Are We Prepared for the CDK4/6 Revolution With HR+/HER2– Breast Cancers? The Importance of Patient Adherence to Adjuvant Therapies

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Cancers continue to represent a leading cause of death and major health care burden globally.[1] Thanks to enormous and sustained research efforts, many effective therapeutic solutions are now becoming available, including CAR-T, gene therapies, vaccines, and myriad chemotherapeutics.[2] In the case of breast cancer, one of the holy grails has been to identify small molecule chemotherapeutic and chemopreventive agents with high efficacy and ease of manufacture. Using precision medicine approaches and targeting the pathways governed by the cyclin-dependent kinase receptors, spectacular breakthroughs have recently been made through CDK4/6 inhibitors which promise to revolutionize prevention and treatment of HR+/HER2– breast cancers.[3] No less than 3 effective agents have been fast tracked through regulatory approval: Palbociclib, Abemaciclib, and Ribociclib, the latter being designated by the National Comprehensive Cancer Network (NCCN) as a category 1 preferred first-line treatment.[4] Such is the excitement that the entire class has been characterized as "game changing" for oncology patients.[5,6] Such expectations however need to be tempered by one of the historical barriers to chemotherapeutics which, while well understood, remains a major obstacle—that of patient medication adherence.[7] The CDK4/6 and many other related approaches work most effectively when coupled to adjuvant endocrine therapy (AET),[8] typically involving dosing of an aromatase inhibitor or estrogen receptor antagonist.[9] For optimal outcomes, the patient needs to adhere to the AET over a sustained period of years to avoid potential relapses, obliterating the benefits accrued by the primary therapeutic agent. Many patients experience side effects and other events related to the AET and these coupled with other factors can lead to overall adherence rates of <50%.[10] In addition to leading to adverse health outcomes for the patient, subsequent relapses contribute significantly to the economic costs of managed care absorbed by payers, thus it represents a pivotally important problem in need of solving.[11,12] Historical evidence on patient adherence to medication points to a complex multidimensional problem tied to social and economic, health system-related, condition-related, therapy-related, and patient-related factors.[7] More recent analyses on aversion to AET highlight the importance of deep understanding of behavioral aspects of the patient,[9] and the need for parallel strategies to effect adaptive change.[13] A universal observation in addition to AET-induced adverse events is a general lack of appreciation of the harms inflicted by dose skipping, underscoring the need for an educational component in any intervention.[14,15]

Given our interest in optimizing patient outcomes with novel cancer therapies, we undertook primary and secondary market research involving discussions with health care professionals (HCPs), and global commercial patient adherence solution developers to identify pain points and adherence motivators and barriers.[16] From this, 5 main touch points emerged, in broad agreement with previously reported studies.[17]

Factors Contributing to Poor Patient AET Medication Adherence

- Adverse treatment-related side effects;
- Incomplete understanding of the importance and implications of taking adjuvant therapy over sustained periods of post-surgery;
- Lack of ongoing care coordination between the HCPs and patients compromising onboarding, persistence, and perceived value of medication;
- Inadequate social or emotional support structures;
- Need for prompts and reminders to take medication regularly.

Health care professionals related to these concerns and cited insufficient communication with their patients contributing to inadequate oversight of patient adherence and a need for deeper patient education on the role of adjuvant therapies and symptom side effect management.[14,16] We followed this analysis by conducting workshops with breast cancer patient advocates representing more than 1 million breast cancer patient views, where themes and potential interventions were examined.[16] Of the myriad options, 3 that resonated most clearly were the following:

- Augmenting care through remote monitoring with patient support provided through bi-directional communication channels;

- Education programs on adjuvant medications (side effect profiles, benefit of the therapies, etc), which are personalized and universally accessible;
- Highly personalized psychosocial approaches which are sympathetic to individual patient needs including behavioral therapy, and nurse-led coaching sessions.

Each of these inter-related touchpoints require careful approach and consideration of the individual needs of patients based on (1) where they are in their treatment path, (2) how they perceive information, and (3) what their unique adherence drivers and barriers are. It is evident that success will require a multipronged approach. Digital tools in their various forms may have the potential to offer dynamic and scalable solutions to many patient needs when deployed to augment traditional care models. Indeed, there is already emerging evidence to support telehealth and smartphone-based interventions for cancer patients using commercial platforms.[18] These solutions will need to stand the scrutiny of large-scale clinical and population-level studies, but there is promising evidence emerging on the role of digital health in symptom management and behavioral support.[19-21] In comparison to the daunting challenges of bringing a new drug to market (<1% overall success rates, up to $2B investment and 10+ year time lag), such interventions would seem achievable as they represent pure play end-user needs as opposed to a technology push, which has impeded the widespread adoption of many digital health products to date.[22] As we pursue clinical evaluation of these approaches, we encourage others in the field to continue to do likewise and regularly report findings to enable best practices to be shared and help address the poor patient outcomes and $500B+ lost to poor medication adherence globally. There is also optimism that new technologies can emerge and positively affect adherence rates when incorporated into a digital support system. Some near-term possibilities include the following:

1. Remote patient monitoring technologies. These can range from actively captured data supplied by patients to those derived from passive sensors and detectors, which warn patients ahead of adverse events. As an example by leveraging patient facing remote monitoring applications to collect symptom-related information that is connected to their HCP's workflow. Such might have built-in algorithms to perform digital triage, providing educational tools to allow patients to address manageable symptoms or prompting HCP intervention for more severe symptoms. Such could help HCPs focus on urgent, acute patient needs, and yet provide continued background support and care to help prevent AE-related drop offs. Another example could be to detect biomarker levels with on-body sensors. A wrist-worn monitor for cortisol has already been developed, and there is potential for the same technology to be applied for low-level AET analytes,[23] prompting a patient action in the same way a blood sugar monitor functions for type 1 diabetics. Also, although non-passive, a number of home testing kits for analytes and metabolites are available based on urinary analysis and might be customized for AET adverse events and function as an adherence prompt.
2. There is evident potential for AI and ChatGPT platforms to intelligently and sensitively interact to help with patients' emotional well-being and management throughout their treatment journey. This could include provision of educational prompts that are tailored to the scientific and technical literacy preferences of each patient.[24] Many of the commercial offerings incorporate elements of these, and as the powerful technology grows more capable, one can expect to see impact for breast cancer patients through highly personalized and customized interactions. Such might enable scalable interventions, with additional touchpoints to help patients stay on track with their medications.
3. Improved understanding of behavioral nuances encountered by breast cancer patients to inform design of more effective adherence drivers. This is especially relevant given that patients are expected to adhere to medications for a number of years despite encountering side effects. For example, neurocognitive mechanisms such as attention bias modification (ABM) may serve to engage patients and also up-regulate immune function,[25] in the same manner that improved psychological well-being has been correlated with improved outcomes.[26] Harnessing these approaches in digital devices might offer the potential for medication reminder prompts which are keyed to a person's daily calendar, event schedule, and psychological status. Improving our understanding of patient behavioral science will ultimately allow the design of more relevant, engaging, and thus effective digital companions.

There are many other components to the multipronged approach that can and will be investigated, and it is incumbent on us to ensure no stone is left unturned in the quest to help patients find methods to improve medication adherence.[27] Given the great promise of the CDK4/6 therapies for breast cancer, we must hope this call to arms results in long-term solutions being identified, allowing the full benefits of these therapies to be realized globally.

Declarations

Ethics approval and consent to participate

N/A. This manuscript does not contain any studies with human or animal subjects.

Consent for publication

N/A. This manuscript does not contain any studies with human or animal subjects.

Author contributions

Seyla Azoz: Conceptualization; Writing – original draft; Writing – review & editing.
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Graham Jones: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

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Trial registration

N/A. This manuscript does not contain any clinical trials.

Guarantor

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