Proceedings of the International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/6/20230169

Efficacy and mechanism of cyclin-dependent kinase inhibitors against cancer

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Abstract. This paper focuses on an overview of the development progress of different cyclin-dependent kinase (CDK) inhibitors. The CDKS are a group of kinases that are indispensable in the cell cycle. However, when it comes to cancer, the cell cycle is not healthy which causes malignancy of the cell that is able to mitosis infinitely. Considering the CDK are a group of molecules that is fundament during mitosis, researchers have developed its inhibitors to inhibit the effect that it has during the cell cycle to postpone the growth of cancer and lead to cancer cell apoptosis. This paper targets on the CDK inhibitors of pan-CDK, CDK4/6, 7, 9, and 12, also introducing their development history and current stages in clinical trials, as well as the drugs related to these CDK inhibitors that are FDA-approved for cancer treatment. In addition, the paper also introduces the future potentials of CDK inhibitors in the treatment and therapy of cancer-related diseases.

Keywords: CDK, breast cancer, combination therapy.

1. Introduction

Cancer is essentially caused by unregulated cell divisions that cause abnormal proliferation [1]. In other words, it is the stages involved in the cell division, including the synthetic phase, mitotic segregation phase, and two intervenient phases respectively [1]. Extrinsic and intrinsic factors determine whether a cell can commence the cell cycle in the absence of these factors, otherwise, the cell would become dormant [1]. Cyclin-dependent kinases (CDKs) promote chromosome DNA synthesis and chromosomes' segregation by phosphorylating their substrates [1]. CDKs are involved in critical cellular processes, including transcription, secreting insulin, synthesizing glycogen, etc., which are indispensable processes involved in cell division [1]. The CDK inhibitors are a family of medicines that inhibit the CDK's enzymic activities, which intervene in the cell division processes [1].

In addition, the CDK inhibitors have great potential to be involved in varying cancer treatments because they can be categorized into different subgroups, which allows them to target the abnormal activities of the cancer cell division processes [1]. For instance, CDK inhibitors can be categorized into CDK 4/6, CDK7, CDK 9, and CDK12 [1]. CDK4/6 inhibitors have been indicated in the treatment of metastatic breast cancer by interfering with the cell cycle progression [2]. More specifically, CDK 4/6 inhibitors intervene in the intracellular and mitogenic hormonal signals that promote the proliferation of cancer cells [2]. Palbociclib, ribociclib, and abemaciclib are FDA-approved CDK4/6 inhibitors that have

DOI: 10.54254/2753-8818/6/20230169

shown strong efficacy in treating breast cancer [2]. CDK 7, cyclin H, and MAT 1 are the components that form the CDK-activating complex, also known as the CAK, which is a significant transcriptional factor of the cell cycle [3]. CDK7 phosphorylates RNA polymerase II at the sites of active gene promoters which would induce the transcription process [3]. In other words, CDK7 is being dependent on many varying types of cancers [3]. The dependence of CDK7 activity on cancer has drawn attention much attention as a target for cancer treatments [3]. There are at least four clinical trials of CDK7 inhibitors that can have been registered on ClinicalTrials.gov. [3]. Therefore, CDK7 inhibitors have been shown to have highly potent efficacy in causing cancer cell cycle arrest, apoptosis, and suppressing the transcription process in cancer [3]. CDK9 functions as a transcription regulator, [4]. By inhibiting CDK9, gene expressions such as MYC which is an oncogenic gene can be regulated and controlled [4]. Lastly, CDK12 is a key signaling molecule of cancer development. During transcription, CDK12 binds to cyclin K and phosphorylates RNA Pol II at the CTD, facilitating transcription elongation [5]. Additionally, CDK12-mediated RNA Pol II phosphorylation links mRNA 3′ end process also contributes to transcription termination [5]. Moreover, CDK12 is crucial for controlling translation, intronic polyadenylation, and epigenetics [5]. Also, genomic instability caused by CDK12 deletion or mutations that impair function may serve as a biomarker for ovarian and prostate cancer [5]. Overall, CDK12 inhibitors can potentially counteract the key steps that CDK12 is involved in the cell cycle, which can target various types of cancer during treatment [5]

1.1. The history of development of CDK inhibitors as anti-cancer therapy

Pan-CDK inhibitors made up the majority of CDK inhibitors discovered in the initial phases, which effectively suppressed more than four CDKs or other kinases. [6]. Clinical studies for a few pan-CDK antagonists have begun, but they haven't been able to become commercialized because of their side effects [6]. Contrasting to pan-CDK inhibitors, multi-CDK inhibitors were researched afterward, focusing on decreasing the negative effects caused by pan-CDK inhibitors by inhibiting a smaller range of CDKs [6]. However, this strategy did not succeed in accelerating the research of CDK inhibitors, and similarly to pan-CDK inhibitors, neither of the multi-CDK inhibitors has received FDA approval [6].

The strengths of pan-CDK were observed during the early development stages as it not only causes cell-cycle arrest, and apoptosis, but also inhibits transcription during the cell cycle such as the drugs, alvocidib, and seliciclib [6]. However, there have been more cons than pros as the pan-CDK entered clinical trials [6]. For instance, at least ten of the pan-CDK inhibitors have now advanced to the clinical stage [6]. However, only six of these pan-CDK inhibitors are now in phase I/II clinical trials, while the rest have been removed from clinical trials [6]. For instance, SNS-032, a CDK1/2/4/7/9 pan-CDK blocker, was discontinued in the first stage studies because of an alternation in the target of development for solid tumors and minor effects on patients who received prior treatment for multiple myeloma [6]. RGB-286638, a pan-CDK inhibitor targeting solid tumors also didn’t pass phase I clinical trials because of no tumor responses were seen in patients [6]. Additionally, the sponsor of the pan-CDK inhibitor, RGB-286638’s phase I trial for hematological malignancies withdrew in 2012 [6]. It is believed that the toxicity associated with pan-inhibition against ambiguous CDKs and some kinases from other categories has restricted the clinical application of RGB-286638 [6]. Overall, even though there are still pan-CDK inhibitors in clinical development, it still lost its advantage in impacting the cell cycle from its inevitable side effects and potential harm that it may act on the patients [6].

Furthermore, the clinical development of CDK4/6 inhibitors has illustrated great potential in cancer treatments [7]. In short, the significance of CDK4/6 is presented when the cyclin D1 expression and CDK4/6 activation boost the cell cycle and contribute to the proliferation of breast cancer [7].

2. Clinical results of CDK inhibitors

2.1. Summary of clinical trials of CDK4/6 inhibitors

Hormonal therapy is the foundation of treatment for patients with metastatic estrogen receptor-positive (ER+)/HER2-negative (HER2) breast cancer (MBC). [7]. Sequential hormonal therapy helps MBC

DOI: 10.54254/2753-8818/6/20230169

patients maintain their higher quality of life (QOL) throughout their treatment [7]. However, using estrogen inhibitors or fulvestrant to treat people who have become resistant to hormonal therapy offers substantial challenges [7]. Therefore, it is crucial to develop therapies that can overcome the resistance to endocrine therapy and enhance results. Retinoblastoma protein (Rb), among other proteins, is phosphorylated by cyclin-dependent kinases 4 and 6, which are triggered by D-type cyclins, to start the transition from the G1 phase to the S phase [7]. In ER+ breast cancer, several oncogenic signals combine to promote cyclin D1 production and CDK4/6 activation, which fuel breast cancer growth [7]. In vitro studies reveal that cyclin D1 and CDK4 are still required for the promotion of development in breast cancer that has resisted prior endocrine therapy [7]. According to preclinical research, the luminal subtype increased cyclin D1 and Rb protein expression, and decreased p16 expression are all indicators of palbociclib sensitivity [7]. Palbociclib was created to be the first-ever CDK inhibitor for ER+ MBC [7]. Further CDK4/6 inhibitors for MBC, abemaciclib, and ribociclib have also been developed. Palbociclib and ribociclib share a similar chemical structure, however, abemaciclib has a unique one [7]. Naturally, CDK4/6 inhibitors exclusively block CDK4 and CDK6, although abemaciclib has a substantially stronger CDK4/6 binding activity than palbociclib and ribociclib [7]. Worldwide, investigator-initiated trials (ITTs) are also being conducted to demonstrate the clinical advantage of utilizing CDK4/6 inhibitors following conventional Early-stage breast cancer therapy [7]. Additionally, ITTs to create fresh approaches to treating MBC are in progress [7].

The regimen for palbociclib administration that was shown to be most effective was palbociclib plus letrozole, administered 3 weeks on, 1 week off schedule [7]. Two cohorts were used in Phase II research (PALOMA-1): the first cohort included women who are postmenopausal with MBC and local recurrences of ER+/HER2, while the second cohort included patients with a similar diagnosis who also needed to have a prognostic marker (Cyclin D1 gene amplification, loss of p16, or both) [7]. One-to-one randomization was used to assign the patients to either the letrozole alone or the letrozole plus palbociclib. Investigator-assessed progression-free survival (PFS) was the main measurement [7]. Parts 1 and 2 of the final analysis were released together [7]. The characteristics of the patients were distributed equally between the two arms [7]. In comparison, when palbociclib and letrozole were given simultaneously to patients had a therapeutic advantage of 10 months more of PFS and decreased hazard ratio [7].

PALOMA-1 investigation showed rofound outcomes, both PALOMA-2 and PALOMA-3 phase III trials were planned and executed globally [7]. The PALOMA-2 (letrozole study) and PALOMA-3 (fulvestrant studies) compared endocrine therapy alone for individuals with ER+ MBC, compared to a combination with palbociclib [7]. Both were randomized, double-blind clinical trials. [7].

In the double-blind research, palbociclib plus letrozole or placebo plus letrozole were randomly assigned to over six hundred women post to menopause who suffered from ER+, HER2 breast cancer and were not treated for severe medical conditions [7]. In the palbociclib group, the objective of the study was served, including more than 50% of PFS compared to the placebo group, as well as less hazard ratios. [7].

The PALOMA-3 study recruited female patients who suffered from advanced breast malignancy that was ER+/HER2 and had either reverted before or in the meantime when treated with hormonal therapy [7]. Palbociclib plus fultresvant demonstrated increased efficacy in the endocrine-resistant context compared to fultresvant plus placebo. Palbociclib plus fultresvant showed results of approximately 50% more PFS compared to fulvestrant with the placebo group [7].

Additionally, based on outcomes from a first stage trial, the suggested abemaciclib administration were discovered to be continual [7]. The MONARCH-1 study demonstrated that abemaciclib monotherapy was efficient for severely treatedER+MBC patients who were treated with at least two chemotherapies, with objective response rates (ORR) and clinical benefit rates (CBR) of 19.7 and 42.4%, respectively [7]. Abemaciclib and letrozole or fultresvant were combined in global phase III studies as treatments for female breast cancer patients. The phase III results in when combining abemaciclib and fulvestrant in treatment, female cancer patiens undergoing hormonal therapies, the survival rate would increase around 60%. [7].

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A worldwide (except Japan) phase I trial was used to determine the recommended administration route and treatment period for ribocilib [7]. In a Japanese phase 1 research, liver dysfunction, unfortunately, emerged as a dose-limiting hazard in a few patients within a 300 mg dose group [7]. Therefore, it was decided that 75 mg per 12 hours would be the recommended amount in Japan [7]. Japanese participants were consequently excluded from the worldwide phase III research (MONALEESA-2) [7]. For the therapy of women after menopause who has breast cancer, the MONALEESA-2 phase III research showed in comparison from placebo and ribociclib, ribociclib and letrozole showed higher survival rate and decreased hazard ratios [7].

2.2. Summary of CDK7 inhibitors

Given that CDK7 plays a crucial role in controlling cell mitosis, it is a promising therapeutic target for cancer patients [8]. Research of specific CDK7 inhibitors for cancer therapy has received significant research attention [8]. To investigate how CDK7 inhibitors work to reduce the transcription of oncogenes linked to super-enhancers and dependent on CDK7, researchers have shown effective clinical results [8].

There are five clinical trials registered with the National Institutes of Health that target CDK7 in advanced solid cancers [8]. SY-1365 (NCT03134638), a covalent CDK7 inhibitor, was tested in a stage 1 research to evaluate the safety and antitumor effects on advanced ovarian and breast cancer in order to determine the suggested dosage, also the course of treatment. [8]. Despite preclinical testing that showed a substantial anticancer impact of SY-1365, this trial was recently stopped since Syros Pharmaceuticals prioritized the development of SY-5609 [8]. As of November 14, 2017, Although it is still recruiting patients, a second phase 1/2 multicenter clinical trial of CT7001 (NCT03363893) monotherapy in severe malignancies is now being conducted [8]. For a subset of patients with castrate-resistant prostate cancer, triple-negative breast cancer, and breast cancer with hormone receptor positivity but negative for human epidermal proliferation factor-2, CT7001 will be evaluated both by itself and when used simultaneously with other treatment plans [8]. As for patients with these disorders, CT7001 will also be examined in combination with fulvestrant [8].

SY-5609 (NCT04247126), a contemporary non-covalent CDK7 inhibitor, was a competitor to SY-1365 until SY-5609's development was prioritized and SY-1365's further development was stopped. SY-5609 was previously tested in vitro and in vivo [8]. Leukemic HL60 cells were subjected to SY-5609, which hindered DNA damage repair, led to apoptosis, and stopped the cell cycle. In vivo antitumor activities with dose-dependent cancer, progression suppression was observed in mice xenograft models made from patient cell lines, accompanied by a striking reduction of multiple cancer addictions [8]. Later, a study evaluating the relationship between pharmacology, pathophysiology, and cancer progression inhibition revealed that SY-5609 generates transcriptional and cell cycle aberrations as well as intervenes in the progression of tumors in xenograft models of diverse solid malignant tumors [8]. Additionally, in contrast to mice without RB gene abnormalities, sustained tumor shrinkage was observed in models with RB gene modifications, demonstrating a special vulnerability of tumor cells with faulty mitosis process regulation to treatment [8].

LY3405105 is a different CDK7 inhibitor, started its first stage clinical trial to examine its adverse effects on cancer patients on the 31st of January 2019, and it is now complete. However, not much information is offered, and the study's findings have not been disclosed. [8]. Early in 2021, LY3405105 was taken out of Eli Lilly and Company's research pipeline [8]. XL102 is another CDK7 inhibitor, formerly known as AUR102; the business provides much less information [8]. Advanced solid tumors are the subject of this medication's phase 1 clinical research (NCT04726332), which examines the drug's bioavailability, antitumor efficacy, pharmacosafety, tolerability, and influence on biomarkers [8].

However, in theory, blocking CDK7 ought to cause decreased cancer progression and inhibits CDKs [8]. Different cancer types respond differently to CDK7 inhibitors' regulatory actions on cell cycle progression. [8]. CT7001 significantly lowers CDK1 and CDK2 phosphorylation while completely blocking the entire cell cycle [8]. Furthermore, CDK7 inhibition has combinatorial antitumor effects on cancer treatment because it can cause cancer cells to apoptosis [8].

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2.3. Summary of CDK9 inhibitors

The medication that is most frequently tested in CDK9 antagonist studies in the medical field is flavopiridol. Those suffering from acute myelogenous leukemia (AML) who received 2 schedules of flavopiridol in a randomized phase II study along with cytosine arabinoside and mitoxantrone experienced over half of active response, though less than 10% who participated discontinued due to side effects and 13% of them passed away [9]. The rest 56 participants in the second trial respectively, while full response to the medication was around 2% [9]. One study looked at flavopiridol alone in leukemia patients, while the other looked at flavopiridol in combination with cisplatin in primary peritoneal carcinoma (PPC) [9]. All patients in this most recent trial experienced negative effects, with a high risk of 87%. Due to a negative reaction, 26% of the patients discontinued their flavopiridol therapy [9]. Seven out of the twelve Phase I clinical trials for flavopiridol have not produced a full response. The trials detailed numerous negative outcomes, including thrombocytopenia, embolism, neutropenia, and tiredness. Consequently, more than 50% during the first phase trials did not meet the patient's needs [9]. There are also only three studies with complete responses that are less than 10%, and one in which three out of nine patients were in complete remission but eight of them had anemia [9]. The study that found a relationship between the previously mentioned mitoxantrone and cytosine arabinoside (40%), even though more than half of the patients suffered tumor lysis syndrome, is the one with the greater percentage [9].

Dinaciclib is a distinct CDK9 blocker that has just undergone testing in Phase I and II clinical studies [9]. A partial response to the medication was observed in all of the second-phase research involving it, and 75–95% of the patients experienced negative side effects [9]. Additionally, the drug's Phase I tests showed several negative side effects and no overall full response [9].

Another CDK9 inhibitor participating in stage one trials is seliciclib which doesn’t indicate significant negative impacts; however, they also don't prove that those who had treatment fully recovered. SNS-032, a CDK 2, 7, and 9 inhibitor, was the subject of a Phase I trial that was stopped midway through the dose escalation. Clinical side effects occurred in 100% of the patients [9]. It was evident from clinical investigations that patients did not respond to its therapeutic potential., with 75% experiencing negative side effects. A potent multitargeted CDK inhibitor that targets CDK9, RGB-286638, did not provide a full therapy response in its initial human trial and had 23% of the negative effects that patients reported [9].

It should be noted that none of the 5 inhibitors employed in clinical trials are specific to CDK9 [9]. Additionally, they inhibit many CDKs and enzymes, therefore, a lack of selectivity may be to blame for the ineffective therapy with these medications that cause several side effects [9].

2.4. Summary of CDK12 inhibitors

In Drosophila and human cells, CDK12 is involved in transcription elongation and can phosphorylate the RNA pol II CTD serine at the second position [10]. Certain enzymes, namely those needed for DNA damage response (DDR), DNA synthesis, and restoration, are transcriptionally elongated by CDK12 [11]. The pre-mRNA polyadenylation, cleavage, and splicing processes are also carried out by CDK12 [11]. Additionally, CDK12 phosphorylates the translation suppressor 4E-BP1 to work with mTORC1 to control the translation of a subgroup of mRNAs [11]. As a tumor suppressor and oncogene, CDK12 arises. Breast, ovarian, and prostate malignancies all had CDK12 mutations, confirming the tumor suppressor function of this gene [11]. The use of CDK12 as a tracer in medical studies has begun, and CDK12 alterations in prostate cancer are associated with a dynamic subpopulation that has a poor prognosis [11]. There have been multiple studies that demonstrated CDK12 as a prospective treatment aim for cancer in addition to its potential biomarker function [11].

Cancer preclinical models have demonstrated the effectiveness of CDK12 inhibitors [11]. However, due in part to the poor pharmacokinetic characteristics of these inhibitors, none have entered clinical trials. By adding water-soluble moieties to molecules, this problem can be resolved, and additional orally accessible CDK12 inhibitors will soon appear [11]. Numerous preclinical studies have shown that inhibiting CDK12 is a useful way to halt cancer progression and inhibit biomarkers through synthesized

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fatal associations have also been discovered [11]. It requires logical clinical trial design and careful patient selection to see whether this preclinical research could translate into patients [11]. We anticipate the introduction of CDK12 inhibitors into clinical trials as well as the discovery of efficient CDK12 inhibitor-adjuvant combos with more medications targeting malignancies [11].

3. Conclusion

Overall, the different inhibitors were targeted and expected to become a treatment option for varied categories of cancers. However, of all the inhibitors mentioned in this article, CDK4/6 inhibitors have the highest potency in treating breast cancers and have the most mature clinical results, also the only inhibitor category that has successful drugs approved by the FDA and entered the market. On the other hand, pan-CDK, CDK7, CDK9, and CDK12 have a large variety of development progresses, either undergoing clinical trials or having been abandoned because of disadvantages that may appear during treatments. Fortunately, other CDK inhibitors are in the progress of development which has the potential of combination therapy in the future as more CDK inhibitor drugs are being approved by the FDA.

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