Case Report

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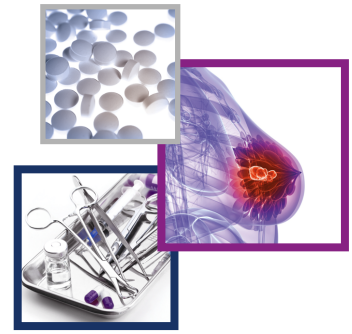
Breast Cancer Management



Palbociclib in a patient with HR+/HER2- advanced breast cancer and HIV1 infection: a case report

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The use of drugs that affect the cell cycle represents one of the common strategies for the control of some unrelated pathologies, such as chronic viral HIV infections or cancer. The authors report the case of a patient followed for a hormone receptor-positive (HR+)/HER2 negative (HER2-) advanced breast cancer, treated with hormone therapy and CDK 4/6 inhibitors, and a concomitant HIV infection under antiretroviral treatment. The authors consider the function of the sterile alpha motif and HD domain-containing protein-1 (SAMHD1) enzyme, its implications in the control of viral replication and the correlation between its activity and the mechanism of action of the CDK 4/6 inhibitor palbociclib.

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Case report

This report presents the case of a 55-year-old woman who was diagnosed in March 1993, when she was 28, with HIV-1 infection during a febrile illness corresponding to HIV seroconversion, as demonstrated by immunoblotting. The patient was the partner of an HIV-positive male who was an intravenous drug user and had been followed in an outpatient clinic for infectious diseases. At the time of seroconversion, she presented a $CD4^+$ cells count of 357/mmc; HIV viral load was not available. In June 1996, she began antiretroviral treatment with didanosine and stavudine as recommended by international guidelines of the time. The first determination of HIV RNA was available in June 1997, showing a viral load <500 copies/ml but, as expected with dual therapies, in December 1998 a virological failure of 2230 copies/ml occurred. Treatment history continued with the use of non-nucleoside reverse transcriptase (NNRTI) and protease inhibitors (PI) maintaining a mean $CD4^+$ count of above 400 cells, but with a mean HIV viral load of 2000 copies/ml during that period.

In 2003, at the age of 38 years old, a tumor in the right breast was detected by mammography and the patient underwent lumpectomy with sentinel node biopsy. The pathological report showed an 11-mm infiltrating ductal carcinoma grade 2, estrogen receptor 75%, progesterone receptor 80%, Ki-67 10%, HER2 score 1+, with no nodal involvement. Complementary radiotherapy on residual breast and adjuvant hormone therapy with tamoxifen 20 mg/day was suggested.

HIV genotyping in 2005 showed HIV-1 subtype B, with discriminatory and thymidine analog mutations (TAMs) and major NNRTI (67N 70R 118I 179I 184V 188L 215C 215F 215V 219Q), conferring resistance to NRTI and NNRTI [1]. No genotype resistance to PI was detected and after switching to ritonavir-boosted atazanavir, emtricitabine and tenofovir disoproxil, the patient reached an HIV RNA undetectability (<20 copies/ml) that was maintained with ritonavir-boosted darunavir monotherapy [2] until 2017 and then subsequently with dual treatment with lamivudine and dolutegravir despite the archived mutation in NRTI [3]. In 2005, an excellent immunological recovery of $CD4^+$ cells count was obtained, reaching 1085 $CD4^+$ cells/mmc in May 2017 with a 3:1 $CD4^+$:$CD8^+$ ratio (50.9%, 16.6%) [4].

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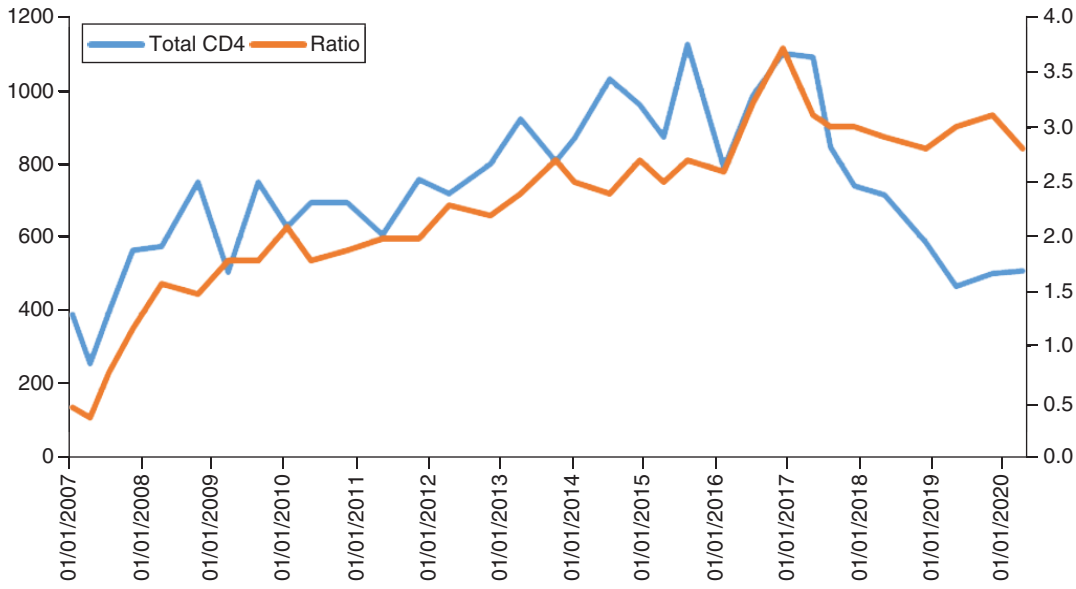

Figure 1. Trend of total $CD4^+$ and $CD4^+$:$CD8^+$ ratio between 2007 and 2020.

In 2017, following an increase in tumor markers CEA and CA 15-3, the patient received a chest CT scan that showed a recurrence of pleuro-pulmonary, mediastinal nodes and muscle lesion (pectoralis minor) breast cancer. The muscle lesion was surgically resected, and the pathological examination confirmed the same phenotype of the primary tumor. In July 2017, the patient started first-line therapy with letrozole 2.5 mg/day and palbociclib 125 mg/day for 21 days followed by a 7-day break. Boosted darunavir monotherapy was stopped at this time due to the drug's interaction with palbociclib, based on ritonavir's inhibition of CYP3A4. An instrumental clinical complete response was achieved and maintained to date. Since 2017, the patient's $CD4^+$ cells count has been affected by the anticancer treatment, showing a reduction in total $CD4^+$ counts: 620 in October 2020, but with an optimal 3:2 $CD4^+$:$CD8^+$ ratio (53.4–16.6%). In fact, neither delay nor dose reduction of palbociclib has been necessary due to this drug-related adverse event, to date. Figure 1 shows $CD4^+$/$CD8^+$ ratio and total $CD4^+$ during the period 2007–2020.

Discussion

This clinical case report describes the history of a woman diagnosed with and treated for HIV and metastatic breast cancer. While not directly related to each other, these two conditions, linked to multiple and independent etiopathogenetic factors, share a common driver: cell cycle control. Nucleotide metabolism plays a key role in the complex mechanism of cell cycle control. Agents capable of interfering with the physiological nucleotide metabolism (reduction of synthesis, increase in degradation, direct or indirect antagonism) have always been a weapon for the treatment of both cancer and viral infections. In recent years, several authors have investigated the role of the sterile alpha motif and HD domain-containing protein-1 (SAMHD1) both in the control of viral replication and tumor cell proliferation.

SAMHD1 is an enzyme with deoxynucleoside triphosphate triphosphohydrolase (dNTPase) activity, capable of degrading intracellular deoxynucleotides (dNTPs) [5]. The activity of SAMHD1 keeps the pool of intracellular dNTPs at adequate levels, to allow DNA replication and/or repair, hindering potential mutagenic events [6]. Therefore, the gene encoding the SAMHD1 enzyme acts as a tumor suppressor, and recent studies indicate that its reduced expression or possible mutations are related to different types of cancer [7,8]. Furthermore, SAMHD1 acts as a viral restriction factor. It has been shown in cell cultures [5,9–11] and in knock-out mouse models [12,13] that the activity of this enzyme can potentially interfere with the replication of lentiviruses, such as HIV, reducing the dNTPs pool available for the proper functioning of viral reverse transcriptase (RT) [14]. On the other hand, the viral accessory protein X (Vpx), encoded by some simian immunodeficiency virus (SIV) strains and the human immunodeficiency virus 2 (HIV2), has the ability to induce degradation by proteasome of SAMHD1, increasing the dNTPs pool available for viral RT [14,15]. So, SAMHD1 would appear to be able to affect only HIV1 replication.

SAMHD1 expression levels are similar both in cells primarily resistant to HIV1 (monocytes, quiescent lymphocytes) and in cells susceptible to HIV1 infection (macrophages and activated lymphocytes). This suggests that the activity of SAMHD1, which is fundamental to the control of infection in myeloid cells, is controlled by post-transcriptional mechanisms, such as cyclin-dependent kinase (CDK)-mediated phosphorylation [16–18]. CDKs are a serine-threonine kinases family that acts as regulators of cell cycle progression. Physiologically, the mitogenic stimuli drive cells from the G0 to G1 phase by inducing the expression of D cyclins, which activate CDK4 and CDK6. Subsequently, the latter induces the expression of cyclins E, which in turn activates CDK2, leading to the beginning of phase S. Finally, the activation of CDK 1 determines the mitosis prosecution [19,20]. HIV1 replication is strongly influenced by the phase of the cell cycle at the time of infection and by the available dNTPs pool. During the cell cycle, active CDK2 is able to phosphorylate and inhibit SAMHD1; in this way, the nucleotide pool is available both for the continuation of the cell cycle and for viral replication increases. HIV1 replication is facilitated in rapidly proliferating cells [16–18,21].

Cell cycle deregulation is one of the hallmarks of cancer [22,23]. In recent years, several molecularly targeted agents able to act on this pathway have been developed with the aim of inhibiting neoplastic growth. CDK4/6 inhibitors are a family of new-generation anticancer agents, which in recent years have become part of the standard treatment of HR+ and HER2- locally advanced or metastatic breast cancer, in association with hormone therapy. The introduction of these agents into clinical practice represented a breakthrough in the treatment of breast cancer, with an important improvement in terms of survival for patients [24].

In 2014, Paul *et al.* analyzed the effects of palbociclib, the first approved CD4/6 inhibitor, on HIV infection. Palbociclib inhibits the signaling pathway downstream of CDK 4 and 6. The latter in particular, once inhibited, cannot activate cyclin E and CDK2, preventing the consequent phosphorylation of SAMHD1, which can carry out its degradation function of intracellular dNTPs. In the absence of nucleotide substrates, reverse transcriptase fails to complete replication of the viral genome, limiting the spread of the infection. However, this activity is not maintained if the Vpx protein is expressed, since Vpx degrades SAMHD1 via the proteasome. The antiretroviral effect of palbociclib is intrinsically related to the activity of the SAMHD1 enzyme, therefore, it seems to work only on HIV1 infection. On the other hand, palbociclib limits the growth and proliferation of all cells with a high proliferative index, including activated macrophages and $CD4^+$ T lymphocytes, which represent the immune cells most susceptible to HIV infection. Thus, in addition to directly hindering the replication of the virus, palbociclib reduces the number of cells that the latter can infect [25].

Finally, the activity of SAMHD1 correlates with the efficacy of NRTIs, one of the most used classes of antiretroviral agents in the treatment of HIV infection. Once these drugs enter the infected cell, they are converted into their respective triphosphate form, competing with intracellular NTPs to be incorporated into the rising proviral DNA chain. Once incorporated, viral replication is blocked, as these analogs do not possess the 3′-hydroxyl group to attack the subsequent nucleoside triphosphate. Some studies have shown that when SAMHD1 is inactivated, the pool of intracellular NTPs available for viral RT increases, which compete with NRTIs, reducing their activity. Palbociclib indirectly enhances the antiretroviral action of NRTIs, by increasing the activity of the SAMHD1 enzyme [26]. Subsequent studies have shown that the other CDK4/6 inhibitors currently used in clinical practice (e.g., ribociclib and abemaciclib) also have the same correlation with the enzyme [27].

The work of Paul *et al.* explains the biological rationale behind the antiretroviral effect of CDK4/6 inhibitors. However, there is minimal data in the literature regarding women with metastatic breast cancer and HIV infection. In the pivotal trials of CDK4/6 inhibitors, HIV-infected patients were not eligible due to the high risk of myelotoxicity associated with these drugs. It is true that these two pathological conditions are not directly connected (as happens with some tumors caused by oncogenetic viruses), but, given the high incidence of breast cancer worldwide, these two conditions may be present in the same patient quite frequently. In the scenario of two complex pathological conditions, linked to multiple factors, it becomes important to know the existence of any common drivers that can be exploited in synergistic management. It would also have been interesting to evaluate the variation in the activity of CDK2 and SAMHD1 in the host cells of the patient's infection after the introduction of therapy with CDK 4/6 inhibitor, but this is not a routine operation. Future studies could explore this issue.

Another important aspect to consider in this case and generally in patients with metastatic breast cancer and HIV infection is the possible interaction between the drugs used for the treatment of the two diseases. Palbociclib (as well as ribociclib and abemaciclib) is well known to be metabolized by hepatic CYP3A4, of which some antiretroviral drugs (e.g., ritonavir, darunavir) are enzyme inhibitors. This explains why, in 2017, concurrently with the introduction of palbociclib, it was decided to switch the patient's anti-HIV treatment from ritonavir-darunavir

to dolutegravir-lamivudine, despite the absolute $CD4^+$ count and the $CD4^+$:$CD8^+$ ratio that were optimal in those years.

Monitoring the progress of infection in these cases can be challenging, as both viral infection and antineoplastic treatment can contribute to immunocompromise. Suppression of plasma viremia is the primary goal in these cases, since assessing the immune structure can be unreliable. Plasma viremia in patients with cancer is monitored approximately every 2 months during active treatment, and every 4 months during follow-up, but there are no specific guidelines. Further data is needed on patients with the simultaneous presence of these two conditions, to optimize their monitoring and treatment.

Conclusion

There is a strong relationship between the cell cycle regulation, through the inactivation of CDK6 upstream of CDK2, and the activation and functioning of SAMHD1. The effect of CDK4/6 inhibitors on this pathway in combination with the direct cytostatic effect against the host cells of the infection (activated macrophages and $CD4^+$ T lymphocytes), could represent a new potential antiretroviral strategy.

The patient in this clinical case had pleuropulmonary, mediastinal nodes and muscular recurrence of HR+/HER2- breast cancer, which required the introduction of a CDK 4/6 inhibitor in association with hormone therapy, according to international guidelines and clinical practice [28]. Palbociclib, in addition, to induce a complete disease response, may have contributed to the control of the HIV infection, for which the patient continued to take specific antiretroviral therapy with lamivudine and dolutegravir. There is little data to determine the real contribution of palbociclib to infection control.

In light of the evolution of antiretroviral therapies in recent years, it would be interesting to conduct further studies to understand whether the use of cycline inhibitors in the treatment of HIV infection could represent an additional advantage for all infected patients, including those not diagnosed with breast cancer.

Summary points

- Cancer and HIV infection share the same driver: cell cycle control, in which nucleotide metabolism plays a key role.
- SAMHD1 enzyme degrades intracellular dNTPs, acting both as a tumor suppressor and as a viral restriction factor.
- During the cell cycle, the activation of the cyclin-CDK pathway inhibits SAMHD1, increasing the pool of nucleotides available for both cell proliferation and viral replication.
- By inhibiting the cyclin-CDK pathway, palbociclib allows SAMHD1 to perform its function, hindering viral reverse transcriptase.
- Palbociclib limits the proliferation of macrophages and $CD4^+$ T lymphocytes, the immune cells most susceptible to HIV infection.
- Further studies should be conducted to understand whether the use of cycline inhibitors in the treatment of HIV infection could represent an additional advantage for all infected patients.

Author contributions

F Canino, L Moscetti, V Borghi, M Dominici and F Piacentini collected and interpreted the data and drafted the manuscript. All authors revised and approved the final submitted manuscript.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved. The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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- **This work describes the relationship between SAMHD1 and palbociclib.**

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