

Repurposing Nelfinavir for Cancer Therapy

Subjects: Oncology & Oncogenics

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Definition

Nelfinavir is an anti-infective agent that has extensively been used to treat acquired immunodeficiency syndrome (AIDS) in adult and pediatric patients. In addition to its anti-infective properties, nelfinavir has demonstrated potent off-target anti-cancer effects, suggesting that it could be a suitable candidate for drug repurposing for cancer.

1. Introduction

Human immunodeficiency virus (HIV) protease inhibitors (PIs) are a group of drugs designed to target the aspartyl protease enzyme of the virus. The ribonucleic acid (RNA) in HIV encodes for two polyproteins—gag and gag-pol—which are cleaved at specific regions by an aspartyl protease for the maturation of the nascent virions through morphologic changes and condensation of the nucleoprotein core ^[1]. To date, ten HIV-PIs have been approved by the United States Food and Drug Administration (FDA); they contain a synthetic analogue of the gag-pol polyprotein, having a sequence of phenylalanine-proline at 167 and 168 regions ^{[2][3]}. The HIV-PIs currently available in the market are nelfinavir, saquinavir, ritonavir, indinavir, amprenavir, fosamprenavir, lopinavir, atazanavir, darunavir, and tipranavir ^{[3][4]}. The HIV-PIs exert their therapeutic benefit by inhibiting subsequent HIV infection in a patient; however, they do not exert any action on cells already carrying integrated proviral DNA ^[1]. Thus, HIV-PIs have been in use in combination with reverse transcriptase inhibitors to treat HIV-infected patients, constituting the standard protocol of highly active antiretroviral treatment (HAART) ^[5].

Rational drug design of the HIV-PIs as peptidomimetics—based on the amino acid sequence recognized by the HIV aspartyl protease—was intended to drive competitive binding of the drug at the active site of the enzyme and disrupt the enzyme–substrate reaction ^[6]. Mammalian aspartyl proteases are weaker in cleaving and inhibiting maturation of HIV polyproteins than the HIV-residing enzyme; thus, it was expected that the HIV-PIs would spare the human proteases and induce minimal toxicity. However, soon after the introduction of the HIV-PIs in the HAART protocol, pleiotropic off-target effects of the HIV-PIs were reported. The emergence of reports of remission from AIDS-associated cancers suggested anti-neoplastic properties of HIV-PIs to be a potentially important off-target effect. For instance, Niehuse et al. reported a case of complete regression of AIDS-associated Kaposi's sarcoma (KS) in a 5-year-old child undergoing HAART regimen consisting of HIV-PI nelfinavir and reverse transcriptase inhibitors zidovudine and lamivudine ^[7]. Lebbé ^[8] and Krischer ^[9] also reported regression of KS in HIV-infected adults undergoing combination therapies of HIV-PIs and reverse transcriptase inhibitors. Initially, the reduction in AIDS-associated cancers was attributed to the immune reconstitution of the body as a result of improved CD4+ T cell count and the reduction in overall viral load; however, later reports suggested that direct off-target anti-cancer action by HIV-PIs could be possible. Sgadari et al. suggested that the antiangiogenic properties of indinavir and saquinavir contributed to the regression of Kaposi's sarcoma in mice models ^{[10][11]}, whereas Schmidtke et al. demonstrated that ritonavir could affect the cellular proteasome activity in addition to its immunomodulatory and virus-reducing actions ^[12]. Thus, multiple preclinical reports suggesting the pleiotropic effects of HIV-PIs initiated the research for their possible anti-neoplastic properties.

Nelfinavir is a first-generation HIV-PI, which was approved by the FDA in March 1997^{[13][14]} for treating HIV infection. Due to the emergence of second- and third-generation HIV-PIs, nelfinavir has been progressively displaced from the HAART protocol ^[15]; however, nelfinavir exhibited maximum anti-neoplastic efficiency among the HIV-PIs. Wu et al. suggested that a unique cis-decahydroisoquinoline-2 carboxamide moiety may be responsible for the higher anti-neoplastic efficiency of nelfinavir. Analysis through a bioinformatical virtual docking system suggested that nelfinavir can potentially bind at the ATP binding site of the EGFR (ERBB1) protein, which was structurally compared with the same-site binding of the EGFR inhibitor lapatinib ^[16]. Further molecular docking approaches predicted the probability of binding of nelfinavir with cellular kinases ^[17] and Hsp90 β protein ^[18], which may also contribute to its anti-cancer properties. In 2007, in a landmark paper by Gills et al., the preclinical anti-neoplastic efficiency of nelfinavir was demonstrated in the NCI60 cancer cell panel ^[19].

Long-term treatment with nelfinavir in HIV-infected patients led to adverse events such as hyperglycemia, insulin resistance, and lipodystrophy, denoting mechanisms of action of nelfinavir disparate from its anti-viral activity [1]. One of the mechanisms by which insulin resistance is triggered in the body is by the inhibition of the IGF/Akt pathway, which is upregulated in many cancers. Thus, from the observation of insulin resistance, it was postulated that nelfinavir could act as an inhibitor of the Akt pathway in cancer, which was later demonstrated in preclinical studies [19]. To date, multiple research groups have used multipronged approaches to understand and implement the anti-cancer properties of nelfinavir in preclinical settings and clinical trials, with the aim of repositioning the drug as a potential chemotherapeutic agent against a multitude of cancers.

Repositioning already approved drugs for cancer therapeutics is desirable for two reasons: to reduce the timeframe of the drug development pipeline, and to increase the affordability of chemotherapeutics for patients. At present, it takes approximately a decade to go from target identification to FDA approval of a new drug, and these new drugs themselves remain cost prohibitive for large segments of the population, especially in low-income countries. Data available from preclinical studies and toxicity profiling may contribute to the rapid repurposing of nelfinavir in the clinical setting. Furthermore, the recent emergence of nelfinavir in generic form [20] following patent expiration may reduce the cost of treatment as a result of drug repurposing. Minimal toxicity in clinical trials and ease of introduction through oral route may also be an important consideration for repurposing nelfinavir.

2. Current Status of Clinical Trials: Anti-Tumor Effects

Promising preclinical data regarding nelfinavir, as a single agent or in combination with other cancer therapies, on multiple cancers, prompted a series of clinical trials. For instance, Rengan and colleagues reported the outcome of a phase I/II trial of nelfinavir with concurrent chemoradiotherapy on locally advanced unresectable stage IIIa/IIIb NSCLC [21][22]. In the phase I study, the maximum tolerated dose of nelfinavir was determined to be 1250 mg per oral route twice daily. Nelfinavir was administered 7 to 14 days prior to and concurrently with cisplatin, etoposide, and radiotherapy at a 66.6 Gy dose. No significant predetermined dose-limiting toxicity was observed. Five of the nine evaluable patients showed complete response, whereas the remaining four patients showed partial response in post-treatment positron emission tomography (PET)-derived metabolic evaluation [21]. The phase I study progressed into a phase II study where 35 patients with locally advanced unresectable stage IIIa/IIIb NSCLC were treated with nelfinavir with concurrent chemoradiotherapy. Observed median survival was 41.1 months and a median progression-free survival was 11.7 months without any unexpected grade 3 or 4 toxicities beyond those of standard chemoradiotherapy [22].

Radiotherapy is a front-line management option for inoperable locally advanced pancreatic cancer (LAPC); however, resistance to radiation is frequent and local disease progression leads to the demise of patients. In the preclinical setting, nelfinavir was shown to increase the sensitivity to radiation via the downregulation of Akt [23], reducing hypoxia [24], and improving tumor microvasculature [25]. Brunner et al. first reported a phase I trial with the use of nelfinavir in conjunction with chemoradiotherapy in inoperable LAPC patients [26]. In this study, 12 patients started nelfinavir three days before the initiation of radiation therapy and chemotherapy with cisplatin and gemcitabine. Of the 10 evaluable patients, 5 showed complete metabolic response in PET and 6 underwent secondary resection. The median overall survival was 18 months, and most patients showed downregulation of p-Akt in PBMCs. Nelfinavir did not contribute to additional or unexpected toxicity to the regimen [26]. The study escalated into phase II, where 23 patients with estimated life expectancy ≥ 12 weeks received nelfinavir 1250 mg twice daily prior to and concurrently with radiotherapy and chemotherapy (cisplatin and gemcitabine) [27]. In this study, the median overall survival time was 17.4 months, (90%CI: 12.8–18.8%) and one-year overall survival rate was 73.4% (90% CI: 54.5–85.5%). Four of the six recruited patients for a sub-study showed reduced hypoxia in 18F-fluoromisonidazole positron emission tomography (FMISO-PET) with a concurrent increase in computed tomography (CT) perfusion denoting increased blood flow. Additionally, 8 of 13 evaluable patients demonstrated the downregulation of p-Akt following initial nelfinavir treatment. However, a high incidence of grade 3 or above gastrointestinal toxicity raised concern, which was attributed to the gemcitabine-cisplatin combination with concurrent large-field radiotherapy [27][28]. To address the need to optimize the chemoradiation regime for LAPC, a large-scale multicenter randomized study SCALOP-2 began in March 2016. The study aims at investigating the benefit of induction-chemotherapy by gemcitabine and nab-paclitaxel followed by escalating doses of radiation with or without the radiosensitizer nelfinavir [28]. Recently, Lin et al. reported two trials testing the simultaneous use of nelfinavir with stereotactic body radiotherapy (SBRT) on patients having locally advanced or unresectable pancreatic adenocarcinoma [29][30]. In the phase I study, patients received three-week cycles of gemcitabine/leucovorin/fluorouracil

followed by combinations of nelfinavir and escalating doses of radiation therapy. In this study, a median overall survival was estimated to be 14.4 months, and the maximum tolerated dose combination was deemed SBRT (40 Gy)/nelfinavir (1250 BID) [29]. Additionally, in a prematurely terminated trial, Lin et al. tested a chemoimmunotherapy combination gemcitabine/leucovorin/fluorouracil/oregovomab followed by SBRT (40 Gy)/nelfinavir (1250 BID) in LAPC patients [30].

In a few studies, nelfinavir was tried as a monotherapy, unlike the mostly tested regimen of nelfinavir in combination with chemotherapy and with or without radiation therapy. Hoover et al. reported a phase II clinical trial in patients with recurrent adenoid cystic carcinoma who no longer responded to the available standard therapeutic options. Patients received doses of 1250 mg of nelfinavir twice daily; however, the progression-free survival did not improve significantly [31]. Conversely, in a phase I study conducted by Pan et al., 6 patients out of 20 (30%), having recurrent, metastatic or unresectable liposarcoma, showed clinical benefits at different dose levels of nelfinavir [32]. Nelfinavir was reasonably tolerated without any dose-limiting toxicity, and dose escalation was effective up to 3000 mg due to auto-induction of increased plasma clearance at higher doses [32]. Blumenthal et al. investigated the effects of nelfinavir monotherapy on adults having advanced solid refractory tumors of different origins [33]. Patients showed well tolerability to nelfinavir with manageable toxicities and the maximum tolerated dose was determined at 3125 mg. Dose-limiting toxicity was reported as grade 4 neutropenia at a high dose level (3750 mg), which was reversible quickly upon temporary discontinuation of the treatment. Out of 28 patients, one showed partial response, three showed minor response and six showed stable disease on tumor evaluation. Importantly, this study reported the beneficial effect of nelfinavir on a neuroendocrine tumor (NET). Patients showed decreased p-Akt, enhanced p-eIF2 α and enhanced expression of ATF3 and CHOP analyzed from PBMCs following nelfinavir treatment [33].

Decreased UPR, especially silencing of IRE1 α /XBP1 in MM cells has been shown to confer resistance to proteasome inhibitor bortezomib [34]. In a phase I study, Driessen et al. observed the upregulation of UPR proteins in response to nelfinavir—with or without bortezomib—in PBMCs of advanced MM patients [35]. Among six bortezomib and lenalidomide refractory MM patients, three showed partial response, and two demonstrated minor response to the combination of nelfinavir (2 \times 2500 mg) and bortezomib. Nelfinavir also showed mild inhibition of proteasome activity, which was further enhanced by bortezomib [20][35]. In a phase II trial 34 patients of bortezomib-refractory MM, a twice daily dose of 2500 mg of nelfinavir lead to an objective response rate of 65% (90% CI, 49–76%) and was observed with 12 weeks of progression-free survival and a median overall survival of 12 months [20]. Recently, Hitz et al. reported a regime of nelfinavir/lenalidomide/dexamethasone, a triad of orally given drugs, tried on 29 patients with lenalidomide refractory MM [36]. Ten of the 29 patients had lenalidomide-bortezomib double-refractory MM; 16 patients showed minor response or better (55%, 95% CI 36–74%), and 9 patients showed partial response (31%, 95% CI 15–51%), with median overall survival of 21.6 months. Lenalidomide and nelfinavir both act as substrates for multidrug-resistant 1 (MDR-1) pump which may have caused competing interaction and inhibited drug efflux, thereby increasing intracellular concentration and clinical effects [36].

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Keywords

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