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Safety and quality of life of CDK4/6 inhibitors therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: a multicenter cross-sectional survey in China

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Abstract

Background To investigate the treatment pattern, adverse events, and quality of life of Chinese patients treated with CDK4/6 inhibitors (CDK4/6i) for hormone receptor (HR)+/HER2- advanced breast cancer.

Methods This multicenter cross-sectional survey enrolled patients with HR+/HER2- advanced breast cancer currently treated with CDK4/6i. The patients reported adverse events and quality of life during CDK4/6i treatment with a questionnaire and EORTC QLQ-BR23. Meanwhile, the oncologists collected the treatment information, adverse events and patient characteristics from medical record.

Results The analysis included 1254 patients. Most patients received only one CDK4/6i, of which 38.92% received dalpiciclib, 35.81% received abemaciclib, 15.07% received palbociclib, and 0.47% received ribociclib, while 9.73% patients were treated with two CDK4/6i sequentially. The oncologists reported adverse events occurred in > 81.17% of patients, and most common AEs were leukopenia (63.30%) and neutropenia (58.73%). The most common symptomatic adverse events reported by the patients were fatigue (34.13%), alopecia (14.02%) and weakness (11.30%). The incidence of alopecia in patients receiving dalpiciclib was lower than in those receiving palbociclib (8.81% vs. 16.40%, $P < 0.001$) and abemaciclib (8.81% vs. 19.82%, $P = 0.027$). Regard to quality of life, breast symptom

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scores were lower in the palbociclib group than in the abemaciclib group (3.84 ± 8.57 vs. 5.70 ± 9.81, $P = 0.047$). Patient reported alopecia was associated with body image, systemic therapy side effects, breast symptoms, arm symptoms, and upset by hair loss (all $P < 0.001$).

Conclusions The safety profile of different CDK4/6i varies and has different impacts on patients' quality of life, which needs more attention in clinical practice.

Keywords Abemaciclib, Advanced breast cancer, Dalpiciclib, Palbociclib, Ribociclib

Background

Breast cancer is the most common cancer in women worldwide. Global cancer statistics showed that in 2022 there were 20 million new cancer cases and 9.7 million deaths worldwide. Of these, about 2.3 million new cases of breast cancer and 670,000 deaths of breast cancer [1]. In 2022, there were about 357,200 new cases in China and about 75,000 deaths [2]. The important discrepancy between the incidence and mortality of breast cancer indicates an ever-growing number of patients living with the disease, often for several years or even decades, leading to greater strain on healthcare resources [3].

About 65-70% of breast cancers are hormone receptor (HR) positive and human epidermal growth factor receptor 2 (HER2) negative in United States [2]. Fortunately, HR positivity is an actionable tumor characteristic, and blocking estrogen action (either by directly blocking estrogen signaling or blocking estrogen synthesis) is a recognized treatment strategy [4–6]. Nevertheless, despite optimal treatments, about 30% of patients with early breast cancer will eventually have disease progression [6, 7]. The 5-year survival rates for patients with HR+/HER2- breast cancer could be as high as 88-96% [8], during which time patients continue to receive antitumor therapy and treatment-related adverse events lead to a decreasing quality of life. In addition, advanced breast cancer is a special stage of breast cancer and has its own characteristics in terms of treatment and efficacy [6, 7]. Evidence from previous studies suggests that patients with breast cancer treated with endocrine therapy alone indicative for a poor prognosis, and targeted therapy combined with endocrine therapy is a promising strategy to overcome endocrine resistance [9].

The approval of new targeted drugs helps extend the overall survival of patients with advanced breast cancer, and improving the quality of life has become paramount to ensure quality survivorship [10]. The treatment of HR+/HER2- advanced breast cancer is constantly evolving with the approval of new drugs like cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) [11] and endocrine therapeutic agents [12]. Based on evidence from multiple pivotal clinical trials [13, 14], the combination of CDK4/6i with endocrine therapy has become the standard of care for first-line treatment for patients afflicted with HR+/HER2- advanced breast cancer [6, 7, 11].

The approved CDK4/6i for the treatment of breast cancer in China include palbociclib, abemaciclib, dalpiciclib, and ribociclib. Previous studies showed that the combination of CDK4/6i with endocrine therapy was manageable and tolerable, and improved progression-free survival and overall survival in patients with metastatic breast cancer [11, 13, 15–18]. On the other hand, the completed clinical trials of CDK4/6i included only small proportions of Asian or Chinese patients, and there is currently no large-scale real-world evidence on the treatment pattern and adverse events related to the use of CDK4/6i in Chinese. In addition, the disparity between Chinese and Western breast cancer patients, e.g., a younger age [19, 20], and different safety profiles of various CDK4/6i, e.g., neutropenia induced by palbociclib treatment is more common in Asian patients [21], raised interested in the investigation of real-world safety and treatment switch of CDK4/6i among Chinese patients.

In addition to adverse effects, the quality of life is also relevant issues to consider, especially in the presence of significant co-morbidities or advanced age. The MONALEESA-7 study demonstrated that ribociclib in combination with endocrine therapy improved the overall quality of life in patients with HR+/HER2- advanced breast cancer [22]. However, there are no studies comparing the impact of different CDK4/6i on patient quality of life in the real world. The reasons for the adjustment of CDK4/6i treatment regimens in Chinese patients with advanced breast cancer are also unclear.

Therefore, this cross-sectional survey among patients with HR+/HER2- advanced breast cancer aimed to investigate the treatment pattern and adverse events of CDK4/6i currently used to treat HR+/HER2- advanced breast cancer in China and their impacts on patients' quality of life. The results will provide important data to optimize survivorship among patients with advanced breast cancer.

Methods

Study design

This study was a multicenter cross-sectional survey that recruited HR+/HER2- advanced breast cancer treated patients with CDK4/6i to complete the questionnaire from January to September 2023. This survey was designed to enroll 1500 patients from different

geographical regions of China. The questionnaire survey collected patient disease and treatment-related information, adverse events occurring during treatment with CDK4/6i, and quality of life information from the physician and patient perspectives, respectively.

The study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center (Approval Number: 2209261-4) as the lead center, as well as by the ethics committee of all participating centers. The participants provided informed consent before completing the survey. The study was conducted following the tenets of the Declaration of Helsinki and the Good Clinical Practice.

Oncologists recorded data from medical record including: (1) patient characteristics: age, height, weight, etc.; (2) treatment-related information: ECOG performance status, current treatment regimen (including drug name, dosage, time of drug initiation, drug cycle, frequency, and drug switch); (3) safety data: records of adverse events during current treatment regimen.

The patients filled in three parts of information: (1) patient characteristics: education level, annual household income, treatment costs, smoking history, history of alcohol consumption, etc.; (2) safety data: a questionnaire about self-assessment adverse events during current treatment; (3) quality of life assessment: the EORTC QLQ-BR23 Chinese version will be used to assess the quality of life of patients [23].

Participants

The inclusion criteria for surveyed patients were (1) females aged ≥ 18 years old, (2) diagnosed with HR+/HER2- advanced breast cancer, (3) received first-line treatment or later-line treatment for advanced breast cancer, (4) received at least one cycle CDK4/6i and endocrine therapy, e.g., aromatase inhibitors or fulvestrant, switch from one CDK4/6i to another CDK4/6i was permitted, (5) complete medical record information, (6) no history of other malignant tumors at enrollment (except for non-melanoma skin cancer, cervical cancer in situ, or other cancers that underwent curative treatment and were free of disease for at least 5 years), and (7) voluntarily signed the informed consent form.

The exclusion criteria for surveyed patients were (1) unknown HR status, (2) severe heart, liver, and renal dysfunction before receiving the combination treatment (CDK4/6i combined with endocrine therapy), 4) mental or cognitive impairment who were unable to cooperate in completing the questionnaire, or 5) investigators' judgment of ineligibility.

Questionnaire distribution and data collection

The patients reported adverse events and quality of life related to their treatment through a questionnaire. The oncologists recorded the patients' baseline characteristics, treatment information, and adverse events of treatment regimens based on medical history. The treatment regimen was decided by oncologists and patients together. The patients received only one CDK4/6i was assigned to appropriate CDK4/6i group, and patients treated with two CDK4/6i sequentially were assigned to CDK4/6i switch group regardless of the current treatment.

The patients' quality of life was evaluated using the EORTC QLQ-BR23 developed by the European Organization for Research and Treatment of Cancer and validated in Chinese [24–26]. The EORTC QLQ-BR23 had 8 domains and 23 items: 4 function domains: body image (4 items), sexual functioning (2 items), sexual enjoyment (1 item), and future perspective (1 item); and 4 symptom domains: systemic therapy side effects (7 items), breast symptoms (4 items), arm symptoms (2 items), and upset by hair loss (1 item). When scoring, forward items were scored from 0 to 4, that was, 1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much. The Raw Score for each domain was obtained by dividing the sum of the scores of the items in this domain by the number of items in this domain. The Raw Score could be converted to a Standard Score within 1-100 by linear transformation using polarization. Higher scores in the function domain indicated a better quality of life and higher scores in the symptom domain indicate a worse quality of life.

The oncologists invited the patients to participate in the survey and explained the survey to the patient. Patients who agreed to participate were provided with electronic informed consent forms and questionnaires through a secure online platform. Each study site was supported by dedicated clinical research coordinators (CRCs) who guided patients through the entire digital completion process in real time. Participants were required to complete the questionnaire within 5 days of distribution, with automatic reminders sent at 24-hour intervals to ensure timely completion. Any questionnaires not completed within the 5-day window, or those with missing quality-of-life data or incomplete adverse event reports, were excluded from the final analysis. This standardized digital workflow, supported by onsite CRC oversight, ensured complete and high-quality data collection across all participating centers.

Statistical analysis

Statistical analysis was performed using SAS 9.4 software. The continuous data were tested for normal distribution using the Kolmogorov-Smirnov test. The continuous data with a normal distribution were presented as means ± standard deviation and analyzed using Student's t-test or analysis of variance (ANOVA); those not meeting the normal distribution were presented as

median (maximum, minimum) and analyzed using the Mann-Whitney U-test of the Kruskal-Wallis H-test. The categorical data were presented as n (%) and analyzed using the chi-squared test or Fisher's exact test. Ordinal data were presented as n (%) and analyzed using non-parametric methods. All analyzes were performed as unadjusted comparisons between treatment groups without correction for potential confounding variables (e.g., age, disease stage, prior treatments), as this was an exploratory descriptive analysis. Unless otherwise specified, the α was 0.05 (two-sided), and P-values < 0.05 were considered statistically significant.

Results

Characteristics of the patients with HR+/HER2- advanced breast cancer

Oncologists at participating centers identified eligible patients during routine clinical practice. Among those approached, a total of 1,262 patients consented and completed the questionnaires. Eight questionnaires were excluded (patients were early breast cancer), resulting in 1254 valid responses from 10 hospitals across China (Fig. 1). The patients who participated in this study covered 14 provincial administrative districts or municipalities across China (Fig. 2). The questionnaire response rate was 100% (1,262/1,262), and the questionnaire validity rate was 99.37% (1,254/1,262). The median age of the patients was 55.0 years old. Of the sites of metastasis, 28.15% of patients had bone metastases only, while 42.50% had concomitant visceral metastases. There were 6.38% patients had no medical insurance, 88.36% had overall treatment costs ≥ 50,000 RMB. Of the surveyed patients, 98.64%had no smoking history, and 98.33% had no history of alcohol consumption. The Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 43.78% of the patients and 1 in 51.52% (Table 1).

Treatments

In this study, patients were treated with different CDK4/6i, of which 38.92% (488/1254) were treated with dalpiciclib, 35.81% (449/1254) were treated with abemaciclib, 15.07% (189/1254) were treated with palbociclib, 0.47% (6/1254) were treated with ribociclib, and 9.73% (122/1254) switched from one CDK4/6i to another. The survey showed that 98.64% of the patients with HR+/HER2- advanced breast cancer were receiving CDK4/6i combined with endocrine therapy when they completed the survey. Among the surveyed patients, 64.35% received first-line treatment; among them, 62.45% received an aromatase inhibitor (AI) combined with CDK4/6i, and 28.13% received fulvestrant combined with CDK4/6i. In the first-line treatment of advanced breast cancer, the highest proportion of patient used abemaciclib (42.38%), 34.08% with dalpiciclib, 19.21% with palbociclib. And 3.84% (31/807) of the patients switched from one CDK4/6i to another (Supplementary Table 1).

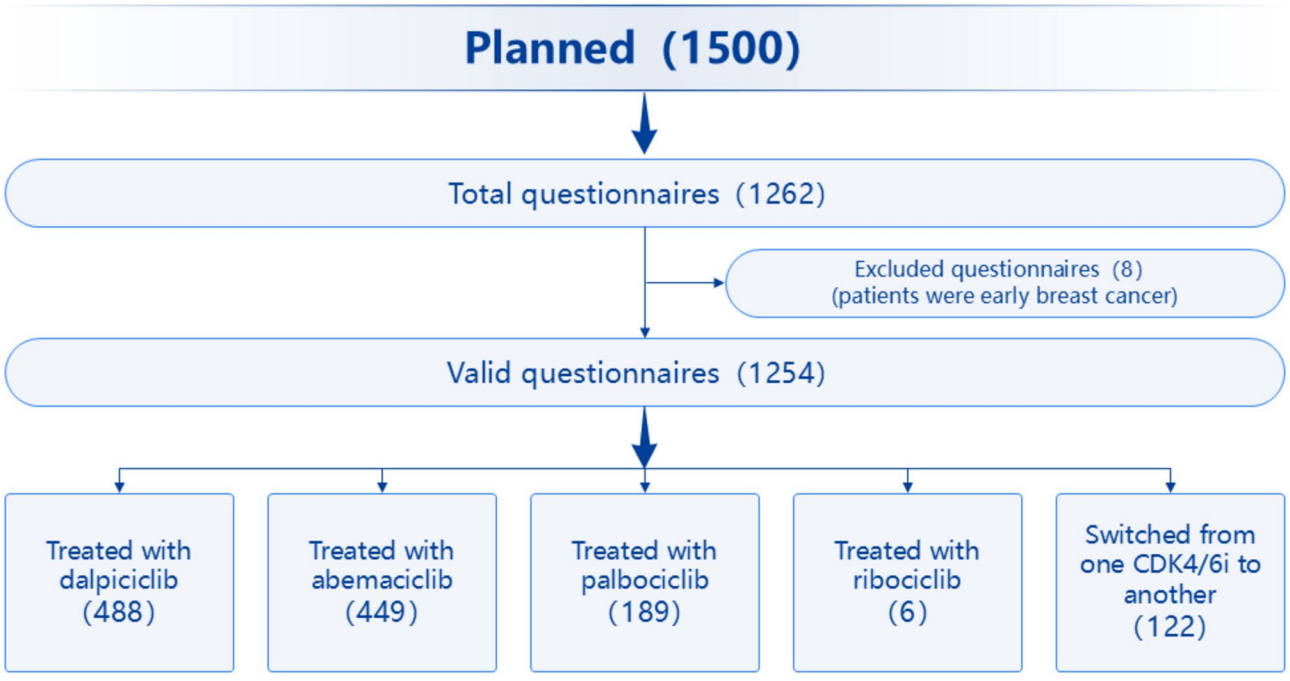

Fig. 1 Flow chart showing the recruitment process. The survey was designed to recruit 1500 patients from 10 hospitals across China. A total of 1262 responses were obtained from distribution of 1262 questionnaires. Eight questionnaires were excluded (patients were early breast cancer), resulting in 1254 valid questionnaires. Patients were treated with different CDK46i, including dalpiciclib (488), abemaciclib (449), palbociclib (189), ribociclib (6), and an additional 122 patients had their CDK46i switched during the treatment

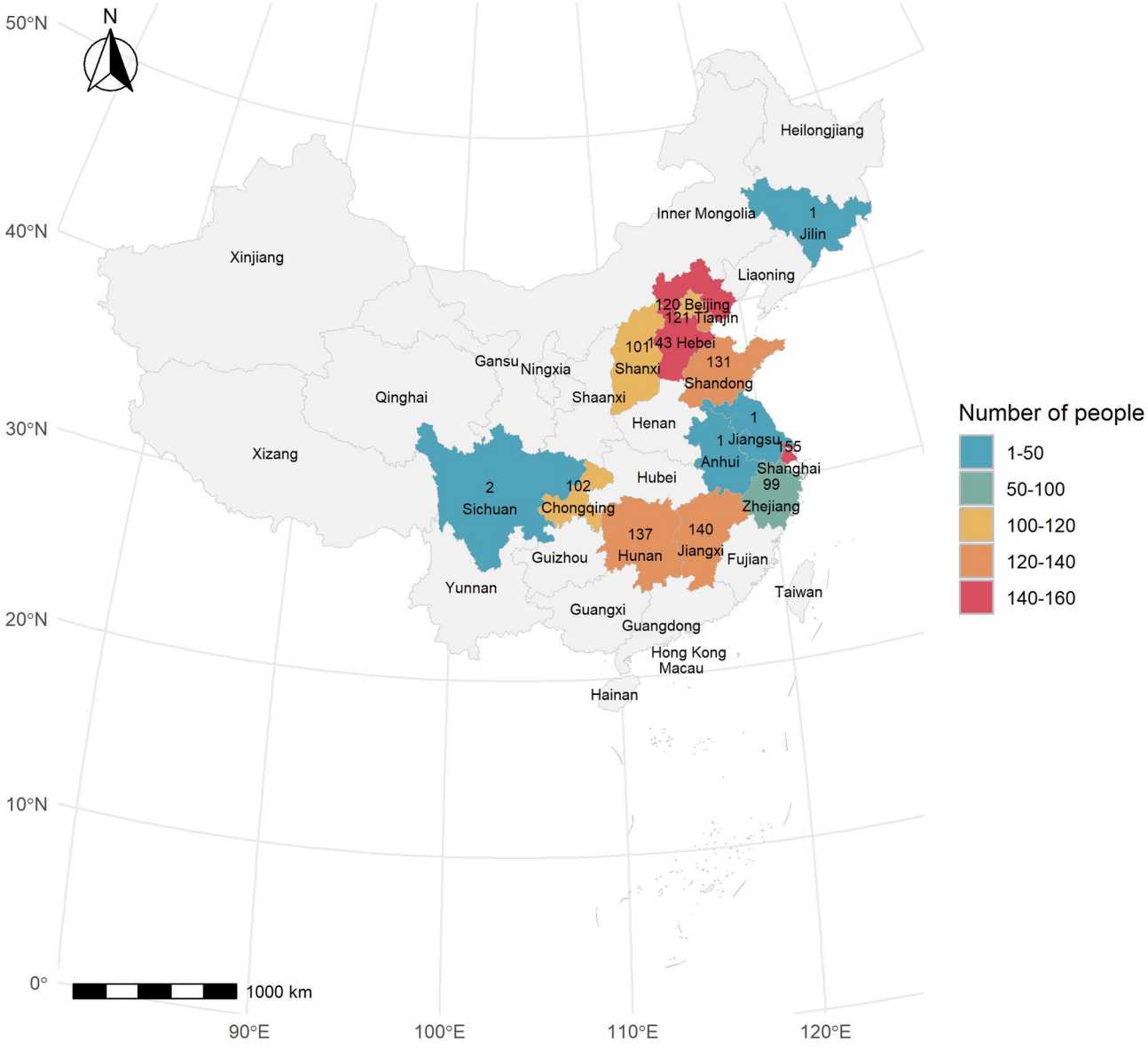

Fig. 2 Geographical distribution of patients. The patients who participated in this study covered 14 provincial administrative districts or municipalities across China

There were 35.65% of patients who received later-line treatment, and the treatment regimen was dominated by fulvestrant combined with CDK4/6 inhibitor (64.65%) and AI combined with CDK4/6i (30.65%). In the later-line treatment of advanced breast cancer, dalpiciclib was most frequently used (47.65%), 23.94% of patients treated with abemaciclib and only 7.61% treated with palbociclib. And there were 20.36% (91/447) of patients experienced CDK4/6i switching (Supplementary Table 1).

The results of the study showed that 15.71% (197/1254) of patients had adjusted their CDK4/6i combination regimen. The most common treatment regimen adjustments were switching to another CDK4/6i (64.47%), dose reduction (30.96%), treatment suspended (7.61%), and so on. Patients adjusted their CDK4/6i treatment regimen because of safety considerations (51.78%), disease progression (45.18%), economic and transport factors (7.61%), resistance during long-term medication (6.09%), poor response (2.54%) and other reasons (5.08%).

Adverse events of CDK4/6i

The oncologists evaluated the adverse events of treatment regimens based on patients' medical records, and adverse events occur in 81.17% of breast cancer patients in clinical practice. The most common adverse events were leukopenia (63.30%), neutropenia (58.73%), diarrhea (36.30%), anemia (34.21%), and thrombocytopenia (29.49%). Among the surveyed patients, 12.14% reported

Table 1 Characteristics of the participants with HR+/HER2− advanced breast cancer

	Total (*n* = 1,254)
Age (years)	
Median	55.0
Height (cm)	
Median	158.00
Weight (kg)	
Median	60.00
Metastatic sites	
Bone metastasis only	353 (28.15%)
Visceral metastasis	533 (42.50%)
Other sites of metastasis	368 (29.35%)
Payment method	
Urban medical insurance	603 (48.09%)
Coordinated medical insurance for serious illnesses	229 (18.26%)
New Rural Cooperative Medical Scheme	342 (27.27%)
Own expense	56 (4.47%)
Others	24 (1.91%)
Overall treatment costs (RMB)	
<10,000	30 (2.39%)
≥10,000, <50,000	116 (9.25%)
≥50,000, <100,000	188 (14.99%)
≥ 100,000, <150,000	277 (22.09%)
≥150,000	643 (51.28%)
Smoking history	
No	1237 (98.64%)
Yes	17 (1.36%)
History of alcohol consumption	
No	1233 (98.33%)
Yes	21 (1.67%)
ECOG performance status	
0	549 (43.78%)
1	646 (51.52%)
2	51 (4.07%)
3	6 (0.48%)
4	2 (0.16%)

grade 3/4 neutropenia, and 9.87% experienced grade 3/4 leukopenia. The comparison of different CDK4/6i showed that there were significant differences in adverse events such as diarrhea, neutropenia, leukopenia, thrombocytopenia, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), and anemia recorded in the medical history of the patients taking different CDK4/6i ($P<0.001$) (Fig. 3A). For example, the incidence of diarrhea was significantly lower in patients in the dalpiciclib group than in the abemaciclib and palbociclib groups (10.45% vs. 69.71%, $P<0.001$; 10.45% vs. 20.63%, $P=0.012$, respectively) (Fig. 3A). Abemaciclib-treated patients showed significantly lower rates of neutropenia compared to dalpiciclib (50.11% vs. 64.55%, $P<0.001$). Similarly, palbociclib was associated with reduced thrombocytopenia incidence versus dalpiciclib (20.11% vs. 37.70%, $P<0.001$). The incidence of elevated ALT in patients in the dalpiciclib group was the lowest (4.71%), with the incidence for other CDK4/6i ranging from 7.41 to 14.75%. The incidence of elevated serum creatinine was significantly lower in patients in the dalpiciclib group than in the abemaciclib group (5.1% vs. 11.1%, $P=0.002$). The incidence of elevated serum creatinine in patients in the CDK4/6i switch group was significantly higher than that in dalpiciclib group (12.3% vs. 5.1%, $P<0.001$) and palbociclib group (12.3% vs. 1.1%, $P<0.001$).

According to the survey, the symptomatic adverse events reported by the patients mainly were fatigue (34.13%), alopecia (14.02%), weakness (11.3%), insomnia (11.3%), dizziness (9.38%) and hot flashes (8.97%). The comparisons among different CDK4/6i showed that there were significant differences in patient-reported adverse events such as fatigue, alopecia, and hot flashes ($P<0.001$) (Fig. 3B). The incidence of alopecia in patients receiving dalpiciclib was lower than in those receiving palbociclib (8.81% vs. 16.40%, $P<0.001$) and abemaciclib (8.81% vs. 19.82%, $P=0.027$). The adverse events reported by the patients also included body pain, gastrointestinal toxicity (such as nausea, vomiting and appetite loss), and dermal toxicity (such as skin rash). For example, the incidence of diarrhea was significantly lower in the dalpiciclib group than in the abemaciclib group (8.61% vs. 72.38%, $P<0.001$). Patients receiving abemaciclib reported significantly lower rates of skin rash compared to those treated with dalpiciclib (17.59% vs. 25.82%, $P=0.014$).

The oncologists are more concerned about adverse events such as hematological toxicity and diarrhea, resulting in a high average rate of 80% of such adverse events being treated by oncologists. Non-hematological adverse events such as patient-perceivable symptoms, pain, and other digestive system reactions accounted for 37% of the adverse events that needed to be treated.

Quality of life

For the symptom domains in quality of life assessment, the score of systemic therapy side effect was 9.46 ± 10.25, the score of breast symptoms was 5.51 ± 10.09, the score of arm symptoms was 8.53 ± 13.74, and the score of upset by hair loss was 23.53 ± 23.58. The comparisons among different CDK4/6i are shown in Fig. 4A. There were differences in total scores of breast symptoms and upset by hair loss ($P=0.045$ and $P=0.005$, respectively). Patients treated with abemaciclib and dalpiciclib demonstrated significantly worse breast symptom-related quality of life compared to palbociclib (5.70 ± 9.81 vs. 3.84 ± 8.57, $P=0.047$; 6.03 ± 10.81 vs. 3.84 ± 8.57, $P=0.040$, respectively). Patients in the abemaciclib group had worse quality of life related to upset by hair loss than those in the dalpiciclib group (27.91 ± 23.84 vs. 19.75 ± 22.63,

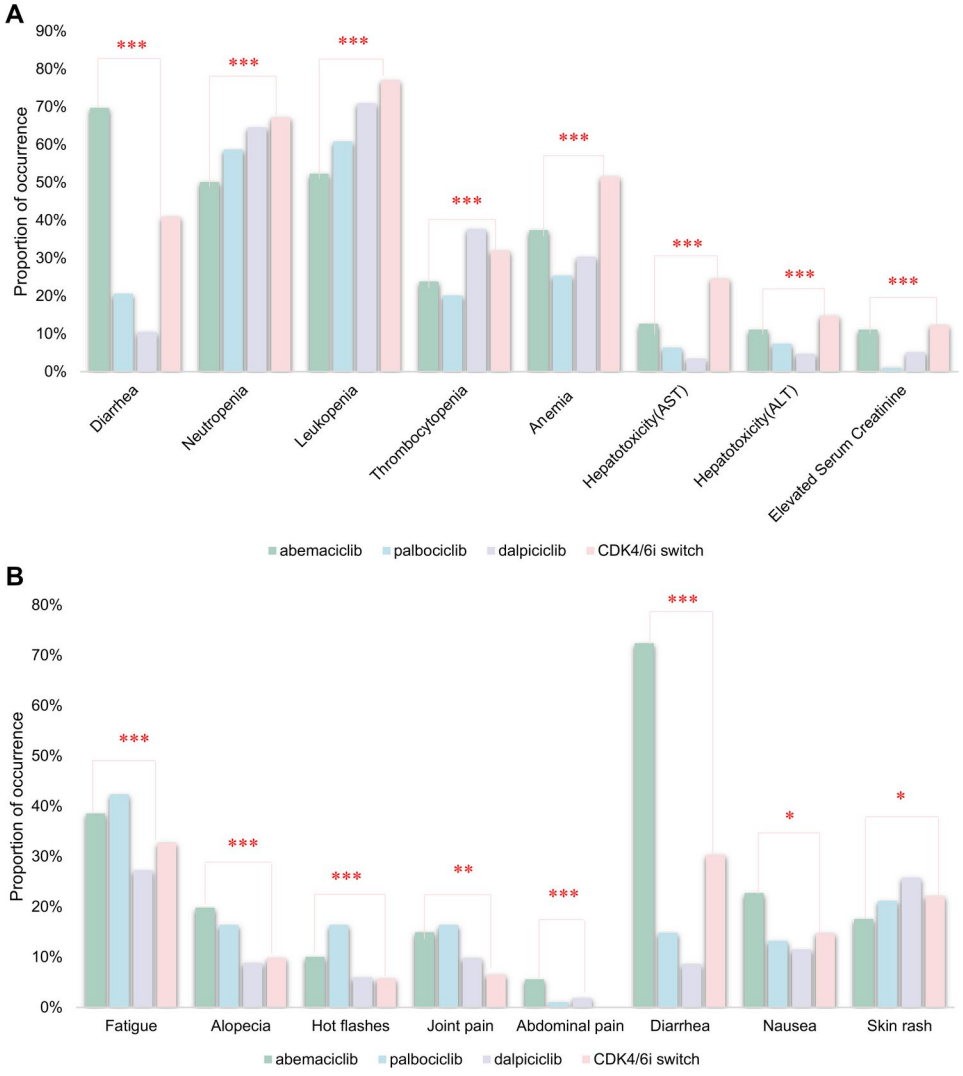

Fig. 3 Comparison of common adverse events between different CDK46i. The four groups were abemaciclib group, palbociclib group, dalpiciclib group, and CDK46i switch group. (**A**) Differences in clinical-assessed rates of adverse events associated with different CDK46i (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$). (**B**) Differences in patient-reported rates of adverse events associated with different CDK46i (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$)

$P = 0.003$). To avoid the effect of prior treatment toxicity, subgroup analyzes were performed on the patients treated with CDK4/6i for more than 6 months (Supplementary Fig. 1). The score of upset by hair loss among patients treated with CDK4/6i for more than 6 months differed between the different CDK4/6i groups ($P < 0.001$). The upset by hair loss scores were significantly lower in the dalpiciclib group than in the abemaciclib group (12.50 ± 17.70 vs. 28.95 ± 24.89, $P < 0.001$). This suggested that quality of life related to upset by hair loss remained worse in patients treated with abemaciclib for more than 6 months.

For the function domains in quality of life assessment, the body image score was 89.98 ± 19.25, the sexual functioning score was 4.42 ± 11.50, the sexual enjoyment score was 34.51 ± 15.07, and the future perspective score was 75.91 ± 28.66. The comparisons among different CDK4/6i are shown in Fig. 4B, and there were differences only in sexual functioning total scores ($P = 0.032$). However, no significant difference was observed in the comparisons between different regimens.

We evaluated the impact of metastatic sites (e.g., bone metastasis only, visceral metastasis and other sites of metastasis) on quality of life. Visceral metastases were radiologically confirmed in liver, lung, adrenal gland, or peritoneum, while excluding bone-only, pleural, or lymph node metastases [27]. This study showed that patients with visceral metastasis had worse quality of life related to sexual functioning than those with metastases from other sites (3.52 ± 10.20 vs. 5.59 ± 13.24, $P = 0.027$). Patients with other metastasis sites (e.g., lymph node metastasis) had worse quality of life related to breast

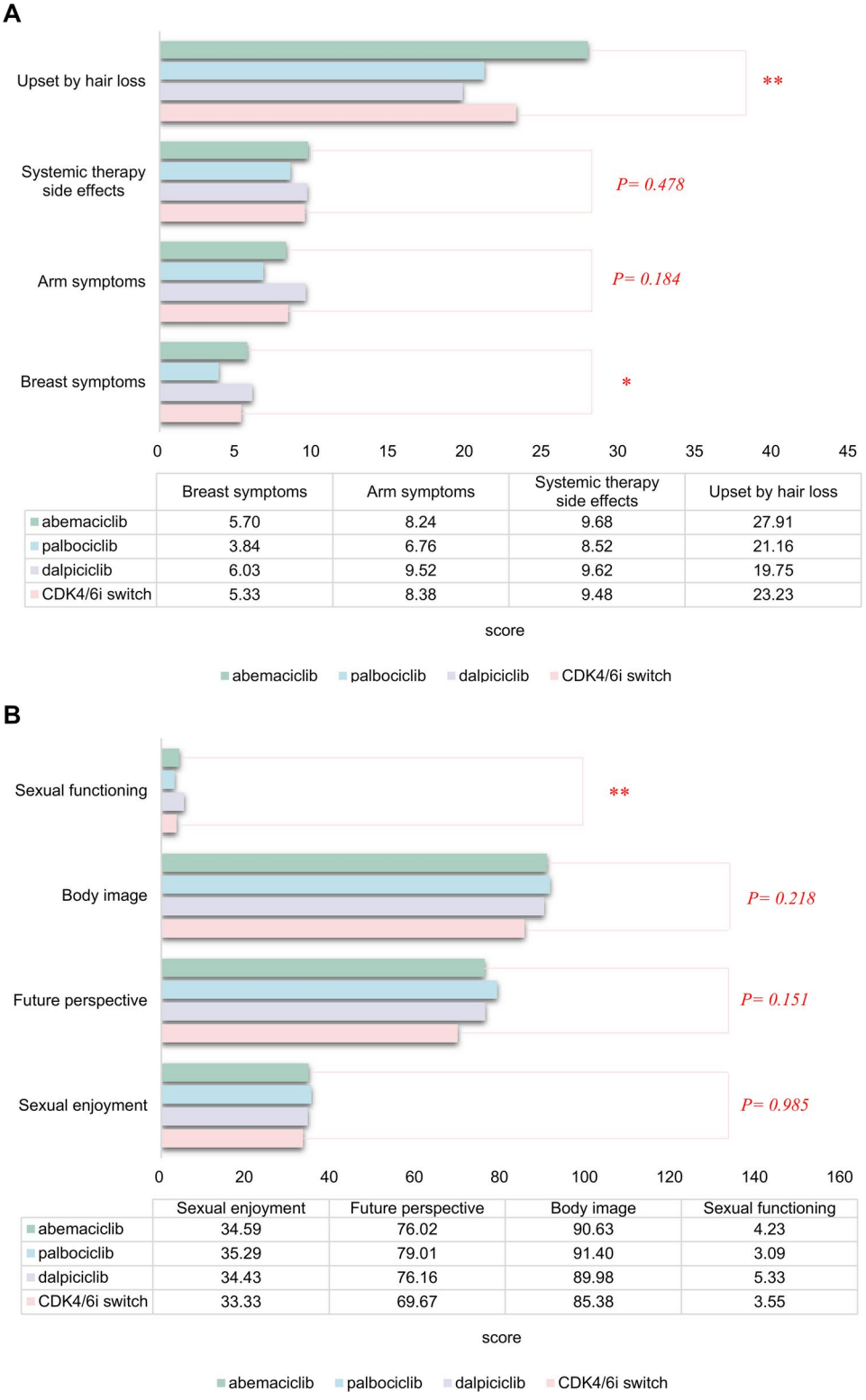

Fig. 4 Comparison of quality of life between different CDK46i. The four groups were abemaciclib group, palbociclib group, dalpiciclib group, and CDK46i switch group. (**A**) The symptom domains in quality of life assessment between different CDK4/6i (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$). (**B**) The function domains in quality of life assessment between different CDK4/6i (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$)

symptoms than those with bone metastasis and visceral metastasis (7.10 ± 11.51 vs. 4.72 ± 8.15, $P = 0.019$; 7.10 ± 11.51 vs. 4.94 ± 10.12, $P < 0.001$). Among patients treated for more than 6 months, patients with bone-only metastases had worse quality of life related to arm symptoms than those with visceral metastases (9.52 ± 12.98 vs. 7.29 ± 13.11, $P = 0.039$) (Supplementary Fig. 2A).

Quality of life was also affected by the number of different treatment lines. Patients in the later-line treatment had worse quality of life related to systemic therapy side effects than those in the first-line treatment (10.19 ± 9.97 vs. 9.06 ± 10.39, $P = 0.005$) (Supplementary Fig. 2B). Patients in the later-line treatment had worse quality of life related to breast symptoms than those in the first-line treatment (5.82 ± 9.32 vs. 5.33 ± 10.50, $P = 0.047$). However, the score of upset by hair loss was lower in the later-line treatment patients than in the first-line treatment (18.99 ± 22.69 vs. 26.22 ± 23.73, $P < 0.001$), it suggested that patients receiving first-line treatment had a worse quality of life related to upset by hair loss. The upset by hair loss score distribution was similar in patients received CDK4/6i more than 6 months (first-line: 24.80 ± 22.76, later-line: 20.99 ± 26.59, $P = 0.084$), whose adverse events were almost not contributed to previous chemotherapy.

Discussion

Considering the differences in the characteristics of breast cancer between Chinese and Western patients [19, 20], this multicenter cross-sectional study aimed to investigate the adverse events and quality of life of CDK4/6i currently used to treat HR+/HER2- advanced breast cancer in China. Our findings showed that there were numerous combinations of CDK4/6i and endocrine therapy in clinical practice, and oncologists and patients need to consider how to choose individualized regimen. More than half patients adjusted CDK4/6i combination regimen because of safety considerations, which suggested that toxicity remains an extremely important consideration in precise therapy. The present study reconfirmed diverse safety profile of four CDK4/6i. There were also significant differences in adverse events recognition between oncologists and patients. In addition, quality of life in patients with advanced breast cancer is affected by both disease progression and adverse events. The analysis revealed that improving and managing non-hematological systemic adverse events may result in better quality of life for patients.

Treatments

In this study, the highest proportion of breast cancer patients were treated with abemaciclib in the first-line treatment and dalpiciclib in the later-line treatment. The varied CDK4/6i accessibility and health insurance payment indication may contribute to the clinical application across CDK4/6i agents in China. A real-world study from United States showed that 88.2% of patients were treated with palbociclib, 7.2% were ribociclib, and 4.6% were abemaciclib in the first-line treatment [28]. Another real-world study suggested that letrozole accounted for 61.6% and fulvestrant for 30.2% of the CDK4/6i combination endocrine regimens, which is similar to the results of the present study [29]. Evidence from another real-world study showed that 69.34% of patients with HR+/HER2- metastatic breast cancer had progression after first- line treatment with CDK4/6i (palbociclib, abemaciclib, ribociclib), leading to later-line treatment. In the later-line treatment, 29.7% of patients opted for chemotherapy and 36.0% continued a CDK4/6i (mostly the same CDK4/6i as first-line treatment) [28]. It suggests that in the real world most patients may adjust their treatment regimen due to disease progression. Continuation of CKD4/6i after disease progression is a common treatment option. The study results demonstrated that, in addition to disease progression, treatment costs and adverse events were also reasons for patients to modify their CDK4/6 inhibitor-based combination regimens. Biomarker development may be needed to better predict progression and guide timely therapy changes. Socioeconomic barriers also highlight the importance of addressing non-clinical factors in treatment continuity. In addition, toxicity monitoring and dose optimization may reduce unnecessary CDK4/6i switches due to adverse events. Moreover, the MAINTAIN study demonstrated that for patients progressing on prior CDK4/6 inhibitors, ribociclib plus endocrine therapy significantly prolonged progression-free survival by 2.5 months compared with endocrine therapy alone (5.29 vs. 2.76 months, $P = 0.006$) [30]. This suggests that switching to an alternative CDK4/6i may provide a viable treatment option, potentially improving clinical outcomes and quality of life for these patients.

Adverse events of CDK4/6i

In the present study of Chinese patients, the oncologists mainly reported leukopenia (63.3%), neutropenia (58.73%), and diarrhea (36.3%), while the patients mainly reported fatigue (34.13%), alopecia (14.02%), and hot flashes (8.97%). In the study by Cardoso et al. [31] in 96 patients with HR+/HER2- advanced breast cancer treated with CDK4/6i, 83% of the patients experienced at least one side effect. The most common adverse effects reported by the patients were fatigue (54%), low libido (50%), loss of appetite (41%), back pain (38%), and hot flashes (36%). However, alopecia was not mentioned by patients. Furthermore, physician-reported adverse events were not collected to analyze the difference between physician and patients [31]. Our study compared the types of adverse events recorded by physicians with those

reported by patients and found significant differences. Oncologists concerned about adverse events detected by laboratory tests, while patients concerned about perceivable adverse events. It suggested that adequate communication between physicians and patients is necessary to know the whole picture of adverse events. A previous meta-analysis of six trials on CDK4/6i reported frequencies of 49.1% for neutropenia, 17.0% for leukopenia, 9.9% for nausea, 6.2% for fatigue, and 4.7% for diarrhea [32]. In contrast to the present study, incidence of fatigue and diarrhea was relative lower. Adverse events data varied in different population, study design, or data source. Therefore, the present study gives novel real-world evidence of CDK4/6i in Asian patients.

Different CDK4/6i have different safety profiles, but head-to-head comparison is rare. Existing evidence indicates that neutropenia represents the most frequent adverse event for palbociclib, ribociclib and dalpiciclib, whereas diarrhea predominates with abemaciclib therapy [14, 33]. The meta-analysis also showed heterogeneity existed across trials for diarrhea, vomiting, and increased AST [32]. Physician-reported adverse events, such as diarrhea, neutropenia, leukopenia, thrombocytopenia, and anemia were significant different among CDK4/6i in the present study. Therefore, adverse events of different CDK4/6i should be considered when determining the treatment regimen.

The treatment-related adverse events (TRAEs) evaluated by oncologists were mainly based on clinical examination indicators, such as neutropenia and leukopenia. In addition to the examination indicators, adverse events reported by the patients also included their own subjective feelings, such as physical pain, fatigue, insomnia, loss of appetite, etc., which cannot be revealed by laboratory tests. It follows that TRAEs differ in the perspectives of physicians and patients. Therefore, the combination of the two sources of information can more comprehensively reflect the severity of the patients' symptoms and the impact of drug treatment on quality of life. This is rarely seen in previous studies. Indeed, the quality of life are now considered important data for evaluating the safety of anticancer drugs [34, 35]. Breast cancer patients have a long survivorship compared with other types of cancers [36]. Therefore, it is important to take the quality of life into account in the management of patients, especially in those with advanced breast cancer [37], besides treatment related adverse events. Two studies based on the matching-adjusted indirect comparison methodology suggested that patients treated with abemaciclib reported worse quality of life in both symptom domains and function domains compared with palbociclib and ribociclib [38, 39]. In the present study, we observed that the upset by hair loss scores were lower in the dalpiciclib group than in the abemaciclib group, but it was not included in the previous studies.

Quality of life

Quality of life of HR+/HER2- advanced breast cancer patients is affected by several factors. The results of the quality of life assessment showed that alopecia had a great impact on patients' quality of life. CDK4/6i are anti-proliferative agents affecting rapidly proliferating hair matrix cells [40]. Some studies have shown that it is the combination of endocrine and CDK4/6i therapy that may exacerbate alopecia [41]. Patients with visceral metastases had poorer sexual functioning related quality of life than that of other metastases. Quality of life was also worse for patients receiving later-line treatment than first-line treatment. To investigate the influencing factors of quality of life, this study also analyzed the correlation between the quality of life and adverse events, which showed a weak correlation. The symptom domains were positively correlated with all adverse events ($r > 0$). Diarrhea was negatively correlated with body image, sexual functioning, sexual enjoyment and future perspective ($r < 0$), suggesting that diarrhea patients had a worse quality of life. Alopecia was negatively correlated with body image, sexual enjoyment and future perspective ($r < 0$), whereas alopecia was positively correlated with systemic therapy side effects, breast symptoms, arm symptoms, and upset by hair loss ($r > 0$). This suggested that alopecia, as a single adverse event, could be indicative of all-round deterioration in the quality of life of patients. And the correlation between alopecia and upset by hair loss was somewhat stronger ($r = 0.2464$), suggesting that patients with alopecia may have more anxiety and a poorer quality of life.

In addition, alopecia was significantly related to body image, systemic therapy side effects, breast symptoms, arm symptoms, and upset by hair loss (all $P < 0.001$). Considering that most patients with breast cancer are female, changes in physical appearance, including alopecia, may have a greater impact on the patients' mood than for other tumors with a male predominance, thus affecting the patients' quality of life. The meta-analysis showed a higher incidence of alopecia in advanced breast cancer patients treated with ribociclib than with other CDK46i [1]. In a real-world study, the most frequently reported cutaneous events were alopecia (44.2%), rash (18.7%), and pruritus (15.2%) [42]. The incidence of alopecia and rash in the present study was 14.02% and 21.79%, respectively. Notably, patients treated with dalpiciclib exhibited a significantly higher incidence of rash compared to other CDK4/6i ($P < 0.05$). Rash generally occurred in the first month and alopecia generally occurred in the second month, with breast cancer patients reporting possible discontinuation as a result [42]. Another multicenter

retrospective study also described the types of skin toxicity that occurred during treatment with CDK46i in patients with advanced breast cancer, with the most frequent cutaneous reactions were pruritus (62.0%), alopecia (31.6%) and eczematous lesions (30.4%) [43]. Cutaneous toxicities were usually mild in severity, with only four patients (5%) requiring treatment discontinuation due to the severity of skin lesions, and most skin toxicities were controlled with topical treatments [43]. Alopecia shares same biological mechanisms with other side effects and may help oncologists quickly assess patients' risk for toxicity. Meanwhile, patients' self-reported alopecia can help oncologists remotely assess the patients' risk of toxicity and reduce unnecessary follow-up visits. In conclusion, reducing the incidence of alopecia may improve patients' quality of life.

The strengths of this study are the inclusion of a large number of women with HR+/HER2- advanced breast cancer and treated with different CDK4/6i, and the collection and comparison of physician-recorded and patient-reported adverse events. In addition, factors influencing patients' quality of life, such as number of treatment lines, metastatic sites, etc., were analyzed. The correlation between quality of life and adverse events was also analyzed. Still, this study also has limitations. First, the statistical analyses were performed without adjustment for potential confounding variables, which may affect the interpretation of between-group differences. Second, the data of quality of life is self-reported and could be biased by the participants' level of education and comprehension. Third, the questionnaire was completed without supervision. CDK4/6i are expensive and are taken by patients with a higher socioeconomic status or medical insurance, possibly biasing the results. Finally, the patients who were unable to complete the survey because they were in palliative care could not be included, potentially limiting the generalizability of our findings.

Conclusions

This study provided the adverse events and quality of life of a large sample of Chinese women treated with CDK4/6i for advanced breast cancer. The safety profile of different CDK4/6i varies and has different impacts on patients' quality of life. Therefore, the quality of life should be taken into account when evaluating the safety of anticancer drugs and to manage patients with HR+/HER2- breast cancer, which is characterized by a long survivorship.

Abbreviations

ANOVA	Analysis of variance
AI	Aromatase inhibitor ()
ECOG	Eastern Cooperative Oncology Group
HR	Hormone receptor ()
HER2	Human epidermal growth factor receptor 2
TRAEs	Treatment-related adverse events

Supplementary Information

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Supplementary Material 1

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Author contributions

JW had the idea of this study. BY, ZS, QO, ZT, SW, HL, ZN, XW, YC, CG, HW, JW designed the questionnaire to collect data. LM, HW, MT, ZH, XG, XW, FX, QC, YS were involved in acquisition of the data. BY wrote the first draft of the article. BY, ZS, QO revised the manuscript. All authors reviewed the results, interpreted the data, contributed substantially to development of the article. JW, CG, HW reviewed and approved the final version for submission.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available due to the privacy of the individual patients involved, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center (Approval Number: 2209261-4) as the lead center, as well as by the ethics committee of all participating centers. The participants provided informed consent before completing the survey. The study was conducted following the tenets of the Declaration of Helsinki and the Good Clinical Practice.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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