Clinical Cancer Research

Molecular Pathways: CDK4 Inhibitors for Cancer Therapy

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Abstract

Unrestrained growth is the hallmark of cancer, and disrupted cell-cycle regulation is, therefore, common. CDK4 is the key regulator of the G_1–S transition. In complex with cyclin D, CDK4 phosphorylates retinoblastoma protein (Rb) and drives cell-cycle progression, a process inhibited by p16. The p16–CDK4–cyclin D–Rb is aberrant in the majority of cancers and is, thus, a logical target for anticancer therapy. Previous attempts to block CDK4 with nonselective cyclin-dependent kinase (CDK) inhibitors led to toxicity and little efficacy. However, the recent development of selective CDK4 inhibitors launched the first successful efforts to target the pathway for cancer therapy. Three oral selective CDK4 inhibitors have entered clinical trials: palbociclib (PD0332991), LEE011, and LY2835219. CDK4 inhibitors have *in vitro* activity against a broad range of cancers and in patients have shown antitumor activity in breast cancer, lymphoma, sarcoma, and other tumors. Major efforts are under way to develop biomarkers of response, understand potential mechanisms of resistance, and develop rational combinations of CDK4 inhibitors with chemotherapy and other targeted drugs. *Clin Cancer Res; 20(13); 3379–83. ©2014 AACR.*

Background

The cell cycle describes the various phases of growth, chromosomal replication, and mitosis that are required for cell division and replication. A complex set of interacting proteins tightly regulates progression through the cell cycle in mammalian cells. The key components are the cyclin-dependent kinases (CDK), a group of serine/threonine kinases. These CDKs cooperate with proteins called cyclins to regulate cell-cycle checkpoints (1).

Because unrestrained growth is the hallmark of cancer, disruption of cell-cycle regulation in malignant cells is common, and although targeting the pathways that regulate the cell cycle has been a major interest in oncology for many years, the more recent development of selective and potent inhibitors of specific CDKs has led to burgeoning interest in the field.

Cells must progress through the four phases of the cell cycle to divide and replicate: G_1, S phase (DNA synthesis), G_2, and M phase (mitosis). The key regulator of the G_1–S transition is CDK4. Cyclin D1 (CCND1) forms a complex with CDK4 and phosphorylates the retinoblastoma (Rb) protein, thus inactivating it. This relieves the Rb-mediated inhibition of the transcription factor E2F, which commits the cell to progression through the cell cycle (see Fig. 1). Although regulation of Rb is thought to be the primary effect of the CDK4/cyclin D1 complex, recent work has identified the transcription factor FOXM1 as another potential phosphorylation target (2). [This observation has, however, been contested (3), and the therapeutic implications are not yet clear.]

Other CDK and cyclin complexes regulate later stages of the cell cycle. In late G_1, CDK2–cyclin E further phosphorylates Rb, irreversibly committing the cell to proceed to S phase (the so-called checkpoint). Later in S phase and G_2, CDK1 and CDK2 play important roles with their partners cyclin A and B. This review, however, focuses on the CDK4–cyclin D complex.

CDK4–cyclin D regulation is perturbed in a large proportion of human cancers. This can occur through several mechanisms: (i) Amplification or overexpression of cyclin D1. The archetype is mantle cell lymphoma in which a t(11;14) translocation places cyclin D1 under the control of the immunoglobulin promoter. Overexpression of cyclin D1 is also observed in a variety of solid tumors (4). (ii) Amplification of CDK4. This is seen with highest prevalence in well-differentiated and dedifferentiated liposarcoma, a disease in which CDK4 amplification is nearly universal (5, 6). CDK4 amplification has also been observed at lower frequency in other solid tumors and hematologic malignancies (4). (iii) Activating mutation of CDK4. Curiously, these are very rare and are described in cases of familial melanoma (7, 8). (iv) Loss of the CDK4 inhibitor p16 (CDKN2A). This is a common event in many cancers.

Clinical–Translational Advances

The observed frequent activation of the p16–CDK4–cyclin D–Rb axis in cancer led to efforts to block the pathway pharmacologically. The first-generation CDK inhibitors were nonselective CDK inhibitors that blocked CDK4 but also had significant off-target effects. Flavopiridol is one of the

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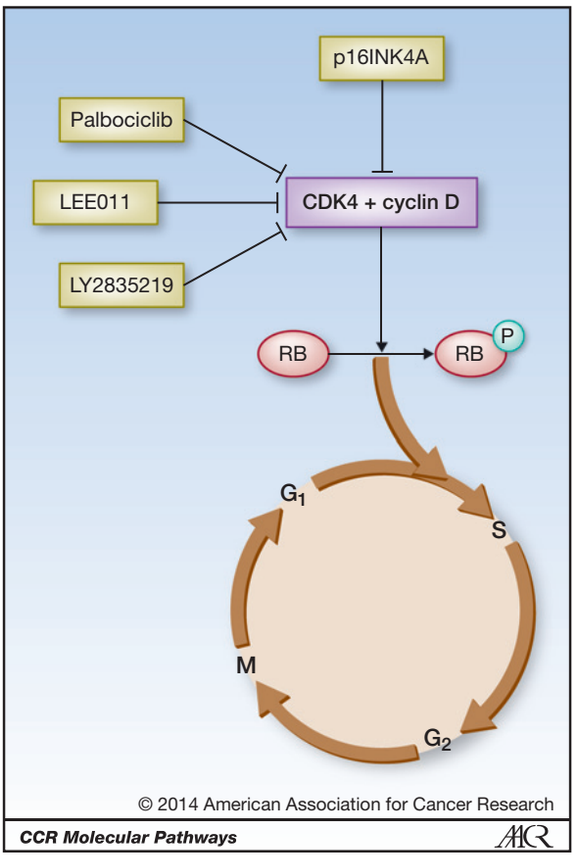

Figure 1. CDK4 and cyclin D form a complex that phosphorylates Rb and drives progression through the cell cycle. The pathway is activated in many cancers through p16 loss, CDK4 amplification, cyclin D overexpression, or Rb loss. Three selective CDK4 inhibitors currently in clinical development inhibit the pathway and show promising antitumor activity.

most studied drugs in this class. A semisynthetic alkaloid, flavopiridol inhibits many CDKs, including CDKs 1, 2, 4, 6, 7, and 9 (9). Although it has been tested in a variety of tumors, it showed limited efficacy, possibly because of limited selectivity. *In vivo*, the CDK9 effect is likely dominant. Inhibition of CDK9 does not have a specific effect on the cell cycle but rather inhibits transcription, which is broadly toxic to cells. In the clinic, flavopiridol was troubled by complex pharmacokinetics requiring prolonged intravenous administration, and toxicities, including diarrhea (10). Nevertheless, flavopiridol has significant activity in certain hematologic malignancies, although it cannot be considered a truly selective CDK inhibitor (11).

The next generation of inhibitors was developed to target selectively the ATP-binding site of the CDK4–cyclin D complex. (These drugs also target CDK6, a closely related but likely redundant protein, but none of the other CDKs.) In clinical development, the most advanced drug in this class is PD0332991 or palbociclib (Pfizer). Palbociclib inhibits CDK4 at nanomolar concentrations and is highly selective compared with a range of other protein kinases (12, 13). *In vitro*, palbociclib acts as expected, preventing Rb phosphorylation at serine 780 and 795 and inducing a G_1 cell-cycle arrest. This has antiproliferative effects in multiple cell lines, both in CDK4-amplified tumors such as liposarcoma and also in many other tumors (including mantle cell lymphoma, myeloma, and breast, ovarian and colon cancers) as long as Rb, the downstream target of CDK4, is intact.

Palbociclib is an orally bioavailable drug that is now well characterized in the clinic. Two completed phase I studies have established dosing regimens of 200 mg daily for 2 weeks of 3, or 125 mg daily for 3 weeks of 4 (14, 15). In each case, neutropenia was the dose-limiting toxicity and the 1-week break was required for neutrophil recovery. This toxicity profile will likely be seen with all selective CDK4 inhibitors and is probably a result of transient growth arrest in hematopoietic precursor cells (16). Unlike cytotoxic drugs associated with severe neutropenia, there was relatively little gastrointestinal toxicity, alopecia, or mucositis, and although neutropenia was common, serious sequelae such as fever or infection were rare. Encouraging clinical activity was observed even in the phase I studies, including a patient with germ cell tumor (teratoma) who had a durable partial response (PR; ref. 17).

Palbociclib was tested in CDK4-amplified liposarcoma in a phase II study of the 200-mg dose (18). As expected, >90% of the patients with well-differentiated and dedifferentiated liposarcoma screened for the study had CDK4 amplification. The results showed an encouraging progression-free survival rate of 66% at 12 weeks and occasional responses in a disease otherwise relatively impervious to chemotherapy. A follow-up phase II study with the 125-mg dose confirmed these results with similar response rates and toxicities (19).

Palbociclib has also shown promising activity in mantle cell lymphoma, a disease characterized by cyclin D1 overexpression. In a phase II study of 17 patients, substantial single-agent activity was shown, with a response rate of 18% (20).

The development of palbociclib as a treatment for breast cancer is most advanced. Palbociclib has broad activity in breast cancer cells *in vitro*, especially the estrogen receptor (ER)–positive luminal type (21). This observation led to a phase Ib study of palbociclib in combination with letrozole, an antiestrogen. Of 12 patients, 3 had PR (22). A large randomized phase II study was then performed with 165 patients randomized to palbociclib plus letrozole versus letrozole alone. Preliminary results from the study showed median progression-free survival durations in the combination group of 26 months, compared with 7.5 months in patients receiving letrozole alone (23). On final analysis the difference was less marked but still impressive: 20.2 months versus 10.2 months (24). Toxicity was again principally neutropenia. A confirmatory randomized phase III study is now under way for patients with ER-positive, HER2-negative breast cancer (NCT01740427), which will allay concerns about potential bias in the phase II study, which was open-label and used investigator-assessed progression as the primary endpoint.

The second selective inhibitor of CDK4 is LEE011 (Novartis). Like palbociclib, LEE011 is an orally bioavailable

small molecule that inhibits CDK4/6 at nanomolar concentration (25). As expected, *in vitro* LEE011 causes G_1 arrest and has antitumor activity in several models, including melanoma with BRAF or NRAS mutation and breast cancer. Results for 78 patients treated on the phase I study of LEE011 have been reported (26). Both intermittent and continuous doses were evaluated with recommended phase II doses of 600 mg daily (continuous) and 900 mg daily for 3 weeks of 4. As with palbociclib, neutropenia was the major toxicity, although complications were rare. Encouraging responses were observed in breast cancer and melanoma.

The third selective CDK4 inhibitor is LY2835219 (Eli Lilly). This is another orally bioavailable drug that selectively inhibits CDK4/6 in the nanomolar range (27). Preclinical data show antitumor activity in a number of models, and the drug has also been shown to cross the blood–brain barrier (28). Preliminary results for 75 patients treated on the phase I study of LY2835219 have been reported (29). Unlike the regimen for palbociclib and LEE011, patients were treated with continuous daily (or twice daily) dosing of LY2835219. The maximum tolerated dose was 200 mg twice daily. The principle adverse events were diarrhea, fatigue, and neutropenia. Early activity was observed in lung, breast, and ovarian cancer, and in melanoma. An expansion cohort of patients with metastatic breast cancer has also recently been reported, showing that the drug has activity in hormone receptor–positive breast cancer even when given as a single agent, without an antiestrogen (30).

The three selective CDK4 inhibitors in clinical development so far seem quite similar in structure, function, toxicity profile, and antitumor activity. The next step will be to define more clearly the spectrum of cancers that could benefit from CDK4 inhibition. CDK4 inhibitors would be expected to be active in tumors with ubiquitous CDK4 amplification, such as well-differentiated and dedifferentiated liposarcoma. CDK4 inhibition should also be effective in cyclin D–amplified tumors such as mantle cell lymphoma, as previously demonstrated with palbociclib (20) and currently being tested with LY2835219 (NCT01739309). Cancers with p16 loss may also be sensitive to CDK4 inhibition, with preclinical data supporting this in melanoma and lung cancer among others (7, 31).

In contrast, certain cancers are likely to be intrinsically resistant to CDK4 inhibition. Tumors that lack Rb function are likely to fall into this class, because the antitumor effect of CDK4 inhibition depends on downstream Rb. This category of predicted CDK4-resistant tumors includes those with Rb loss at the gene level (such as Rb) and also those with functional inactivation of Rb protein, such as squamous cell carcinomas of the oropharynx, cervix, and genital tract in which the E7 oncogene of HPV16 inactivates Rb (32).

Even among cancers that are predicted to be sensitive to CDK4 inhibition, not all tumors will respond. An important effort will be the development of predictive biomarkers of response. Early work suggests that, at least in ovarian cancer, those cell lines with low p16 levels and high Rb expression are most sensitive (33, 34). In the clinic, preliminary results from the breast cancer trials suggest that p16 loss and cyclin D1 amplification at baseline do not necessarily predict sensitivity to CDK4 inhibition (30, 35). More work in this area is under way, and biopsies before and after treatment start will be essential to elucidate this further. Moreover, as with other targeted therapies, the phenomenon of acquired resistance is likely to emerge. Potential mechanisms may include upregulation of cyclin D1 or CDK4, mutation in CDK4, or loss of Rb function.

As with other new targeted therapies, the potential for combination with existing chemotherapeutics should be explored. The available preclinical data suggest, however, that this will not be straightforward. Although some groups have shown that the combination of a CDK4 inhibitor with 5-fluorouracil is synergistic *in vitro* (36), others demonstrated that CDK4 inhibitors may in fact protect cells from the toxic effects of DNA-damaging chemotherapy. In particular, treatment with palbociclib led to a temporary growth arrest that shielded cells from the effects of doxorubicin or carboplatin and in fact reduced the efficacy of those drugs in xenograft models (16, 37). Thus, combinations of CDK4 inhibitors with cytotoxic drugs should not *a priori* be assumed to be synergistic or even additive, and in fact may be antagonistic. Careful preclinical modeling will be required to elucidate this further. An ongoing phase I study of paclitaxel with palbociclib will assess this complex and important issue in the clinic (NCT01320592).

Given the modest single-agent activity of CDK4 inhibitors, exploring combinations with other targeted therapies will be important and potentially fruitful. Combining palbociclib with letrozole has already shown considerable promise in breast cancer, and a definitive phase III study is under way (NCT01740427). In addition, combinations of palbociclib with anastrozole (NCT01723774) or fulvestrant (NCT01942135) are being tested. Triple-drug combinations are also being explored in breast cancer, including LEE011 with antiestrogen therapy and either the mTOR inhibitor everolimus (NCT01857193) or the PI3K inhibitor BYL719 (NCT01872260). Another important avenue of research is the possible synergy of CDK4 targeting with inhibitors of the RAS–RAF–MEK pathway. This is being tested in two important phase I studies: LEE011 with the MEK inhibitor MEK162 in NRAS-mutant melanoma (NCT01781572) and LEE011 with the BRAF inhibitor LGX818 in BRAF-mutant melanoma (NCT01777776).

In summary, the development of selective small-molecular inhibitors of CDK4, the crucial kinase that regulates cell-cycle progression, has ushered in a new era of targeted cancer therapy. Three oral CDK4 inhibitors have entered the clinic, with promising activity already seen in several diseases, including breast cancer, liposarcoma, and mantle cell lymphoma. Neutropenia seems to be the principal toxicity of drugs in the class, but it is tolerable and manageable. Large phase III studies of CDK4 inhibitors are under way in advanced breast cancer with results eagerly anticipated. Further clinical trials in diseases with CDK4 amplification

such as liposarcoma are warranted. Additional studies of CDK4 inhibitors in combination with other targeted therapies are under way. In the next few years, the further development of CDK4 inhibitors should lead to significant advances in cancer treatment.

Disclosure of Potential Conflicts of Interest

M.A. Dickson was a consultant/advisory board member for Pfizer.

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