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Targeting Hsp90: small-molecule inhibitors and their clinical development

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Abstract

The Hsp90 multichaperone complex has important roles in the development and progression of malignant transformation. Several small-molecule inhibitors of Hsp90 of diverse chemotypes have shown potent antitumor activity in a wide-range of malignancies, and are currently in clinical or late-stage preclinical investigation. This review intends to update the reader on advances made over the past two years in the clinical development of Hsp90 inhibitors in advanced cancers. It will refer to the two 17-AAG formulations, tanespimycin and IPI-504, and to synthetic small molecules, among which are the purine-scaffold Hsp90 inhibitor CNF2024/BIIB021, the isoxazole derivative VER-52296/NVP-AUY922, and the carbazol-4-one benzamide derivative SNX-5422, and will present our current knowledge on their clinical performance.

Introduction

The Hsp90 superchaperone complex has wide-ranging functions that result from the ability of this sophisticated machinery to assist in the folding and function of a variety of oncogenic 'client proteins' [1,2]. In this sense, multiple proteins involved in cell-specific oncogenic processes have been shown to be tightly regulated by the binding of the Hsp90 machinery. These include BCR-ABL in the chronic myelogenous leukemia (CML) [3], nucleophosmin-anaplastic lymphoma kinase (NPM-ALK) in lymphomas [4], mutated FLT3 in acute myeloid leukemia [5], EGFR harboring kinase mutations in nonsmall cell lung cancer (NSCLC) [6], the zeta-associated protein of 70 kDa (ZAP-70) as expressed in patients with aggressive chronic lymphocytic leukemia (CLL) [7], mutant B-Raf in melanoma [8], human epidermal growth factor receptor 2 (HER2) in HER2-overexpressing breast cancer [9], mutant c-Kit in gastrointestinal stromal tumors (GIST) [10], and activated Akt in small cell lung carcinoma [11], to list a few. It is now accepted that at the phenotypic level, the Hsp90 machinery serves as a biochemical buffer for the numerous cancer-specific lesions that are characteristic of diverse tumors. Pharmacologic inhibition of Hsp90 by structurally diverse small molecules destabilizes the cancer cell's aberrant protein subset, leading to protein degradation by the 26S proteasome [12]. Selective depletion of the cancer cell's malignancy driving molecules results in growth arrest, apoptosis, and renders cells vulnerable to the actions of chemotherapeutic interventions that otherwise afford limited benefit [1,2]. Moreover, cancer cells are selectively sensitive to pharmacologic Hsp90 inhibitors, and administration of these agents to multiple cancer animal models results in significant antitumor effects associated mostly with little or no target-associated toxicities [1,2,13].

The successful validation of Hsp90 as a target in cancer through the use of pharmacologic agents has catalyzed the development of these small-molecule tools into anticancer therapeutics [14]. This review will focus on advances made over the past two years in the clinical translation and development of several Hsp90 inhibitor chemotypes.

Geldanamycin-based Hsp90 inhibitors

The first Hsp90 inhibitor to enter clinic was the geldanamycin (GM) derivative 17-allylamino-17-desmethoxygeldanamycin (17-AAG) (Figure 1). Initial clinical evaluation of 17-AAG was of limited success, with hints of activity demonstrated in melanoma, where stable disease (SD) was reported [14]. Improvements in this drug's formulation and delivery have led to more encouraging results in several difficult-to-treat patient populations. Kosan Biosciences has developed both a Cremophor-containing formulation and an injectable suspension formulation of 17-AAG (tanespimycin, KOS-953). At the 2007 Annual Meeting of the American Society of Hematology (ASH), results of a Phase Ib dose-escalating trial that evaluated tanespimycin with bortezomib in patients with relapsed, refractory multiple myeloma were reported [15]. Dose escalations in the entire trial ranged from 100 to 340 mg/m² for tanespimycin, and from 0.7 to 1.3 mg/m² for bortezomib. In the bortezomib-naïve group, the overall response rate (complete, partial, and minor responses) was 47% (9 out of 19 evaluable patients), including 2 complete responses (CRs), 1 near-CR, 2 partial responses (PRs), and 4 minor responses (MRs). In the bortezomib-pretreated group, the overall response rate was 47% (7 out of 15 evaluable patients; 1 CR, 2 PR, and 4 MR). In the bortezomib-refractory group, the overall response rate was 17% (3 out of 18 evaluable patients; 3 PR). In an interesting twist, neuropathy cases, a common side effect seen with bortezomib, were fewer in the combination studies than in bortezomib alone, suggesting a possible neuroprotective effect of tanespimycin. Although the mechanism of this effect has not been yet elucidated, it may relate to induction of Hsp70, a chaperone with antiapoptotic and misfolding-protective abilities, by Hsp90 inhibitors [16]. Kosan has been granted orphan drug status for tanespimycin in multiple myeloma in the US and in Europe (<http://www.kosan.com/clinical-programs.html>).

Tanespimycin has also recently demonstrated promising antitumor activity and tolerability in a Phase II trial in patients with HER2-positive metastatic breast cancer, when administered in combination with trastuzumab (Herceptin®) in patients whose disease progressed following treatment with trastuzumab [17]. Twenty-five patients were enrolled onto four tanespimycin dose levels: 225 mg/m² (*n* = 4), 300 mg/m² (*n* = 3), 375 mg/m² (*n* = 8), and 450 mg/m² (*n* = 10). On subsequent weeks, trastuzumab 2 mg/kg was administered over 30 min, followed by tanespimycin. One patient with trastuzumab-refractory HER2-positive breast cancer had a confirmed PR by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Three additional patients with HER2 amplified breast cancer had tumor regressions of 25, 22, and 21%. Overall, the noted antitumor activity was one PR, four MR, and four SD. Interestingly, tumor regressions were seen only in patients with HER2-positive metastatic breast cancer. An update of the trial was presented at the 2008 ASCO meeting, with a reported 24% response rate and a clinical benefit rate of 57% [18]. Recently, Bristol-Myers Squibb has agreed to acquire Kosan, and continue the development of tanespimycin in MM and metastatic breast cancer (http://newsroom.bms.com/article_display.cfm?article_id=5336).

In a different approach, Infinity Pharmaceuticals has developed a reduced form of 17-AAG, retaspimycin, also known as IPI-504 (Figure 1), that, when isolated as a hydrochloride salt, is water soluble [19]. Data from Infinity's open-label, dose-escalation Phase I clinical trial of retaspimycin hydrochloride in patients with metastatic and/or unresectable GIST were presented at the American Society of Clinical Oncology (ASCO) 2008 Annual Meeting [20]. Although no RECIST-defined responses were observed, 29 of 37 evaluated patients (78%) had

a best response of stable disease. Expansion of the twice-weekly IPI-504 for two weeks with one week of treatment at 400 mg/m² cohort is ongoing. Preliminary data from the Phase I portion of Infinity's open-label Phase I/II clinical trial of retaspimycin hydrochloride in patients with advanced metastatic NSCLC were presented at the AACR-NCI-EORTC International Conference in October 2007 [21]. Preliminary evidence of biological activity was reported in a heavily pretreated population of patients. In seven of nine evaluable patients, disease stabilization by RECIST was achieved over at least one cycle of administration. One patient with a mutation in EGFR and prior history of progression on targeted kinase inhibitors experienced SD for more than six months.

A second-generation GM-derivative, 17-dimethylaminoethylamino-17-desmethoxygeldanamycin (17-DMAG) also known as Alveospimycin and KOS-1022 has also entered Phase I clinical testing (Figure 1). Promising early results were reported in a Phase I trial of 17-DMAG in patients with chemotherapy refractory acute myelogenous leukemia in which 3 of 17 patients had a CR to therapy [22]. Owing to an unfavorable overall toxicity profile, however, Kosan has halted Alveospimycin's clinical development in March 2008.

Although these results are proof for the successful targeting of Hsp90 in clinical settings, several issues intrinsic to the chemical structure of 17-AAG have precluded fulfilling the maximal potential of this target in cancer [23]. The molecule contains a benzoquinone moiety that has been made accountable for the observed elevation of liver enzymes and liver toxicity in clinical settings. Additionally, expression of P-glycoprotein (P-gp) or loss or mutation of the NQO1 gene that is required for the bio-reduction of 17-AAG to the more potent hydroquinone have been proposed as mechanisms of *de novo* or acquired resistance to 17-AAG. For reasons not yet clearly understood, 17-AAG is also less potent in several tumor types sensitive to other Hsp90 inhibitor chemotypes (reviewed in [23]).

Synthetic Hsp90 inhibitors

Novel synthetic Hsp90 inhibitors based on diverse chemical scaffolds have been developed, and several are currently undergoing Phase I/II clinical evaluation in cancers. These are reported to generally have an improved pharmacologic profile when compared to 17-AAG, especially with regard to their availability through synthesis, evasion of multidrug resistance (MDR)-mediated efflux, metabolic stability, water solubility and ease of administration, and retained biological activity over a wider panel of tumors [24,25]. The first synthetic Hsp90 inhibitor to enter clinic is CNF2024/BIIB021, an Hsp90 inhibitor developed initially by Conforma Therapeutics (currently Biogen Idec) based on the purine-scaffold discovered by investigators at Memorial Sloan-Kettering Cancer Center through structure-based design (Figure 1) [24]. There are currently several ongoing Phase I trial studies of oral CNF2024/BIIB021 in advanced solid tumors, lymphomas, B cell CLL, and in HER2-advanced breast cancer, alone or in combination with trastuzumab. Results of the Phase I trials were recently released at the ASCO meeting, 2008 [26]. CNF2024/BIIB021 appeared to be well tolerated, and a dose of 800 mg twice weekly appeared as maximally tolerated. Biological activity was observed with significant induction of Hsp70 and inhibition of the HER2 bio-marker extracellular domain in solid tumors. In CLL, 1 patient at 25 mg had a 39% reduction in lymph nodes, whereas in solid tumors, 11 of 16 patients (68%) reported stable disease. A Phase II evaluation of CNF2024/BIIB021 in patients with GIST was started in March 2008, in which pharmacodynamic assessment of tumor response by 18FDG-Positron Emission Topography has been implemented (<http://www.clinicaltrials.gov/>).

A second synthetic Hsp90 inhibitor to enter clinic is VER-52296/NVP-AUY922 currently in development by Novartis [27]. The lead compound that resulted in AUY922 was a pyrazole scaffold derivative identified through a highthroughput screening effort by investigators at the

Royal Cancer Institute, and further developed in collaboration with Vernalis [25]. A Phase I–II trial of intravenously administered AUY922 is currently open (<http://www.clinicaltrials.gov/>), with the Phase I portion of the trial recruiting patients with several types of cancer, whereas the Phase II portion is limited to patients with either HER2 positive or ER positive locally advanced or metastatic breast cancer.

SNX-5422 is a small-molecule Hsp90 inhibitor based on the 6,7-dihydro-indazol-4-one scaffold (Figure 1) [28]. This agent developed by Serenex, converts to SNX-2122, which is the active Hsp90 inhibitor form (Figure 1). A Phase I trial of orally administered SNX-5422 mesylate opened in late May 2007 in patients with refractory solid tumor malignancies. The results of a Phase I dose-escalation study on the safety and pharmacokinetics of SNX-5422 were disclosed at the ASCO 2008 meeting [29]. The agent was well tolerated at low doses and is currently enrolling at 21 mg/m². In March 2008, Pfizer Inc has announced that it has entered into an agreement to acquire Serenex, Inc (http://pfizer.com/news/press_releases/pfizer_press_releases.jsp).

STA-9090, developed by Synta Pharmaceuticals is claimed to have a chemical structure unrelated to the ansamycin family of Hsp90 inhibitors, such as 17-AAG. STA-9090 is currently enrolling patients in two dose-ranging Phase I clinical trials in solid tumors. The trials are open-label studies in patients with solid tumors and are designed to identify the maximum tolerated dose of STA-9090 based on a twice-a-week or once-a-week intravenous dosing schedule (<http://www.syntapharma.com/PrdHsp90.aspx>).

Conclusions

In conclusion, several Hsp90 inhibitors have now entered clinical evaluation. One lesson from these trials is that the more we have learned how to administer these agents, the better the clinical outcomes have become. It is now expected that through new formulations of 17-AAG and through the novel synthetic Hsp90 inhibitors, also orally administrable, it will be possible to more favorably modulate the schedule and dose these inhibitors are given. It is the hope that these advances will increase the efficacy with which we can deliver these agents to patients, with the promise of better clinical outcomes in a wider range of cancers to follow.

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Figure 1.

Chemical structure of several Hsp90 inhibitors currently in clinical evaluation in patients with advanced cancers.