CI: 0.12–0.40]), median OS (15.3 months vs 8.2 months, HR: 0.37 [95% CI: 0.22–0.64]), ORR (50% vs 0%) and clinical benefit rate (61% vs 9%).[24] Of the 7 patients aged ≥75 years who received SG, 2 had a partial response, 4 had stable disease and 1 had stable disease >6 months as the best response. Furthermore, SG treatment showed improvements versus TPC, although slightly less evident, in terms of PFS (median, 4.6 months vs 1.7 months; HR: 0.46 [95% CI: 0.35–0.59]), OS (median, 11.2 months vs 6.6 months, HR: 0.50 [95% CI: 0.40–0.64]), ORR (31% vs 6%) and clinical benefit rate (41% vs 9%) in patients aged <65 years (SG, n=209; TPC, n=176).

The rates of any grade and grade ≥3 treatment-emergent AEs (TEAEs) were similar in patients ≥65 years treated with SG versus TPC, as were TEAE leading to dose reduction (35% vs 33%), although these rates were slightly lower in patients aged <65 years (19% vs 24%).[24] Key treatment-related TEAEs leading to dose reduction in patients aged ≥65 years in the SG versus

TPC arms were neutropenia (including febrile neutropenia; 14% vs 25%), fatigue (10% vs 4%), diarrhea (6% vs 0%) and nausea (4% vs 0%). TEAEs leading to treatment discontinuation with SG versus TPC were low and comparable between patients aged ≥65 years (2% vs 2%) and those aged <65 years (5% vs 6%).

CLEOPATRA: Trastuzumab plus pertuzumab and docetaxel in patients with HER2+ metastatic breast cancer

The phase III CLEOPATRA study (NCT00567190) compared the efficacy and safety of dual anti-HER2 treatment with trastuzumab plus pertuzumab (TP) and docetaxel versus placebo plus trastuzumab and docetaxel in patients with HER2-positive (HER2+) metastatic breast cancer.[25,26] Notably, dual anti-HER2 blockade is the standard of care for localized HER2+ breast cancer.[27] The primary endpoint was independently assessed PFS.[25] Secondary endpoints included OS, PFS by investigator assessment, ORR and safety. Patients receiving pertuzumab-containing therapy experienced significant improvement in median OS versus those receiving placebo-containing therapy (57.1 months vs 8.0 months, HR: 0.69 [95% CI: 0.58–0.82]), with 8-year landmark OS rates of 37% versus 23%, respectively.[26] In both arms, the most common grade 3–4 AE was neutropenia (49% vs 46%), while treatment-related deaths were lower in patients receiving pertuzumab versus placebo (1% vs 2%).

A subgroup analysis based on age showed a benefit for pertuzumab therapy in patients aged >65 or >75 years; however, of the 808 patients enrolled, only 127 were ≥65 years old.[28]

A PFS benefit was observed with pertuzumab versus placebo regardless of age (<65 years, HR: 0.65 [95% CI: 0.53–0.80]; ≥65 years, HR: 0.52 [95% CI: 0.31–0.86]).[28] It is noteworthy that the safety profile varied with age group, with diarrhea, fatigue, asthenia, decreased appetite, vomiting and dysgeusia being reported more frequently in patients aged ≥65 years versus those aged <65 years. Neutropenia, leukopenia and febrile neutropenia were less common in patients who were ≥65 versus <65 years old. In patients receiving pertuzumab, dose reductions of docetaxel were more common in those aged ≥65 years than those aged <65 years (31.1% vs 24.6%), which probably explains the lower incidence of neutropenia and febrile neutropenia, as well as less frequent use of G-CSFs. While the number of cycles administered was lower in patients aged ≥65 years versus <65 years (6.5 and 6.0 cycles per arm vs 8.0 and 8.0 cycles per arm), this did not appear to affect the efficacy of the treatment.

Notably, in both ASCENT and CLEOPATRA, only a small proportion of patients above 75 years, with a majority of elderly patients being between the age of 65 and 75 years. There is currently no general recommendation for geriatric assessment for this patient population, according to several geriatric oncology experts.[29]

EORTC 7511-10114: Trastuzumab plus pertuzumab and metronomic chemotherapy in older or frail patients with HER2+ metastatic breast cancer

The non-comparative phase II EORTC 7511-10114 study (NCT01597414) assessed the efficacy of TP alone versus TP plus first-line metronomic oral cyclophosphamide chemotherapy (TPM) in 80 patients with HER2+ metastatic breast cancer, aged >70 years or >60 years with frailty (geriatric screening G8 score ≤14).[30] In case of progression, patients were offered trastuzumab emtansine (T-DM1), an antibody-drug conjugate targeting HER2. The primary endpoint was investigator-assessed PFS at 6 months. Secondary endpoints included OS, breast cancer-specific survival and overall response.

The trial met its primary endpoint, with an estimated PFS rate at 6 months of 46.2% with TP versus 73.4% with TPM (HR: 0.65 [95% CI: 0.37–1.12]; p=0.12).[31] Long-term follow-up showed that this clinical benefit with TPM was preserved at 24 months, with PFS rates of 28.7% versus 18.7% with TP alone. More patients died due to disease progression in the TP arm than TPM arm (69.2% vs 53.7%) for TPM. No significant difference in OS was observed between the two treatment arms (median, 32.1 months with TP vs 37.5 months with TPM; p=0.25). The PFS rate at 6 months among those patients who have started T-DM1 (n=40) was 43.6% (notably, this trial was not formally powered for this analysis) and grade ≥3 AEs occurred in 45% of patients. Overall, the safety results from this trial show a very acceptable safety profile and compare favorably against those in CLEOPATRA. While the benefit in terms of clinical outcome may be lower, this study represents an active and relatively well tolerated treatment option for this patient population.[28,31]

SAKK 25/14: Eribulin as first-line treatment in older patients with advanced breast cancer

The multicenter phase II SAKK 25/14 trial investigated the efficacy of a reduced starting dose of eribulin (1.1 mg/m^2 on Day 1 and Day 8) as frontline treatment in 77 older patients (≥70 years) with metastatic breast cancer.[32] The primary endpoint was a disease control rate (DCR) of ≥55%.

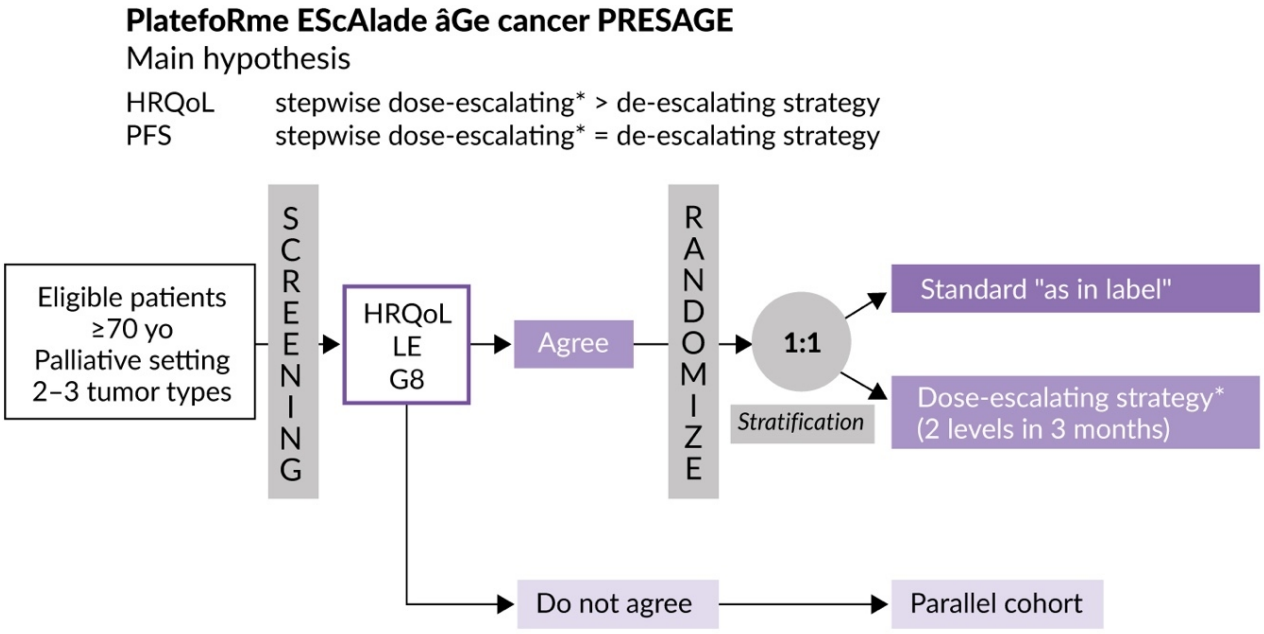

Figure 1. The design of the PRESAGE study.

HRQoL, health-related quality of life; LE, life expectancy; PFS, progression-free survival; yo, years old. Adapted from Brain et al. 2023.[12]

At baseline, the median age was 76 years (range, 70–89), 64% of patients had coexisting morbidities and 45% had liver metastases.[32] The primary endpoint was not reached, with a DCR of 40% at a median follow-up of 25.6 months. The ORR was 22%, including a CR rate of 2.6% and a PR rate of 19.5%. The median OS was 16.1 and the median PFS was 5.4 months. Overall, 57% of patients discontinued treatments due to progressive disease. The reduced dose of eribulin was safe, with grade ≥3 toxicity occurring in 62% of patients, most commonly neutropenia (22%). Taken together, these results do not support first-line chemotherapy with eribulin at a reduced starting dose in older patients.

PlatefoRme EscAlade âGe cancer PRESAGE: Stepwise dose-escalation in older patients with breast cancer

This is a proposed trial to assess whether stepwise dose-escalation (two levels in 3 months) may yield better results for health-related QoL while providing a similar PFS benefit, as compared with "as in label standard" (**Figure 1**).[12] As therapies are often approved irrespective of age and with a similar safety profile, this trial will assess if this is the case in a highly selected population of patients aged ≥70 years in a palliative setting.

Healthcare professional versus patient expectations

Older patients often prioritize feeling safe and maintaining control and independence. A survey among 459 patients with advanced cancer demonstrated that 55% of patients placed equal value on QoL and length

of life (LoL), whereas 27% prioritised QoL and 18% preferred LoL.[33] Older women with estrogen receptor (ER)-positive operable breast cancer may be offered primary ET as an alternative treatment to surgery because of frailty and decreased tolerance to surgical interventions. However, the choice of treatment options often relies heavily on healthcare professionals' opinions rather than on patient's preferences. A study assessed the use of primary ET as an alternative treatment to surgery for ER-positive operable breast cancer in older patients.[34] Following interviewing 34 UK healthcare professionals (20 breast surgeons, 13 nurse specialists and 1 geriatrician) and analyzing data from 252 questionnaires, the prevailing view was that primary ET should not be given to patients aged ≥80 years in the absence of significant comorbidities. While patient preference was generally considered to be the most important factor in treatment decisions, only 26.6% of healthcare professionals responded that all patients aged ≥70 years should be offered primary ET as an alternative treatment option. Currently, there are no guidelines for the treatment of operable breast cancer in this complex group of patients. Implementing patient-reported outcome measures (PROMs), tools and instruments used to collect patient-reported symptoms, functional status and QoL has demonstrated improvement in patient-centered care in surgical oncology populations and survival in patients with advanced cancer.[35]

One concept worth considering is so-called time toxicity (**Figure 2**), which refers to the time spent coordinating care, frequent visits to a healthcare facility (including travel and wait times), seeking urgent/emergent care for side effects, hospitalization and follow-up tests.[36] Although treatment-related time toxicity is relevant across all diseases and treatment settings, it may be particularly important for patients with advanced cancer who weigh treatment options against their limited time. Patients usually want to understand the impact of treatment on their daily lives, including where and how they will spend their time, not just the potential time gained. For example, knowing the difference in time spent at home versus time in medical settings (e.g., hospitals) can influence their treatment choices. However, clinicians often lack the detailed information needed to guide patients and their care partners in making decisions that fully consider time impact.

Recently, a composite measure of time toxicity was proposed: Days with Physical Health Care System Contact (including clinic visits, infusions, procedures, bloodwork, urgent care visits and overnight stays) versus Home Days (days without physical contact).[36] Home Days can be particularly valuable for comparing treatments with varying intents and burdens, to help identify which strategy best aligns with the patient's goals. It accounts for both the quantity of survival and the quality of life. As such, this approach emphasizes the importance of long-term planning to potentially maximize

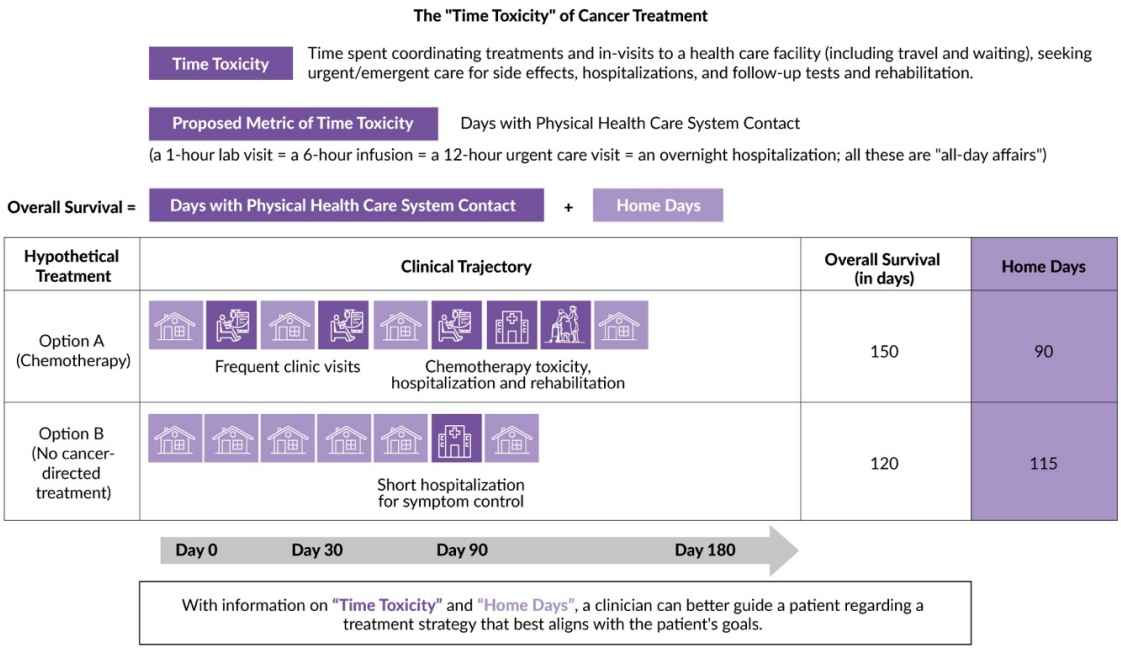

Figure 2. The time toxicity of cancer treatment.

Adapted from Gupta et al. 2022.[36]

Home Days despite short-term hospital stays. Notably, this approach could be easily integrated into clinical trials with minimal additional effort, following practices common in cardiology and neurology studies.

Taken together, the time required to receive certain types of care may offset the gains in survival achieved by patients with advanced disease.[36] Therefore, it is important to match the patient's expectations regarding the time toxicity of cancer treatment compared with receiving no cancer-directed therapy at home. Such a tool may highlight the increased hospital days incurred by older patients who require more dose adjustments.

Impact of geriatric assessment on treatment decision

Age is an independent predictor of adverse outcomes associated with treatment, underlining the pivotal role of oncologists and geriatricians in assessing which patients may benefit most from treatment and avoiding futile treatments for older patients, given the high prevalence of frailty in those aged >70–75 (almost 30% of patients).[12] Integrating a geriatric assessment in treatment decision-making may lead to the alteration of the initial treatment plan in up to 50% of cases with de-escalation and up to 70% of cases with less intensive treatments. Geriatric assessments also offer an opportunity to identify specific interventions such as social support as well as nutritional and polypharmacy intervention to support treatment goals.

Several phase III trials in patients aged ≥70 years across various cancer types (e.g., GAIN, GAP70+, GERICAO and INTEGRATE) have shown that geriatric assessments can decrease the rate of AEs, enhance treatment completion and improve patient QoL, without negatively impacting treatment efficacy.[37-40]

It is important to account for both geriatric and oncology-related factors when treating patients.[12] Geriatric patients may prioritize QoL (e.g., independence, staying at home), while younger patients may focus on social and family obligations and life extension. Similarly, geriatricians may prioritize the quality of survival for their patients, whereas oncologists may prioritize increasing PFS and OS.[12] Both geriatric- and oncology-related factors are key in defining the best strategy, especially in breast cancer. Multidisciplinary expert teams are constantly working on expanding and updating evidence-based recommendations for the management of breast cancer in older patients. The current guidelines including recommendations on geriatric assessment, screening, primary endocrine therapy, surgery, radiotherapy, adjuvant systemic therapy and secondary breast cancer have been summarized in a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the SIOG.[41] The evaluation of anticancer therapy in older patients requires careful consideration due to the scarcity of data for this population, which is often underrepresented in clinical trials. It is critical to recognize that clinical outcomes observed in non-geriatric patients may not directly apply to geriatric patients. For this reason, we need to ensure adequate representation of older patients in clinical trials to accurately assess the risks and benefits of anticancer therapies in this group.

Conclusions

- Current clinical trials underrepresent older patients, creating a data gap in the literature.
- Older patients often require constant dose adjustment and a de-escalation of the treatments that trigger the most important AEs.
- HER2+ metastatic breast cancer in older patients represents an important challenge. However, data have shown that dual anti-HER2 therapy with metronomic chemotherapy is effective and safe. Furthermore, the efficacy of second-line T-DM1 is similar to the general breast cancer population.
- While doses and dose adjustments are important, the integration of geriatric assessment early in the treatment plan is key for older patients with breast cancer.

- For metastatic breast cancer patients aged >70 years, frailty is present in 30–40% of cases (in PALOMAGE it was up to 70%), and it may be as high as 30–40% in earlier stages.
- Clinical trials need to be more inclusive, allowing the geriatric population to receive appropriate treatments by creating relevant and consistent guidelines for these patients.

Conflict of interest

Marcus Vetter received honoraria for consultancy from GSK, Roche, Novartis, Exact Sciences, Pfizer, Stemline, AbbVie and ASC Oncology. These funding entities did not play a role in the development of the manuscript and did not influence its content in any way. Julia Landin has declared that the manuscript was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

The authors have declared that no financial support was received from any organization for the submitted work.

Author contributions

All authors have contributed to and approved the final manuscript.

Submitted: February 08, 2024 CET, Accepted: March 19, 2024 CET

REFERENCES

1. Lemij AA, Bastiaannet E, De Glas NA, et al. Breast cancer in the older population: a global challenge—an epidemiological perspective. *Ann Breast Surg*. 2023;7:17. doi:10.21037/abs-21-89

2. Berger NA, Savvides P, Koroukian SM, et al. Cancer in the elderly. *Trans Am Clin Climatol Assoc*. 2006;117:147-156.

3. Extermann M, Chetty IJ, Brown SL, Al-Jumayli M, Movsas B. Predictors of Toxicity Among Older Adults with Cancer. *Semin Radiat Oncol*. 2022;32(2):179-185. doi:10.1016/j.semradonc.2021.11.004

4. Kojima G, Liljas AEM, Iliffe S. Frailty syndrome: implications and challenges for health care policy. *Risk Manag Healthc Policy*. 2019;12:23-30. doi:10.2147/rmhp.s168750

5. Van Herck Y, Feyaerts A, Alibhai S, et al. Is cancer biology different in older patients? *Lancet Healthy Longev*. 2021;2(10):e663-e677. doi:10.1016/s2666-7568(21)00179-3

6. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol*. 2014;32(24):2595-2603. doi:10.1200/jco.2013.54.8347

7. Veronese N, Custodero C, Demurtas J, et al. Comprehensive geriatric assessment in older people: an umbrella review of health outcomes. *Age Ageing*. 2022;51(5):afac104. doi:10.1093/ageing/afac104

8. Rubenstein LZ, Stuck AE, Siu AL, Wieland D. Impacts of geriatric evaluation and management programs on defined outcomes: overview of the evidence. *J Am Geriatr Soc*. 1991;39(S1):8S-18S. doi:10.1111/j.1532-5415.1991.tb05927.x

9. Bischof E, Hurni B, Vetter M. Management of Elderly and Old Cancer Patients – Geriatric Oncology. *healthbook TIMES Onco Hema*. 2021;10(4):28-33. doi:10.36000//hbt.oh.2021.10.061

10. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. *J Clin Oncol*. 2018;36(22):2326-2347. doi:10.1200/jco.2018.78.8687

11. Decoster L, Van Puyvelde K, Mohile S, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations. *Ann Oncol*. 2015;26(2):288-300. doi:10.1093/annonc/mdu210

12. Brain E. Optimizing Oncologic Care in Older Patients w/ ABC. Presented at: ESMO Congress 2023; 20–24 October 2023. Madrid, Spain. Oral presentation.

13. Vetter M, Bollinger C, Chiru D, et al. Integrating Geriatric Care in Clinical Oncology Practice: Recommendations from an Interdisciplinary Professional Survey Study in a Single-Cancer Center in Switzerland. *healthbook TIMES Onco Hema*. 2023;16(2):14-19. doi:10.36000/hbt.oh.2023.16.106

14. Dougoud V, Vetter M. Geriatric Assessment of Older Patients with Cancer: Recent Data and Updated Recommendations. *healthbook TIMES Onco Hema*. 2023;18(4):50-53. doi:10.36000/hbt.oh.2023.18.131

15. Abdel-Razeq H, Abu Rous F, Abuhijla F, Abdel-Razeq N, Edaily S. Breast Cancer in Geriatric Patients: Current Landscape and Future Prospects. *Clin Interv Aging*. 2022;17:1445-1460. doi:10.2147/cia.s365497

16. Carola E, Pulido M, Falandry C, et al. First-line systemic treatment with palbociclib in women aged ≥70 years presenting with hormone receptor-positive advanced breast cancer: Results from the PALOMAGE program. *J Clin Oncol*. 2023;41(16_suppl):1018. doi:10.1200/jco.2023.41.16_suppl.1018

17. Ismail RK, van Breeschoten J, Wouters MWJM, et al. Palbociclib dose reductions and the effect on clinical outcomes in patients with advanced breast cancer. *Breast*. 2021;60:263-271. doi:10.1016/j.breast.2021.11.013

18. Lagunes MLLR, Sickander F, Thawer A, et al. 254P Impact of palbociclib-dose reduction on survival: A retrospective cohort study. *Ann Oncol*. 2021;32(suppl_5):S470-S471. doi:10.1016/j.annonc.2021.08.537

19. Sonke GS, Van Ommen - Nijhof A, Wortelboer N, et al. Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017-03) on selecting the optimal position of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors for patients with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC). *J Clin Oncol*. 2023;41(17_suppl):LBA1000-LBA1000. doi:10.1200/jco.2023.41.17_suppl.lba1000

20. Slamon DJ, Diéras V, Rugo HS, et al. Overall Survival With Palbociclib Plus Letrozole in Advanced Breast Cancer. *J Clin Oncol*. 2024;42(9):994-1000. doi:10.1200/jco.23.00137

21. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. *N Engl J Med*. 2022;386(10):942-950. doi:10.1056/nejmoa2114663

22. Goetz M, Toi M, Huober J, et al. MONARCH 3: Final overall survival results of abemaciclib plus a nonsteroidal aromatase inhibitor as first-line therapy in patients with HR+, HER2- advanced breast cancer. Presented at: 2023 San Antonio Breast Cancer Symposium (SABCS); 5–9 December 2023. San Antonio, TX, USA. Oral presentation GS01-12; San Antonio, TX, USA.

23. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *N Engl J Med*. 2021;384(16):1529-1541. doi:10.1056/nejmoa2028485

24. Kalinsky K, Oliveira M, Traina TA, et al. Outcomes in patients (pts) aged ≥65 years in the phase 3 ASCENT study of sacituzumab govitecan (SG) in metastatic triple-negative breast cancer (mTNBC). *J Clin Oncol*. 2021;39(15_suppl):1011. doi:10.1200/jco.2021.39.15_suppl.1011

25. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer. *N Engl J Med*. 2015;372(8):724-734. doi:10.1056/nejmoa1413513

26. Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020;21(4):519-530. doi:10.1016/s1470-2045(19)30863-0

27. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline. *J Clin Oncol*. 2021;39(13):1485-1505. doi:10.1200/jco.20.03399

28. Miles D, Baselga J, Amadori D, et al. Treatment of older patients with HER2-positive metastatic breast cancer with pertuzumab, trastuzumab, and docetaxel: subgroup analyses from a randomized, double-blind, placebo-controlled phase III trial (CLEOPATRA). *Breast Cancer Res Treat*. 2013;142(1):89-99. doi:10.1007/s10549-013-2710-z

29. Loh KP, Soto-Perez-de-Celis E, Hsu T, et al. What Every Oncologist Should Know About Geriatric Assessment for Older Patients With Cancer: Young International Society of Geriatric Oncology Position Paper. *J Oncol Pract*. 2018;14(2):85-94. doi:10.1200/jop.2017.026435

30. Wildiers H, Tryfonidis K, Dal Lago L, et al. Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer (EORTC 75111-10114): an open-label, randomised, phase 2 trial from the Elderly Task Force/Breast Cancer Group. *Lancet Oncol*. 2018;19(3):323-336. doi:10.1016/s1470-2045(18)30083-4

31. Wildiers H, Meyskens T, Marréaud S, et al. Long term outcome data from the EORTC 75111-10114 ETF/BCG randomized phase II study: Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer, followed by T-DM1 after progression. *Breast*. 2022;64:100-111. doi:10.1016/j.breast.2022.05.004

32. Hasler-Strub U, Mueller A, Li Q, et al. Eribulin as first-line treatment in older patients with advanced breast cancer: A multicenter phase II trial [SAKK 25/14]. *J Geriatr Oncol*. 2023;14(1):101372. doi:10.1016/j.jgo.2022.09.001

33. Meropol NJ, Egleston BL, Buzaglo JS, et al. Cancer patient preferences for quality and length of life. *Cancer*. 2008;113(12):3459-3466. doi:10.1002/cncr.23968

34. Morgan JL, Collins K, Robinson TG, et al. Healthcare professionals' preferences for surgery or primary endocrine therapy to treat older women with operable breast cancer. *Eur J Surg Oncol*. 2015;41(9):1234-1242. doi:10.1016/j.ejso.2015.05.022

35. Doolin JW, Halpin M, Berry JL, Hshieh T, Zerillo JA. Why focus on patient-reported outcome measures in older colorectal cancer patients? *Eur J Surg Oncol*. 2020;46(3):394-401. doi:10.1016/j.ejso.2019.07.028

36. Gupta A, Eisenhauer EA, Booth CM. The Time Toxicity of Cancer Treatment. *J Clin Oncol*. 2022;40(15):1611-1615. doi:10.1200/jco.21.02810

37. Mohile SG, Mohamed MR, Xu H, et al. Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study. *Lancet*. 2021;398(10314):1894-1904. doi:10.1016/s0140-6736(21)01789-x

38. Li D, Sun CL, Kim H, et al. Geriatric Assessment–Driven Intervention (GAIN) on Chemotherapy-Related Toxic Effects in Older Adults With Cancer: A Randomized Clinical Trial. *JAMA Oncol*. 2021;7(11):e214158. doi:10.1001/jamaoncol.2021.4158

39. Lund CM, Vistisen KK, Olsen AP, et al. The effect of geriatric intervention in frail older patients receiving chemotherapy for colorectal cancer: a randomised trial (GERICO). *Br J Cancer*. 2021;124(12):1949-1958. doi:10.1038/s41416-021-01367-0

40. Soo WK, King MT, Pope A, Parente P, Dārziņš P, Davis ID. Integrated Geriatric Assessment and Treatment Effectiveness (INTEGERATE) in older people with cancer starting systemic anticancer treatment in Australia: a multicentre, open-label, randomised controlled trial. *Lancet Healthy Longev*. 2022;3(9):e617-e627. doi:10.1016/s2666-7568(22)00169-6

41. Biganzoli L, Battisti NML, Wildiers H, et al. Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG). *Lancet Oncol*. 2021;22(7):e327-e340. doi:10.1016/s1470-2045(20)30741-5