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ORIGINAL RESEARCH

Health-related quality of life and clinical complexity of a real-life cohort of patients with advanced HR+/HER2- breast cancer treated with CDK4/6 inhibitors and endocrine therapy

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Abstract

Background: Advanced breast cancer (ABC) is characterized by multidimensional clinical complexity that is usually not considered in randomized clinical trials. In the present real-life study, we investigated the link between clinical complexity and quality of life of patients with HR+/HER2- ABC treated with CDK4/6 inhibitors.

Methods: We evaluated multimorbidity burden assessed with the Cumulative Illness Rating Scale (CIRS), polypharmacy and patient-reported outcomes (PROs). PROs were assessed at baseline (T0), after 3 months of therapy (T1), and at disease progression (T2) using EORTC QLC-C30 and QLQ-BR23 questionnaires. Baseline PROs and changes between T0 and T1 were evaluated amongst patients with different multimorbidity burden (CIRS <5 and ≥5) and polypharmacy (<2 or ≥2 drugs).

Results: From January 2018 to January 2022, we enrolled 54 patients (median age 66 years, IQR 59–74). The median CIRS score was 5 (IQR 2–7), whilst the median number of drugs taken by patients was 2 (IQR 0–4). No changes in QLQ-C30 final scoring between T0 and T1 were observed in the overall cohort (p=0.8944). At T2, QLQ-C30 global score deteriorated with respect to baseline (p=0.0089). At baseline, patients with CIRS ≥5 had worse constipation than patients without comorbidities (p<0.05) and a lower trend in the median QLQ-C30 global score. Patients on ≥2 drugs had lower QLQ-C30 final scores and worse insomnia and constipation (p<0.05). No change in QLQ-C30 final score from T0 to T1 was observed (p>0.05).

Conclusion: Multimorbidity and polypharmacy increase the clinical complexity of patients with ABC and may affect baseline PROs. The safety profile of CDK4/6 inhibitors seems to be maintained in this population. Further studies are needed to assess clinical complexity in patients with ABC.

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Keywords: breast cancer, CDK4/6 inhibitors, clinical complexity, comorbidities, polypharmacy, quality of life, real-life population.

Citation

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Introduction

Hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer (BC) is the most common sub-type of advanced BC (ABC). Current treatment guidelines recommend adding cyclin-dependent kinase 4/6 (CDK4/6) inhibitors to endocrine therapy (ET) both in first and later lines of treatment as they remarkably improve survival outcomes compared with ET alone.[1–9] The efficacy of this strategy

was confirmed in all sub-groups of interest, regardless of age, menopausal status, endocrine sensitivity, and visceral involvement.[10,11] In addition to delaying time to chemotherapy and disease progression (DP), the combination of CDK4/6 and ET has been shown to maintain or even improve health-related quality of life (QoL) thanks to its favourable safety profile.[12–18]

Patients enrolled in randomized controlled trials (RCTs) are usually highly fit and without relevant comorbidities. This selection bias translates into a low generalizability of QoL and efficacy findings in clinical practice. On the other hand, real-life patients are characterized by high interindividual variability in terms of intrinsic (age, sex, multimorbidity, frailty, pharmacogenomics, polypharmacy), disease-related (tumour biology, type of CDK4/6 inhibitor, sites of metastases, burden of symptoms) and contextual (socioeconomic, behavioural, cultural, environmental) factors, whose dynamic interactions lead to multidimensional clinical complexity.[19,20]

In this real-life study, we assessed the clinical complexity and QoL of patients with HR+/HER2− ABC receiving CDK4/6 inhibitor therapy in combination with ET. For this purpose, we used multimorbidity burden and polypharmacy as surrogate indicators of clinical complexity in absence of other reliable tools in oncology. Furthermore, we explored the possible impact of clinical complexity on QoL, given that patients with complex disease are the majority of those treated in real-life practice and on whom the results in terms of QoL modifications during CDK4/6 inhibitor treatment is more doubtful. Thus, this study aims to describe the clinical complexity of a real-life cohort of patients with ABC treated with CDK4/6 inhibitors in terms of comorbidities and ongoing non-cancer-related pharmacotherapy. Furthermore, we assessed QoL variation during treatment using patient-reported outcomes (PROs) and we investigated the possible impact of clinical complexity on QoL.

Methods

Patients

In this prospective, observational, real-life study, we enrolled women in pre-menopause and post-menopause consecutively treated at the Unit of Medical Oncology, ICS Maugeri IRCCS, Pavia, and Italy. All patients had been diagnosed with HR+/HER2− ABC and were planned to start treatment with CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) plus ET (fulvestrant or non-steroidal aromatase inhibitors according to their endocrine sensitivity). Both naive and pre-treated patients with metastatic disease were included. The study was conducted according to the ethical regulations of ICS Maugeri IRCCS, following approval from the Institutional Ethics Committee (C.E. 2295, approved on January 9, 2017) and signing of informed consent. Patient information was extrapolated from medical records and pseudo-anonymized.

Data collection and procedures

Data collection started at the time of first administration of a CDK4/6 inhibitor. It included demographic data, performance status according to the Eastern Cooperative Oncology Group (ECOG), features of concurrent chronic illnesses, pharmacotherapy, index disease (relapsed *versus* de novo BC, visceral *versus* non-visceral disease, prior exposure to chemotherapy), and current antitumour therapy (CDK4/6 inhibitor, line of therapy, dose reduction/drug interruption due to unacceptable toxicity).

In order to evaluate the multimorbidity burden of patients, we used the Cumulative Illness Rating Scale (CIRS), a scoring system assessing presence and severity of disease in 14 biological systems (Table S1; available at: https://www.drugsincontext.com/wp-content/uploads/2023/05/dic.2023-1-7-Suppl.pdf).[21,22] All tumour-related manifestations (primary tumour, metastases and tumour-induced organ failure) were excluded from the final score as they were not considered comorbidities but direct consequences of the index disease.[23,24] We also described the prevalence and characteristics of polypharmacy, excluding drugs related to the index disease.

With the aim of monitoring QoL changes, patients received two questionnaires at three different times, namely prior to starting treatment with CDK4/6 inhibitors (T0, baseline questionnaire), after 3 months of treatment (T1, intermediate questionnaire) and within 30 days from discontinuation for DP or toxicity (T2, final questionnaire). We chose the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire CORE 30 (QLQ-C30), consisting of functional and symptom scales assessing QoL in patients with cancer and the Quality of Life Questionnaire Breast Cancer Questionnaire (QLQ-BR23), a similar tool tailored for patients with BC.[25–27]

As a surrogate of clinical complexity, we have decided to assess multimorbidity and polypharmacy as they represent two of the most important variables determining the clinical outcomes (i.e. length of stay, early and late mortality, dependence, burden on healthcare) and the overall patient management, as already speculated in a previous, large, multicentre study focusing on this issue.[28]

Study data were collected, stored and managed using REDCap electronic data capture tools hosted at ICS Maugeri.[29]

Methods and statistical analysis

To be eligible for the analysis, patients had to be on active anticancer treatment. In addition, clinical information about other concurrent illnesses and drug therapy had to be available. To be suitable for the evaluation of QoL changes, at least one complete cycle of treatment had to be administered.

For each patient, we calculated an individual score for every functional scale, symptoms scale, and global health status scale for QLQ-C30 and QLQ-BR23 at each point in time. We then computed the individual-level change between baseline and intermediate questionnaire scores (T1 to T0 values), and – for patients receiving questionnaires also at the end of treatment – between baseline and final questionnaire scores (T2 to T0 values).

In functional scales, a positive change corresponded to an improvement in outcome, whilst a negative change was associated with deterioration. For symptom scales, a positive change corresponded to a deterioration in outcome, whilst a negative change indicated an improvement. A change equal to zero corresponded to the absence of variation from baseline.

An important difference (ID) is defined as a change in PROs perceived as important by patients.[30] Threshold values for changes from baseline commonly used in previous studies range from 5 to 10 points.[14,15,31] In our study, PROs were considered improved when a positive change of at least 5 points (change ≥+5) was achieved compared with baseline; similarly, PROs worsened when patients reported a reduction in terms of change of at least 5 points (change ≤−5) from baseline. Smaller variations (−5 <change <+5) were categorized as stability.

The median CIRS score and the median number of drugs estimated in our cohort were used as threshold values to divide patients into two sub-groups.

Numeric quantitative variables distribution was described by median and interquartile range (IQR 25th–75th percentiles) and by the minimum and maximum values observed in the available data. Categorical variables distribution was described by absolute and relative (%) frequency. The non-parametric Mann–Whitney test was applied to test for differences in terms of numeric quantitative variables distribution between two groups. The non-parametric Wilcoxon test for paired samples was used for statistically significant differences in terms of numeric quantitative variables distribution between time points. Fisher's exact test was applied to compare the frequency of patients reaching ID between categories. The significance level was set to α=0.05. Statistical analyses were conducted with R statistical software tool v 4.0.5 (www.r-project.org).

Results

Patient characteristics

Our cohort included 54 consecutive patients who started treatment with CDK4/6 inhibitors and ET between January 2018 and January 2022. The demographic and baseline characteristics of the included patients are shown in Table 1.

Table 1. Demographics and clinical characteristics of patients at baseline. Data are presented as absolute and relative frequency (%) or as median and IQR as appropriate.

	N	%
Total number of patients	54	100
Age at the beginning of treatment		
≤65 years	26	48.1
>65 years	28	51.9
Median age	66 years (IQR 59.85–75)	
ECOG Performance status		
0–1	46	85.8
2	8	14.2
Menopausal status		
Postmenopausal	47	87.0
Premenopausal	7	13.0
Endocrine resistance pattern		
Primary	5	9.2
Secondary	20	37.0
Sensitive	29	53.8
De novo disease		
Yes	12	22.2
No	42	77.8
Prior chemotherapy		
No	26	48.1
Yes (neo/adjuvant setting)	23	42.5
Yes (metastatic setting)	5	9.4
Site of metastases		
Visceral	18	33.3
Non-visceral	36	66.7
Line of therapy		
First line	41	75.9
Second line or beyond	13	24.1

(*Continued*)

Table 1. (Continued)

	N	%
Concomitant ET		
Anastrozole	13	24.0
Letrozole	14	26.0
Fulvestrant	27	50.0
CDK4/6 inhibitors		
Palbociclib	40	74.0
Ribociclib	9	16.7
Abemaciclib	5	9.3
Best response		
Complete response	6	11.0
Partial response	26	48.0
Stable disease	19	35.0
Progression disease	3	6.0%
Efficacy outcome		
CBR	51	94.0
ORR	32	59.0
Median PFS	18 months (IQR 12.75–21)	
Dose reduction		
Yes	18	33.3
No	36	66.7
Drug interruption		
Yes	1	1.8
No	53	98.9
Comorbidities (≥1 illness other than index disease)		
Yes	43	79.3
No	11	20.4
Polypharmacy (≥2 drugs)		
Yes	26	49.1
No	27	50.9

CBR, clinical benefit rate; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; ORR, objective response rate; PFS, progression-free survival.

Our dataset included patients aged from 42 to 87 (median age 66 years, IQR 59.85–75). Performance status was generally good (ECOG PS = 0–1 in 85.8% of patients, ECOG PS = 2 in the remaining 14.2%). Most patients were in post-menopause (87.0%) and were relapsing after a first diagnosis of early BC treated with curative intent (77.8%). According to ABC 5 guidelines,[32] 53.8% of patients were endocrine sensitive and primary endocrine resistance was present in 9.2% of patients, whilst secondary resistance was observed in 37%. Visceral disease was present in 33.3% of cases, whilst most patients had non-visceral sites of metastases (including bone, lymph node and skin). Approximately half of the population (51.9%) had received chemotherapy in the (neo)adjuvant or metastatic setting.

Treatment and outcomes

CDK4/6 inhibitors were administered as first-line treatment in 41 patients (75.9%). Of the remaining patients, 7 (13%) received the drug in second line and 6 (11.1%) in third or further lines. The most used CDK4/6 inhibitor was palbociclib (74.0%, *n*=40). Ribociclib and abemaciclib were administered to 9 (16.7%) and 5 (9.3%) patients, respectively. Concerning ET, 26% of patients received letrozole, 24% anastrozole, and 50% fulvestrant, according to endocrine sensitivity status and line of treatment. In the total sample, 48% of patients achieved a partial response as best response, whereas 35% maintained stable disease. Six complete responses were reported (11%). The objective response rate was 59%, and clinical benefit rate was 94%. One-third of patients (*n*=18) received a dose reduction because of treatment-associated toxicity, in most cases due to haematological adverse events. Dose interruption for unacceptable toxicity was rare (*n*=1). Overall, 20 (37%) patients underwent DP during data collection, 16 (29.6%) of whom had received CDK4/6 inhibitors as first-line treatment. At database closure, the median progression-free survival in this sub-group of patients was 18 months (IQR 12.75–21).

Comorbidities

At least one comorbidity of any type and severity was observed in 79.6% of patients (Table 1). In the overall cohort, median CIRS score was 5 (IQR 2–7). Patients older than 70 had higher median CIRS score, especially in the sub-group >80 years (median CIRS 9, IQR 7–9) (Table 2).

In Table 3, we reported the frequency of clinically relevant comorbidities, defined as a CIRS category score ≥2 and generally associated with diseases requiring chronic medical therapy and causing moderate or greater disability. The most represented illnesses belong to the following categories: vascular system (46.3% of patients); upper gastrointestinal system (22.2%); musculoskeletal and cutaneous disorders (12.9%); psychiatric illness (14.8%); and endocrine, metabolic and mammary system (11.1%).

Hypertension, atherosclerosis and chronic venous insufficiency were the most frequent vascular disorders. Gastroesophageal reflux disease and gastritis requiring daily administration of proton-pump inhibitors were the most common upper gastrointestinal diseases. For the endocrine system, the most frequent disorders were

Table 2. CIRS scoring and its distribution by age group. Data are presented as absolute and relative frequency (%) or as median and IQR as appropriate.

CIRS score		
Median (IQR)	5 (2–7)	
Minimum – Maximum	0–13	
CIRS score by age group	**Median (IQR)**	***N* (%)**
42–49 years old	2 (1–2)	5 (9.26%)
50–59 years old	5 (2–7)	10 (18.52%)
60–69 years old	3.5 (2–6.25)	20 (37.04%)
70–79 years old	6 (3.25–8.5)	14 (25.93%)
80–87 years old	9 (7–9)	5 (9.26%)

CIRS, Cumulative Illness Rating Scale.

Table 3. Number of patients with CIRS ≥2 by biological system. Data are presented as absolute and relative frequency (%). Relative frequencies do not sum up to 100% as patients may be characterized by multiple biological systems with CIRS ≥2.

	Frequency of patients with CIRS ≥2 by biological system	
Organ system	***N***	**%**
Cardiac	4	7.4
Vascular	25	46.3
Haematological	1	1.8
Respiratory	4	7.4
Ophthalmological and otolaryngology	3	5.5
Upper gastrointestinal	12	22.2
Lower gastrointestinal	5	9.2
Hepatic and pancreatic	3	5.5
Renal	1	1.8
Genito-urinary	0	0
Musculoskeletal and cutaneous	7	12.9
Neurological	2	3.7
Endocrine, metabolic, mammary	6	11.1
Psychiatric	8	14.8

CIRS, Cumulative Illness Rating Scale.

diabetes mellitus requiring insulin or oral hypoglycaemic agents, obesity, and thyroid disease requiring hormone replacement. We included both reactive and previously diagnosed mental illness requiring daily medications in the category of psychiatric illnesses, which showed a high prevalence in our population (*n*=8, 14.8%). The most represented diseases were insomnia, anxiety disorders and depressive disorders.

Polypharmacy

At the time of data collection, approximately half of our cohort (51.85%) was taking two or more drugs for chronic illnesses other than index disease. The median number of drugs taken by patients was 2 (IQR 0–4). The most represented drug classes were antihypertensive (29.6%) and proton-pump inhibitors (29.6%), followed by analgesics (opioids 24.0%, non-steroidal anti-inflammatory drugs/acetaminophens 20.3%). Consistently with the high prevalence of psychiatric illness, psychotropic agents (including benzodiazepines, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and other sedative/hypnotic drugs) were taken daily by 18.5% of patients (Table 4).

Table 4. Drug classes and their distribution in the study cohort. Data are presented as absolute and relative frequency (%). Relative frequencies of drug classes do not sum up to 100% as patients may be characterized by multiple classes.

	Frequency of patients by drug class	
Drug class	***N***	**%**
Antihypertensives	16	29.6
Antiarrhythmics/β-blockers	9	16.6
Anticoagulants	3	5.5
Hypoglycaemics	0	0.0
Bronchodilators	0	0.0
Proton-pump inhibitors	16	29.6
Laxative agents	9	16.6
Antidiarrheal agents	0	0.0
Antiemetic agents	3	5.5
Steroids	5	9.5
NSAIDs/Acetaminophens	11	20.3
Opioids	13	24.0
Psychotropic agents	10	18.5
Lipid-lowering medications	4	7.4
Hormone replacement therapy	6	11.1

Patient-reported outcomes

Of the 54 patients enrolled in the study, one did not receive questionnaires because of rapid deterioration of clinical conditions and was therefore excluded from PRO data analysis. Out of the remaining 53 patients, 20 (37.7%) experienced DP throughout the duration of the study and received questionnaires at the end of treatment. The median and IQR values for each QLQ-C30 and QLQ-BR23 item distribution at basal, intermediate, and final questionnaires as well as of the corresponding changes from baseline scores are available in the supplementary materials (Table S2 and Table S3).

No statistically significant changes in terms of QLQ-C30 items were observed between baseline and intermediate study times ($p>0.05$), whilst only QLQ-BR23 systemic therapy side-effects increased significantly between the two time points ($n=51$; median change +4.76; IQR 1.19–19.05; $p=0.0138$).

When focusing on the proportion of patients reaching ID (Figure 1), fatigue was the QLQ-C30 item more frequently improved between baseline and intermediate time (50.94%), followed by emotional functioning (49.06%) and global health status (45.29%). On the other hand, physical functioning was the variable characterized by the highest proportion of patients who suffered a worsening in their condition (43.40%), followed by fatigue (30.19%) and emotional functioning (28.3%). Therefore, fatigue and emotional functioning were the two variables characterized by the most contrasting trends, with both a high proportion of patients who experienced improvement and worsening of their status.

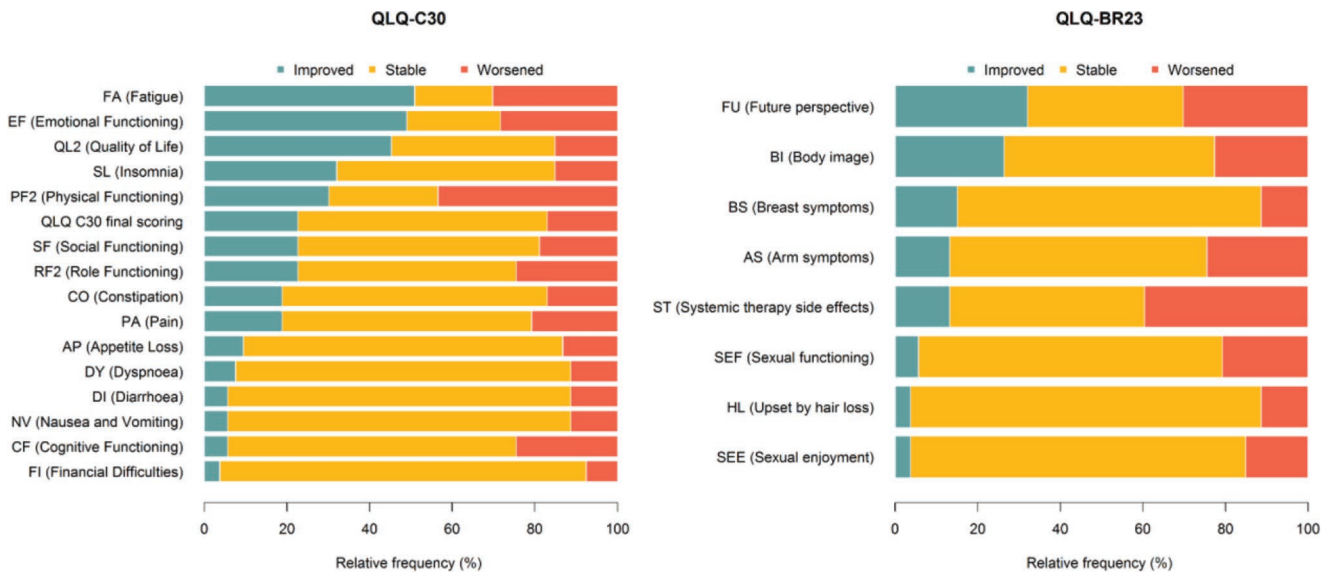
Concerning patients reaching ID for the different QLQ-BR23 items, it was possible to observe that future perspective and body image were the two variables characterized by the highest proportion of patients with improved condition (32.08% and 26.42%, respectively) (Figure 1). The highest number of patients with a worsening in their condition was observed for the systematic therapy side-effects item (39.62%), followed by future perspective (30.19%). Therefore, future perspective was the variable characterized by both a high percentage of patients who experienced improvement and worsening of their status.

With the limitation of a small sample of 20 patients, a statistically significant reduction in terms of QLQ-C30 total score was observed between baseline and the end of treatment ($n=20$, median change −11.28, IQR −19.69 to −0.85; $p=0.0089$). A slight increase was observed between the same time points for QLQ-C30 nausea and vomiting ($n=20$; median change 0; IQR 0–16.67; $p=0.0193$) and QLQ-C30 appetite loss ($n=20$; median change 0; IQR 0–33.33; $p=0.0339$).

Comorbidities and QoL

The study cohort was divided into two groups using the median CIRS score as cut-off (27 patients with CIRS ≥5, 26 patients with CIRS <5), and baseline PROs between the two groups were compared with the aim of revealing a possible correlation between multimorbidity burden and baseline QoL. Scores for each sub-scale of EORTC QLQ-C30 and QLQ-BR23 are reported in Table 5.

Figure 1. Barplots describing the frequency of patients who improved, worsened and remained stable from baseline to intermediate times for QLQ-C30 and QLQ-BR23 items. Barplot widths describe the relative frequency (%) of each category.



QLQ-BR23, Quality of Life Questionnaire Breast Cancer Questionnaire; QLQ-C30, Quality of Life Questionnaire CORE 30.

Table 5. QLQ-C30 and QLQ-BR23 scales distribution at baseline and changes from baseline to intermediate time in patients having CIRS ≥5 and CIRS <5. Variable distributions are described by median and IQR.

	Baseline (T0)			Changes from baseline (T0) to intermediate (T1)		
	CIRS ≥5	CIRS <5	$p^{\#}$	CIRS ≥5	CIRS <5	$p^{\$}$
QLQ-C30 Functional Scales						
Physical	93.33 (76.67–93.33)	86.67 (80–100)	0.7996	-6.66 (-6.67 to 6.67)	0 (-6.67 to 4.96)	0.7657
Role	83.33 (66.67–100)	83.33 (83.33–100)	0.6103	0 (-16.66 to 8.33)	0 (0–0)	0.9691
Emotional	75 (75–91.67)	83.33 (75–91.67)	0.3413	8.33 (-4.17 to 12.5)	0 (-8.33 to 8.34)	0.9857
Cognitive	100 (91.67–100)	100 (87.5–100)	0.8001	0 (-8.34 to 0)	0 (0–0)	0.9386
Social	83.33 (66.67–100)	100 (70.84–100)	0.1728	0 (0–16.66)	0 (0–0)	0.3544
QLQ-C30 Symptoms						
Fatigue	33.33 (22.22–38.89)	22.22 (11.11–44.44)	0.3908	-11.11 (-16.67 to 11.11)	-5.55 (-11.11 to 11.11)	0.8284
Nausea and vomiting	0 (0–0)	0 (0–0)	0.1818	0 (0–0)	0 (0–0)	0.6931
Pain	0 (0–16.67)	0 (0–33.33)	0.4479	0 (0–16.66)	0 (-12.5 to 0)	0.0539
Dyspnoea	0 (0–0)	0 (0–25)	0.6525	0 (0–0)	0 (0–0)	0.5572
Insomnia	33.33 (0–33.33)	0 (0–33.33)	0.3598	0 (-33.33 to 0)	0 (-24.99 to 0)	0.9614
Appetite loss	0 (0–16.67)	0 (0–0)	0.0610	0 (0–0)	0 (0–0)	0.0908
Constipation	0 (0–33.33)	0 (0–0)	0.0456	0 (-33.33–0)	0 (0–0)	0.1472
Diarrhoea	0 (0–0)	0 (0–0)	0.4662	0 (0–0)	0 (0–0)	0.8277
Financial difficulties	0 (0–0)	0 (0–0)	0.5938	0 (0–0)	0 (0–0)	0.1023
QLQ-C30 Global Health Status	133.33 (116.67–141.67)	133.33 (116.67–150)	0.6100	0 (0-16.67)	0 (0–16.66)	0.3910
QLQ-C30 Final scoring	86.62 (81.01–91.37)	94.73 (82.36–97.59)	0.0909	1.62 (-3.94 to 7.01)	0.77 (-1.14 to 2.86)	0.6183
QLQ-BR23 Functional Scales						
Body image	95.83 (66.67–100)	91.67 (68.76–100)	0.9687	0 (0–8.34)	0 (-6.25 to 0)	0.3297
Future perspective	66.67 (33.33–66.67)	66.67 (33.33–100)	0.5593	0 (-33.33 to 33.33)	0 (-33.33 to 33.33)	0.7471
Sexual functioning	0 (0–33.33)	0 (0–33.33)	0.5104	0 (0–0)	0 (0–0)	0.6379
Sexual enjoyment	0 (0–33.33)	0 (0–33.33)	0.7812	0 (0–0)	0 (0–0)	0.2401
QLQ-BR23 Symptoms						
Systemic therapy side-effects	9.52 (0–19.05)	0 (0–9.52)	0.0691	4.76 (-4.76 to 9.53)	4.76 (0–9.52)	0.6029
Upset by hair loss	0 (0–0)	0 (0–0)	0.9903	0 (0–0)	0 (0–0)	0.9431
Arm symptoms	0 (0-5.56)	0 (0-11.11)	0.7788	0 (0–5.56)	0 (0–0)	0.3825
Breast symptoms	0 (0–0)	0 (0–8.33)	0.0631	0 (0–0)	0 (0–0)	0.5431

$^{\#}p$ value from the Mann-Whitney test; $^{\$}p$ value from the Wilcoxon test for paired samples.
CIRS, Cumulative Illness Rating Scale; QLQ-BR23, Quality of Life Questionnaire Breast Cancer Questionnaire; QLQ-C30, Quality of Life Questionnaire CORE 30.

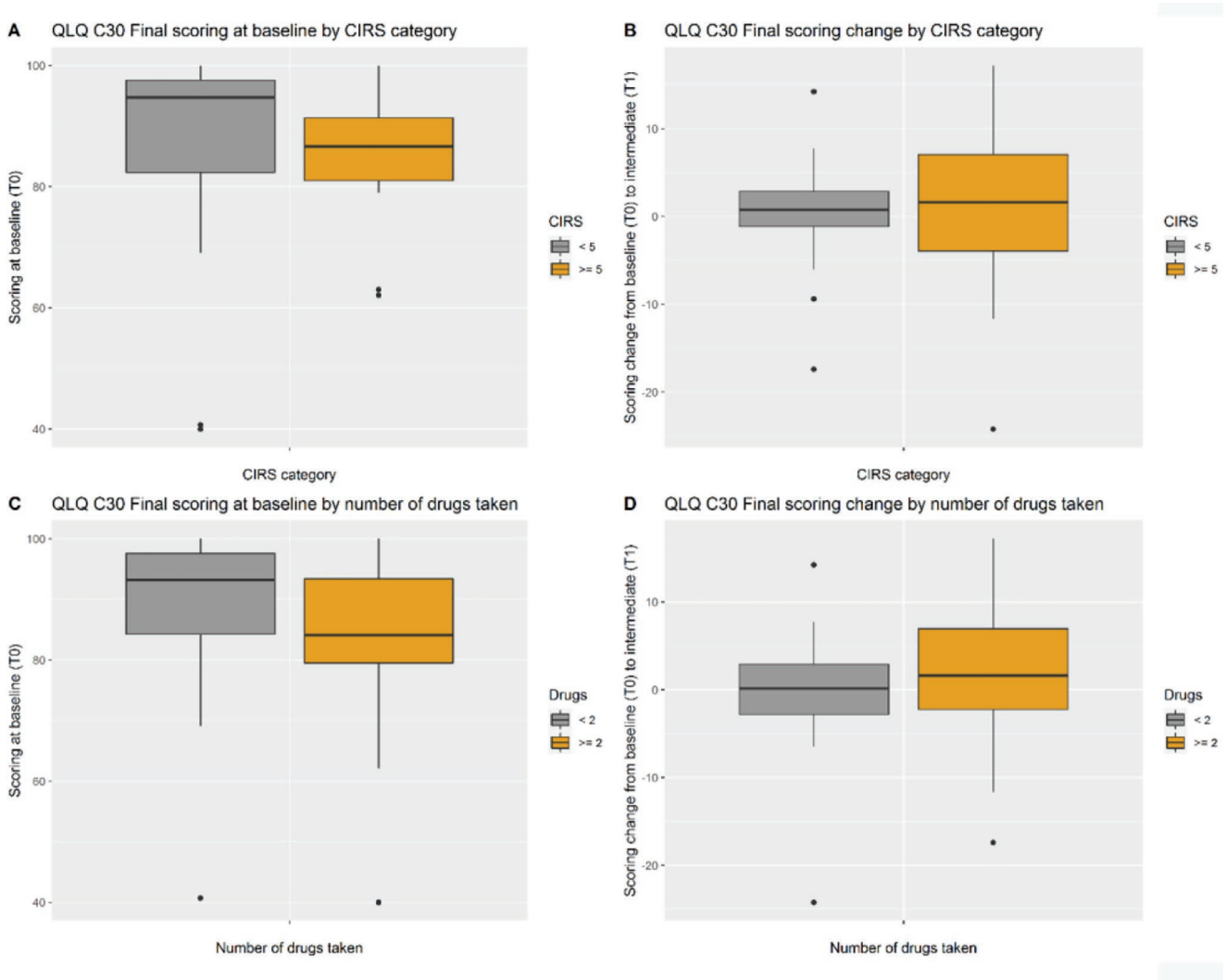
At baseline, patients with CIRS ≥5 had higher QLQ-C30 constipation score compared with patients with CIRS <5 (median 0, IQR 0–33.33 *versus* the median 0, IQR 0–0; p=0.0456); they also had a lower median QLQ-C30 global score (86.62, IQR 79.52–92.63) compared with patients with a lower multimorbidity burden (94.72, IQR 85.4–98.97) (Figure 2A), although no statistically significant differences in terms of QLQ-C30 final scoring (p=0.0909) or remaining QLQ-C30/QLQ-BR23 items were observed between the two groups.

We also investigated the presence of associations between QoL variations from baseline and multimorbidity burden (Table 5); however, no evidence of statistically significant differences in terms of quantitative changes in distributions were observed between the two groups neither for QLQ-C30 final scoring (Figure 2B) nor for single QLQ-C30 or QLQ-BR23 items (p>0.05). Additionally, no statistically significant differences in terms of proportion of patients who improved/worsened their condition based on ID values were observed between patients with CIRS ≥5 and CIRS <5 (p>0.05; Table S4, Table S5).

Polypharmacy and QoL

In the study cohort, the median number of drugs taken by patients was 2 (IQR 0–4). Overall, 27 (50.9%) patients had been prescribed 2 or more drugs for non-index diseases, whilst the remaining 26 (49.1%) patients took less than 2 drugs daily. These two groups were compared in terms of quantitative distribution of baseline QoL, similarly to what was performed for patients with different baseline CIRS scores (Table 6).

Figure 2. Boxplots describing the frequency distribution of QLQ-C30 final scoring at baseline and corresponding change as function of CIRS score and number of therapies. Each boxplot describes from the bottom to the top: lowest non-outlier value, 25th percentile, median value, 75th percentile and top non-outlier value of the corresponding variable's frequency distribution. Outliers with respect to the corresponding distribution are graphically represented as dots.



QLQ-C30, Quality of Life Questionnaire CORE 30.

Table 6. QLQ-C30 and QLQ-BR23 scales distribution at baseline and changes from baseline to intermediate time in patients on polypharmacotherapy (≥2) and in patients taking <2 drugs. Variable distributions are described by median and IQR.

	Baseline (T0)			Changes from baseline (T0) to intermediate (T1)		
	≥2 Drugs	<2 Drugs	*p*#	≥2 Drugs	<2 Drugs	*p*$
QLQ-C30 Functional Scales						
Physical	93.33 (60–93.33)	90 (80–100)	0.3275	0 (-6.67 to 6.67)	0 (-6.67 to 0)	0.6258
Role	83.33 (66.67–100)	83.33 (83.33–100)	0.3501	0 (-16.66 to 0)	0 (0–0)	0.3335
Emotional	75 (70.84–87.5)	83.33 (75–91.67)	0.0851	8.33 (0–12.5)	0 (-8.33 to 8.34)	0.5058
Cognitive	100 (91.67–100)	100 (87.5–100)	0.8001	0 (-16.67 to 0)	0 (0–0)	0.2345
Social	100 (66.67–100)	100 (70.84–100)	0.6195	0 (0–8.33)	0 (0–0)	0.6831
QLQ-C30 Symptoms						
Fatigue	33.33 (22.22–38.89)	22.22 (11.11–44.44)	0.2512	0 (-16.67 to 11.11)	-11.11 (-11.11 to 8.33)	0.9928
Nausea and vomiting	0 (0–0)	0 (0–0)	0.1818	0 (0–0)	0 (0–0)	0.3139
Pain	0 (0–25)	0 (0–12.5)	0.1631	0 (-8.33 to 0)	0 (0–12.5)	0.1226
Dyspnoea	0 (0–33.33)	0 (0–0)	0.3935	0 (0–0)	0 (0–0)	0.9896
Insomnia	33.33 (0–50)	0 (0–33.33)	0.0396	0 (-33.33 to 0)	0 (0–0)	0.3429
Appetite loss	0 (0–16.67)	0 (0–0)	0.0611	0 (0–0)	0 (0–0)	0.2682
Constipation	0 (0–33.33)	0 (0–0)	0.0456	0 (-33.33 to 0)	0 (0–0)	0.1444
Diarrhoea	0 (0–0)	0 (0–0)	1	0 (0–0)	0 (0–0)	0.3206
Financial difficulties	0 (0–0)	0 (0–0)	0.0871	0 (0–0)	0 (0–0)	0.4471
QLQ-C30 Global Health Status	133.33 (108.34–150)	133.33 (120.84–150)	0.3208	16.66 (0–16.67)	0 (0–16.66)	0.1998
QLQ-C30 Final scoring	84.06 (79.51–93.4)	93.17 (84.28–97.59)	0.0107	1.62 (-2.24 to 6.95)	0.13 (-2.8 to 2.8)	0.3021
QLQ-BR23 Functional Scales						
Body image	91.67 (66.67–100)	95.84 (77.08–100)	0.6483	0 (-4.17 to 8.33)	0 (0–0)	0.8709
Future perspective	66.67 (33.33–66.67)	66.67 (33.33–91.67)	0.5469	0 (-33.33 to 16.67)	0 (-33.33 to 33.33)	0.7331
Sexual functioning	0 (0–33.33)	0 (0–33.33)	0.9033	0 (0–0)	0 (0–0)	1
Sexual enjoyment	0 (0–33.33)	0 (0–33.33)	0.9319	0 (0–0)	0 (0–0)	0.5926
QLQ-BR23 Symptoms						
Systemic therapy side-effects	9.52 (0–19.05)	0 (0–16.67)	0.3369	4.76 (-2.38 to 9.52)	4.76 (0–9.52)	0.6155
Upset by hair loss	0 (0–0)	0 (0–33.33)	0.0485	0 (0–0)	0 (0–0)	0.9431
Arm symptoms	0 (0–11.11)	0 (0–0)	0.3870	0 (0–5.56)	0 (0–0)	0.9590
Breast symptoms	0 (0–8.33)	0 (0–8.33)	0.9212	0 (0–0)	0 (0–0)	0.6136

#*p* value from the Mann-Whitney test; $*p* value from the Wilcoxon test for paired samples.
QLQ-BR23, Quality of Life Questionnaire Breast Cancer Questionnaire; QLQ-C30, Quality of Life Questionnaire CORE 30.

Compared with patients taking <2 drugs, those taking ≥2 drugs reported significantly higher QLQ-C30 insomnia (median 33.33, IQR 0–50 *versus* median 0, IQR 0–33.33; p=0.0396) and QLQ-C30 constipation (median 0, IQR 0–50 *versus* median 0, IQR 0–33.33; p=0.0456), and lower QLQ-C30 final scoring (median 84.06, IQR 79.51–93.4 *versus* median 93.17, IQR 84.28–97.59; p=0.0107) (Figure 2C) and QLQ-BR23 scoring in the 'upset by hair loss' item (median 0, IQR 0–0 *versus* median 0, IQR 0–33.33; p=0.0485).

No evidence of statistically significant differences in terms of quantitative QLQ-C30 and QLQ-BR23 changes from baseline to intermediate time scores distributions were observed between patients taking ≥2 and <2 drugs neither for QLQ-C30 final scoring (Figure 2D) nor for the remaining QLQ-C30 or QLQ-BR23 items (p>0.05).

Furthermore, patients who took ≥2 drugs more frequently experienced a worsening of their QLQ-C30 constipation when compared with those taking <2 drugs (33.33% *versus* 3.85%; p=0.0113) (Table S4). No statistically significant differences in the proportion of patients who improved/worsened their QLQ-BR23 score were observed between patients taking ≥2 and <2 drugs (p>0.05) (Table S5).

Discussion

The present analysis of health-related QoL changes during treatment with CDK4/6 inhibitors was performed in a real-life population of unselected patients with ABC. Baseline characteristics, such as age, menopausal status and prevalence of de novo metastatic disease, are consistent with historical data from the literature and from RCTs investigating CDK4/6 inhibitors in this setting. On the other hand, the burden of comorbidities and pharmacotherapy was inevitably more heterogeneous compared with what is found in large, randomized trials, which typically enrol a highly selected population and often omit information about tumour-unrelated conditions.[33] Data on the efficacy and safety of CDK4/6 inhibitors in more fragile patients are derived solely from real-life studies, but the impact of clinical complexity on oncological outcomes and QoL has not been properly investigated. To our knowledge, this is the first prospective study designed to evaluate the impact of clinical complexity, comorbidities and polypharmacy on PROs in a population of patients with ABC.

ID is defined as the smallest change in PROs that patients perceive as important or that may prompt a change in clinical management.[30] Upon revising pertinent literature, we found no clear consensus about the ID cut-off value.[33] Most studies use a cut-off of 10 points,[14,15,31] 5 points[34] and 5–10 points[16] as ID. Evidence for choosing this range derives from the historical study by Osoba et al.,[35] in which an ID ranging from 5 to 10 points was identified as the minimum perceived change in QoL in patients with breast and lung cancer. Considering this evidence, we decided to use an ID of at least 5 points to consider a change in PROs as clinically significant. The lack of standardization of ID needs to be further explored into larger dedicated studies to allow a more homogeneous interpretation of PROs from EORTC questionnaires.

Despite the relevant differences between our small population and those enrolled in the MONALEESA, MONARCH and PALOMA trials,[1–9] we observed that QLQ-C30 final scoring did not deteriorate during treatment with CDK4/6 inhibitors. This information is consistent with data from RCTs[12–18] and is extremely relevant as the maintenance of health-related QoL is crucial in advanced settings given the palliative intent of treatment. Only QLQ-BR23 systemic therapy side-effects showed a significant deterioration during the treatment, although we must be aware that QLQ-BR23 was developed in 1996 and that the systemic therapy item does not specifically reflect CDK4/6 toxicity profile.[26] In the sub-group of patients experiencing DP, we observed a significant deterioration of global health-related QoL and different symptom items (nausea, vomiting and appetite loss). This can be explained by the peculiarity of the moment in which patients generally perceive minimum benefit from the treatment, along with the emerging symptoms of the underlying metastatic disease and the concomitant awareness of being affected by a progressing tumour.

Assuming cancer constitutes the index disease in most cases,[36] quantifying related comorbidities is difficult because no specific tools have been validated for patients with cancer. Additionally, by considering it as the main index disease, the management of other relevant conditions may be overlooked, especially in those patients having a longer life expectancy. For these reasons, a tool addressing this issue would be more than welcome. In fact, the CIRS was specifically designed and validated to provide a quantitative score of chronic illness burden in geriatric patients and those with psychiatric conditions.[37] In 2005, Fortin et al. demonstrated the superiority of CIRS compared with other scales (e.g. Charlson Index and Functional Comorbidities Index) as a measure of multimorbidity when health-related QoL is the outcome of interest.[38] Whilst this scale is currently the best available tool, its use in patients with cancer is still subject to some forced adaptations. In the few studies that explored the impact of comorbidities on patients with cancer, CIRS score was generally modified in order to exclude morbidity derived from the primary tumour or metastases.[39] Similarly, we decided to exclude BC and metastasis-related morbidity from the final CIRS score to reduce confounding when quantifying the burden of concomitant illnesses.

In our cohort, comorbidities were highly represented and heterogeneously distributed, with a median CIRS score of 5. Because our study included also younger patients (48.1% were ≤65 years old), this median value can be considered relevantly high. For comparison, a previous study showed a median CIRS score of 5 at baseline amongst older patients with BC (median age 79 years).[40] Beyond common comorbidities (cardiovascular, gastrointestinal and endocrine), the prevalence of psychiatric illness, both pre-existing and reactive, was unexpectantly high (14.8%). These data underline the importance of addressing mental health alongside other organic diseases, as it is closely linked to global health status.

Amongst patients with CIRS ≥5, we observed a lower median QLQ-C30 global score compared with patients with fewer comorbidities, even if a statistically significant difference was not observed, probably due to the small size. Constipation was the only item significantly worse amongst patients with comorbidities. Of note, no changes were observed between the two groups either for QLQ-C30 final scoring or for single items. According to these results, the safety profile of CDK4/6 inhibitors in combination with ET is preserved also in more fragile patients with a higher burden of comorbidities, as no significant deterioration of QoL was observed during the treatment. Whilst this information is reassuring, patients with multiple comorbidities deserve a comprehensive and, when possible, multidisciplinary assessment before and during treatment as they may be more prone to developing adverse events.[41,42]

At baseline, patients on polypharmacy had a significantly lower QLQ-C30 global score alongside worse symptoms, namely insomnia, constipation, and hair loss. Treatment with CDK4/6 inhibitors does not seem to have a negative impact on PROs even in the presence of polypharmacy as no statistically significant variations were observed from baseline to intermediate time between patients administered ≥2 drugs and those administered less drugs, although an increased risk for pharmacological interactions needs to be considered.

Limitations

The most relevant limitation of our study is the small population size, which inevitably weakened the statistical power of our results. Moreover, most patients included in the present study received palbociclib. The small sample size did not allow sub-group analysis, thus limiting inferences on the impact on QoL associated with other CDK4/6 inhibitors with a less favourable toxicity profile. Abemaciclib and ribociclib were found to maintain health-related QoL both in a systematic review and a recent indirect comparison.[43,44] Further studies are needed to confirm that equal results can be obtained in a comorbid population treated with abemaciclib or ribociclib.

The presence of patient-related variables increases the clinical complexity of cohorts and may impair the applicability of RCT results in a real-life context. Researchers should consider the heterogeneity of patients with ABC, with reference to their multimorbidity burden and related polypharmacy. The clinical complexity of patients with ABC is greater than expected, under-represented in RCTs and frequently neglected in clinical practice. To improve this aspect, clinical complexity should be considered when designing RCTs and interpreting results to identify clinically relevant sub-groups and exclude possible confounders.

Conclusion

We observed that multimorbidity burden and polypharmacy affect baseline QoL. Consequently, clinical complexity may reduce the reproducibility of QoL data and perhaps of survival outcomes into a real-world population. The safety profile of CDK4/6 inhibitors seems to be preserved also amongst patients with 'complexity'. Further studies aiming to validate specific tools to assess clinical complexity in cancer patients are necessary to standardize research on the topic.

Contributions: FS, BT and RP conceived the content of the article. BT, RP, EQ and CT provided patient data. LM, SM, CL and AP collected patient data and compiled the study database. AM and MT performed the statistical analysis. The article was drafted by LM, BT and FS. FS, BT, SM and LM revised the final draft. All authors approved the final article. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

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