CDK4/6 inhibition: What's happening beyond CDK4/6 inhibition may also matter

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SUCCESSES WITH CDK4/6 INHIBITORS

Currently there are three CDK4/6 inhibitors approved for clinical use worldwide– palbociclib, ribociclib, abemaciclib. There are other CDK4/6 inhibitors either approved locally, such as dalciclib in China, or in the R&D（Research& Deveopment） stage of clinical trials. Almost all CDK4/6 inhibitors demonstrate excellent results in advanced hormone-receptor positive, HER2-negative (HR+/HER2-) breast cancer and one of them is even approved in early stage. Endocrine therapy plus CDK4/6 inhibitors had greatly changed the treatment landscape and become the golden standard treatment for the first or second line of HR+/HER2- advanced breast cancer. Abemaciclib was approved also in HR+/HER2- high risk early breast cancer. The main mechanism of CDK4/6 inhibitor targets the cell cycle machinery, arresting progression through the G1/S phase by inhibition of the kinase activity of CDK4/6 and cyclin D1 and the subsequent Rb phosphorylation, potentially causing apoptosis or permanent arrest in the G0 phase.[1]

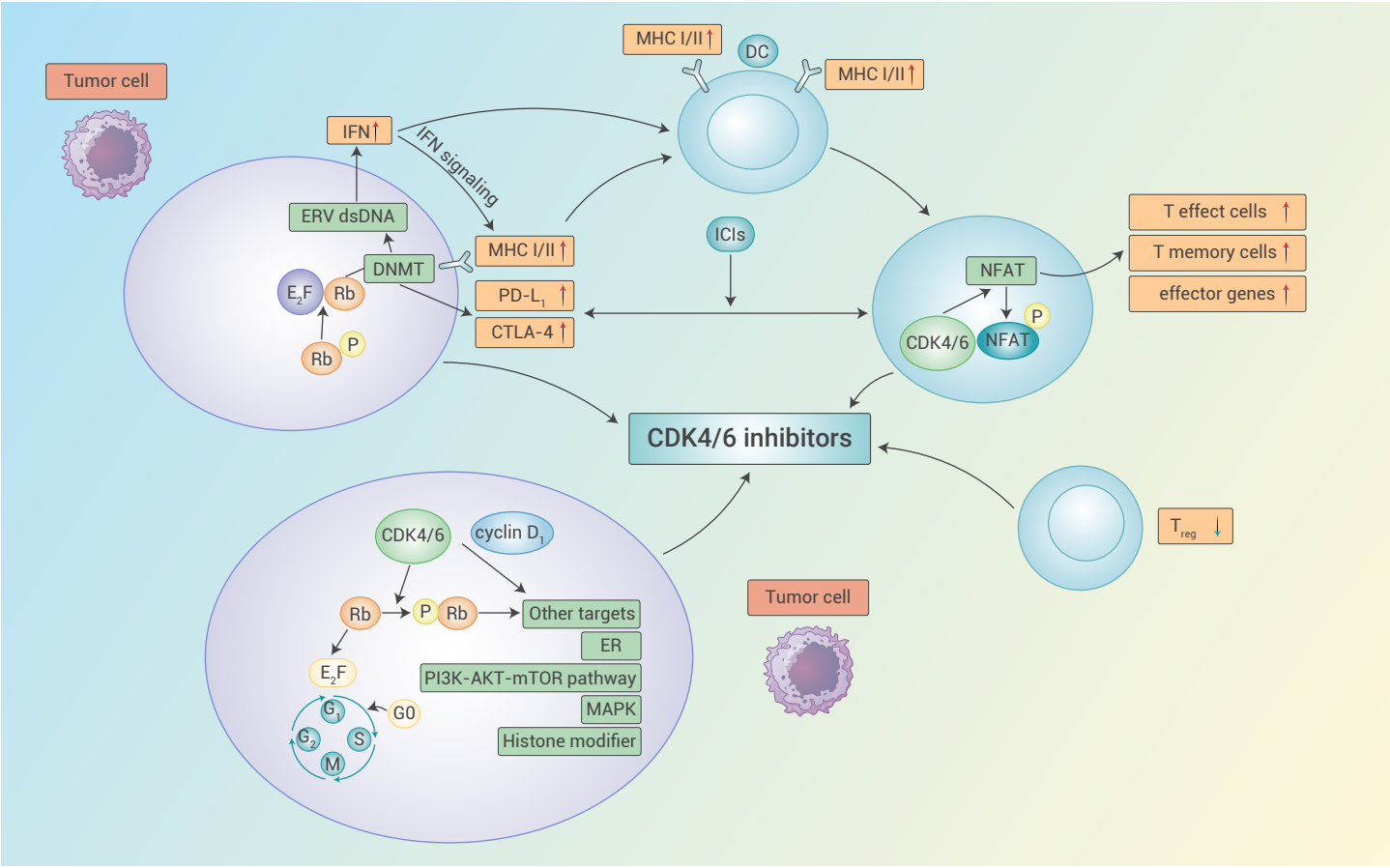

Figure 1. The potential impact of CDK4/6 inhibitors on the immune system IFN, interferon; ERV, endogenous retrovirus; dsDNA, double-stranded DNA; DNMT, DNA methylation transferase; MHC, major histocompatibility complex; PD-L1, programmed cell death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; NFAT, nuclear factor of activated T cells; CDK4/6, cyclin-dependent kinases 4 and 6; ER, estrogen receptor; PI3K, phosphatidylinositol3-kinase; AKT, also known as protein kinase B; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; Treg, T regulatory cells.

THOUGHT-PROVOKING RESULTS FROM CDK4/6 INHIBITOR TRIALS

Although CDK4/6 inhibitors exhibit strong efficacy in advance stage breast cancer, there are some very interesting data needs to be further explored. First, it seems that there are some differences in results among different CDK4/6 inhibitors. For example, palbociclib failed to achieve overall survival benefit despite excellent Progression-Free Survival (PFS). However, ribociclib demonstrate both significant longer PFS and OS (Overall Survival). When it comes to early stage, abemaciclib in MONARCHE trial showed better IDFS (Invasive Disease-Free Survival) in high risk HR+/HER2- early breast cancer while palbociclib in PALLAS trial failed to achieve additional benefit. Whether this is due to study design, drug explosion or intrinsic difference of these agents is still unclear. Second, for those trials with both positive results in PFS and OS, the elongation of progression-free survival was not only translated into overall survival benefit, but also translated into even longer survival benefit. In MONALEESA-2 trial, median PFS, as the primary endpoint, were increased from 16 months to 25.3 months (9.3 months extra), but median OS was increased from 51.4 months to 63.9 months (12.5 months extra). This is

not usually seen in clinical trials, especially in early-lines of advanced stage. Coincidentally, in MONARCH-2 trial, the addition of abemaciclib to fulvestrant brought 7.1 months of extra PFS and 9.4 months of extra OS. More interestingly, In PACE study, when Palbociclib was rechallenged after progression on previous Palbociclib, PFS benefit was only seen in fulvestrant plus Palbociclib plus avelumab, a PD-1 antibody, from 4.8 months for fulvestrant monotherapy to 8.1 months for triplet. Again, longer OS benefit was reproduced, from 27.5 months for fulvestrant monotherapy to 42.5 months for triplet. That is, the benefit of OS was far exceed that of PFS. The underlying mechanism deserved to be deeply undermined and the immune effect of CDK4/6 inhibitors may unravel the mystery.

CDK4/6 INHIBITOR: MECHANISM BEYOND CELL CYCLE ARREST

Data are emerging showing that CDK4/6 inhibition may affect immune system. First, there are ample evidence supporting that CDK4/6 inhibitor increase antigen presentation pathways by upregulating genes encoding MHC (Major histocompatibility Complex), downregulating RB-E2F-DNMT1 axis resulting induction of interferon signaling, therefore activating APCs (Antigen-Presenting Cells) such as macrophages and dendritic cells (DCs).[2]

Secondly, CDK4/6 inhibitors markedly suppress the proliferation of regulatory T cells (Tregs). Tumors treated with CDK4/6 inhibitors had a lower frequency of CD4+ regulatory T cells and a higher frequency of CD8+ memory-like T cells. CD8+ TILs from CDK4/6i-treated mice were inclined toward an earlier and more stem-like differentiation state. In addition, CDK4/6i promotes differentiation of T cells towards memory phenotype, characteristic of functional long-time persistence. These was also observed by Goel et al[2] that in tumor-free mice, both abemaciclib and palbociclib significantly reduced Treg numbers and the Treg:CD8 ratio in the spleen and lymph nodes, demonstrating tumor-independent effects of these agents. The potential impact of CDK4/6 inhibitors on the immune system were listed in figure 1.

It is important to see whether these preclinical speculations were translated into real patients and these basic foundings were clinically validated. Scirocchi et al[3] for the first time provided evidence for the impact of CDK4/6i on the immune system of patients with HR+/HER2- mBC by strongly downmodulating immunosuppressive cell subsets. In their study, immune cell subsets were analyzed using flow cytometry of peripheral blood mononuclear cells (PBMCs) isolated from patients with HR+/HER2- mBC before and during CDK4/6i treatment. The percentage of circulating Tregs and monocytic and polymorphonuclear myeloid-derived suppressor cells(M/PMN-MDSCs) was significantly downregulated from baseline during CDK4/6i-treatment. In particular, the effector Treg subset was strongly reduced. The decrease in Treg levels was significantly greater in responder patients than non-responder patients. Conversely, CDK4/6i treatment was associated with increased CD4+T cells and anti-tumor CD137+CD8+T cells.

In another study exploring the effect of ribociclib (RIB) on immune modulation in a clinical setting, gene expression analysis was performed using paired biopsy Samples from 7 patients in 2 phase I clinical trials (CLEE011A2115C [A2115C], CLEE011X2107 [X2107]) that studied RIB in combination with endocrine therapy (ET) in HR+/HER2− metastatic breast cancer (MBC). RIB + ET increased expression of a gene signature associated with immune response and indicative of a T-cell–inflamed microenvironment including CCL5, HLA-DRA, IL2RG, NKG7, HLA-E, CXCL10, STAT1 etc. Two of 3 patients who experienced a clinical benefit with RIB + ET had an increase in expression from baseline to C1D15 while two patients who experienced no clinical benefit with RIB and ET had decreased expression from base. It was further confirmed in another report by Pascual et al that in CORALLEEN phase 2 trial, neoadjuvant ribociclib plus letrozole, compared with chemotherapy, increase T cells and B cells invasion, especially tumors without complete cell cycle block.

Therefore it is reasonable to assume that the immune effect of CDK4/6 inhibitor may contribute to long-lasting overall survival benefit observed in these clinical trials and whether there are difference among those CDK4/6 inhibitors in terms of immune response deserves to be further studied.

Of course, there are non-canonical effects of CDK4/6 inhibitors may also matter. Senescence induced by CDK4/6 inhibitors may influence in several ways both tumor and immune cells altering tumor progression. CDK4/6 inhibitor was also found to affect cell metabolism by altering glycolytic and oxidative metabolism.

ENDORSEMENT OF CDK4/6 INHIBITION WITH IMMUNE THERAPY

One mechanism of resistance to immunotherapy is the loss of T cells cytotoxic functions, given the effects of CDK4/6 inhibitors on tumor immune microenvironment, combination of CDK4/6i may potentially enhance the effects of immune checkpoint inhibitors and overcome their resistance. This was validated both in vitro and in vivo by several studies.[4] In Schaer's study, abemaciclib did modulate the tumor immune microenvironment and synergize with anti-PD-L1-based immunotherapy. There are indeed some researches of CK4/6 inhibitors plus PD-1/PD-L1 blockade in ovarian cancer, lung cancer or even sarcoma. It may contribute to multiple immune-related pathways, including the upregulation of innate immune pathways related to DC maturation, upregulation of genes associated with a T cell inflammatory and activated phenotype, and modulation of tumor-intrinsic antigen processing and presentation mechanisms.

OUTLOOK

Reports above make a strong argument for the use of CDK4/6i in patients with a strong immunosuppressive environment, with the objective of selectively targeting immunosuppression and preparing the patient for successful immunotherapy. Clinical trials are ongoing assessing whether combination of CDK4/6 and immune checkpoint inhibition is clinically meaningful for the treatment of breast cancer. In a phase Ib trial (NCT02779751) when pembrolizumab was given together with abemacliclib, the overall response rate and disease control rate were 23.1 and 84.6%, respectively. In another trial (NCT02778685), combination of pembrolizumab, palbociclib and letrozole generated a complete response rate of 31% and 25.2 months of PFS. When tested in neoadjuvant setting, in CheckMate 7A8 trial when nivolumab plus Palbociclib plus anastrozole was administered, pCR (pathological Complete Response) was 4.8%, objective response rate was 71.4%. These preliminary data from both preclinical and clinical researches conveyed an important concept that CDK4/6 inhibitor should not be regarded only as a cell cycle agent and combination strategy is very promising and highly anticipated.

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DECLARATION OF INTERESTS

Binghe Xu is an Editorial Board member of The Innovation Medicine. He was blinded from reviewing or making final decisions on the manuscript. The article was subject to the journal's standard procedures, with peer review handled independently of this Editorial Board member and their research groups. The other author declares no competing interests.