Effects of treatment with an Hsp90 inhibitor in tumors based on 15 phase II clinical trials

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Abstract. Heat shock protein (Hsp)90 serves as a chaperone protein that promotes the proper folding of proteins involved in a variety of signal transduction processes involved in cell growth. Hsp90 inhibitors, which inhibit the activity of critical client proteins, have emerged as the accessory therapeutic agents for multiple human cancer types. To better understand the effects of Hsp90 inhibitors in cancer treatment, the present study reviewed 15 published phase II clinical trials to investigate whether Hsp90 inhibitors will benefit patients with cancer. Information of complete response, partial response, stable disease, objective response and objective response rate was collected to evaluate clinical outcomes. Overall, Hsp90 inhibitors are effective against a variety of oncogene-addicted cancers, including those that have developed resistance to specific receptors.

Introduction

Tumors are one of the most common lethal diseases worldwide, with 14 million new cases diagnosed annually. They are also the leading cause of mortality worldwide, causing 8.2 million mortalities annually, as reported in the World Health Organization World Cancer Report 2014. Although cytotoxic chemotherapy has revolutionized the prognosis for patients with most tumor types, survival remains dismal as a whole and exploring the novel therapeutic approaches is required. Considering that oncoproteins serve a pivotal role in tumorigenesis, molecular target therapies in different types of tumor have been more and more crucial and promising.

The molecular chaperone, heat shock protein (Hsp)90, serves an important role in the formation, stability and function of the proteins involved in cell growth and survival signaling pathways (1). The ability of Hsp90 to chaperone protein kinases or transcription factors is dependent on the binding and hydrolysis of ATP at its binding domain (2). Accordingly, multiple mitogenic pathways may be inhibited by synthetic inhibitors of the Hsp90 ATPase activity, including 17-allylamino-17-demthoxygeldanamycin (17-AAG), ganetespib, retaspimycin HCl (IPI-504) and BIIB021 (3-7). Evidence of the activity of Hsp90 inhibitors was shown *in vitro,* and animal models of different types of tumor and numerous clinical trials were performed to search for novel treatments against tumors (8-12). The present study summarized 15 phase II clinical trials using Hsp90 inhibitors and found that the lack of efficacy of Hsp90 inhibitors in these initial phase II studies may be due to the treatment-associated toxicity limitation, accounting for insufficient dose of drug or infrequent schedule of administration, which in turn leads to inadequate inhibition of target proteins. Additionally, the clinical activity of Hsp90 inhibitors suggested a potential cancer therapy against a variety of oncogene-addicted cancer types, including those that have developed resistance to specific receptors.

Methods and materials

Identification of eligible studies. PubMed (http://www.ncbi.nlm.nih.gov/pubmed) was searched using the search terms (last search updated 10th December 2015) 'Hsp90 inhibitor' and 'cancer' with no limitations. In addition, another search strategy was also performed using the terms 'Hsp90 inhibitor' (limited to humans), 'clinical trial' and 'cancer'. Information found on the ClinicalTrials.gov website (www.clinicaltrials.gov), a registry and results database of publicly and privately supported clinical studies using human participants performed worldwide, was also reviewed. All relevant publications were reviewed and duplications of articles from the two search strategies were eliminated. The articles in reference lists were also hand-searched for potentially relevant publications. The search was performed by two investigators. Any disagreements were resolved by consensus with the involvement of a third author.

Inclusion criteria. All human-associated studies, regardless of tumor types, were included once they met the following criteria: Malignant tumor, monotherapy with Hsp90 inhibitor or Hsp90 inhibitor combined with other antitumor drugs,

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histological confirmation, relatively stable administration dosage of Hsp90 inhibitor and sufficient data of clinical outcomes.

Data extraction. Two investigators extracted data independently and reached a consensus on all items. For each study, the following information was collected: First author, year of publication, country of the first author, the number of total and evaluable patients, median age, gender, cancer type, stage, prior treatment, name of Hsp90 inhibitor or other combined drugs, dose regimen, median cycle of treatment, clinical outcomes, including the number of patients who achieved stable disease (SD), partial response (PR), complete response (CR), objective response (OR) or progressive disease (PD). Other evaluation data, including the median overall survival (OS), progression-free survival (PFS), time to progression (TTP) and response of duration (DR) were also collected. For studies including different tumor types, data were extracted separately by tumor types if there was enough information in the text. Additionally, the studies mentioning genomic alteration were extracted separately to investigate if Hsp90 inhibitors have the ability to overcome resistance to receptor-specific targeted treatments.

Results

Literature search. A total of 1,261 published articles were identified from PubMed and 1,110 duplicated and unrelated articles were excluded. Within the remaining 50 publications related to clinical trials, articles were excluded if administration dosage of Hsp90 inhibitor was not stable; all Phase I studies were excluded for this reason. Therefore, a total of 15 articles were eligible for assessment in the present study. Of these 15 articles, 9 mentioned that genomic alteration were extracted separately, as discussed later.

Due to the heterogeneity of patients, Hsp90 inhibitor types, regimens, clinical settings and a large variety of outcome measurement used in these trials and pooling of data for meta-analysis was inappropriate. The results were, therefore, summarized qualitatively.

Study characteristics. Details from 15 eligible trials published between 2006 and 2014 were analyzed in Table I. All first authors were based in the USA. The number of patients in these trials ranged between 11 and 99, with the median age between 51 and 68 years. A total of 10 types of cancer were described in these 15 trials, including breast cancer (13-16), ovarian carcinoma (17), peritoneal carcinoma (17), multiple myeloma (18), renal cell cancer (19), prostate cancer (20,21), melanoma (22,23), colorectal cancer (24), lung cancer (25,26) and gastrointestinal stromal tumor (GIST) (27). The majority of patients had received prior therapies and had metastatic or recurrent diseases at baseline.

Treatment administration. Details of eligible trials with an Hsp90 inhibitor were noted in Table II. The majority of Hsp90 inhibitors were tested in trials of monotherapy: 17-AAG (13,19,20,23), ganetespib (15,24,25), IPI-504 (21,26) and BIIB021 (27). There were also trials of combination of Hsp90 inhibitors, 17-AAG (14,17,18)/IPI-504 (16), with other anticancer drugs, including cytotoxic and molecularly targeted agents.

The majority of Hsp90 inhibitors were administered by intravenous infusion. For 17-AAG, the dosage was 50/175/220/340 mg/m^2 on days 1, 4, 8 and 11 of a 21-day cycle; or 300/450 mg/m^2 on days 1, 8 and 15 of a 28-day cycle; 154 mg/m^2 on days 1, 8 (1,9) of a 21-day cycle; 450 mg/m^2 weekly. For ganetespib, the dosage was 200 mg/m^2 on days 1, 8 and 15 of a 28-day cycle. For IPI-504, the dosage was 400 mg/m^2 on days 1, 4 8 and 11 of a 21-day cycle or 300 mg/m^2 weekly. Treatment with BIIB021 was administered as a 600 mg dose twice a week or 400 mg three times a week. The median cycle of each treatment was summarized in Table II.

In trials combining an Hsp90 inhibitor with other drugs, three added the molecularly targeted agent trastuzumab/bortezomib to 17-AGG or IPI-504, and one added the cytotoxic drug gemcitabine to 17-AGG (14,16-18). The median cycle of each treatment was summarized in Table II.

Clinical outcomes. Response criteria were used, as defined by the Response Evaluation Criteria in Solid Tumors (12-15, 17,20,22-26), the European Group for Bone and Marrow Transplantation criteria (18), the Prostate-Specific Antigen Working Group (19), the NCI Prostate-Specific Antigen Working Group (21) and the EORTC guidelines (27). Overall, Hsp90 inhibitors are effective against a variety of oncogene-addicted cancer types, including those that have developed resistance to specific receptors.

Of the 15 trials that used Hsp90 inhibitors, OR was observed in 7 studies, with ORR ranging between 0.04 and 0.22, demonstrating that in tumors driven by client proteins are hypersensitive to Hsp90 inhibition at the currently deliverable doses and schedules (14,15,17,18,25-27). Modi *et al* (14) demonstrated that 17-AAG is effective in advanced trastuzumab-refractory human epidermal growth factor receptor (HER)2-positive breast cancer. In that previous study, the OR was 22%, the clinical benefit rate (CR + PR + SD) was 59%, the median PFS was 6 months and the median OS was 17 months. Consistent results were observed in metastatic breast cancer (MBC) that used ganetespib as a single agent, the clinical benefit rate (CR + PR + SD >6 months) was 9%, median PFS was 7 weeks and median OS was 46 weeks (15). Socinski *et al* (25) found that ganetespib showed encouraging single-agent activity in heavily pretreated chemotherapy patients with advanced non-small cell lung cancer (NSCLC) that harbored anaplastic lymphoma kinase (ALK) rearrangement. Sequist *et al* (26) observed the identical phenomenon in the trial using IPI-504. Among the three patients with NSCLC harboring the ALK rearrangement, which progressed following epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy, two had PR and the third had prolonged SD. OR was also observed in trials that used 17-AAG combined with gemcitabine (17) or bortezomib (18). This was also observed in trials combining IPI-504 with these drugs (27). The authors hypothesized that an Hsp90 inhibitor performed the action efficiently by degrading the client proteins, including Chk1, proteasome, c-Kit and platelet-derived growth factor receptor α. The results mentioned above were relative to oncogenes, and therefore, the present study extracted trials using the Hsp90 inhibitor in tumors harboring genotype alteration to explore whether the Hsp90 inhibitor has the ability to overcome

Table I. Characteristics of trials using an Hsp90 inhibitor.

		Patient characteristics						
Trial	Authors, year	Total number	Median age (years)	Gender (male/female)	Cancer type	Status	Prior treatment (no. patients)	(Refs.)
1	Gartner *et al*, 2012	11 (7[a])	54	0/11	Breast	Locally advanced or metastatic	Chemotherapy (all) Hormonal therapy (all)	(13)
2	Modi *et al*, 2011	31 (27[a])	53	1/30	Breast	Metastatic	Chemotherapy (n=25) Trastuzumab therapy (all)	(14)
3	Jhaveri *et al*, 2014	22 (6/13/3)[f]	51	0/22	Breast	Metastatic	Chemotherapy (all) Trastuzumab therapy (n=12)	(15)
4	Modi *et al*, 2013	26	53	1/25	Breast	Locally advanced or metastatic	Chemotherapy (all) trastuzumab therapy (all)	(16)
5	Hendrickson *et al*, 2012	29 (11/14[a])[b]	68/65.5	0/25	Ovarian Peritoneal	Relapsed or persistent	Chemotherapy (n=25)	(17)
6	Richardson *et al*, 2010	22 (8/8/6)[c]	62.5	14/8	Multiple myeloma	Relapsed or refractory	Prior-SCT (n=18) Chemotherapy (all)	(18)
7	Ronnen *et al*, 2006	20 (12/8)[d]	68	14/6	Renal	Metastatic	Nephrectomy (n=8/7) Radiation (n=4/2) Immunotherapy (n=11/2) Chemotherapy or hormonal (n=2/0)	(19)
8	Heath *et al*, 2005	17 (15[a])	68	15/0	Prostate	Metastatic	Prostatectomy (n=5) Chemotherapy (n=13) Radiation therapy (n=12) Androgen ablation (n=14)	(20)
9	Oh *et al*, 2011	19 (4/15)[h]	68.5/60	0/19	Prostate	Castration-resistant	Chemotherapy (n=15) hormonal therapy (majority of patients)	(21)
10	Solit *et al*, 2008	15 (6/9)[e]	66/55	12/3	Melanoma	Stage III/IV	Chemotherapy (n=5/9)	(22)
11	Pacey *et al*, 2012	14 (11[a])	60	8/6	Melanoma	Metastatic	Surgery (n=14) Chemotherapy (n=13) Radiotherapy (n=2) Immunotherapy (n=5) Molecularly targeted agent (n=5) Isolated limb perfusion (n=2)	(23)

Table I. Continued.

Trial	Authors, year	Patient characteristics			Cancer type	Status	Prior treatment (no. patients)	(Refs.)
		Total number	Median age (years)	Gender (male/female)				
12	Cercek *et al*, 2014	17	58	11/6	Colorectal	Metastatic	Chemotherapy (all) Anti-EGFR (patients with KRAS wild-type: 6)	(24)
13	Socinski *et al*, 2013	99 (15/17/66)[g]	61	47/52	Lung (NSCLC)	Stage IIIB/IV	Systemic therapy (all)	(25)
14	Sequist *et al*, 2010	76	64	28/48	Lung (NSCLC)	Stage IIIB/IV	Systemic therapy (all) EGFR TKIs (all)	(26)
15	Dickson *et al*, 2013	23	59	14/9	GIST	Refractory	Imatinib (all) sunitinib (all) sorafenib (n=14) nilotinib (n=2)	(27)

[a]The number of patients eligible for the assessment of clinical outcomes. [b]Patients enrolled in two groups, eotjer exposure to gemcitabine or not, which also apply to the following data. [c]Patients were divided into three groups of dosage with 340, 175 or 50 mg/m^2. [d]Patients enrolled in clear-cell RCC cohort or papillary RCC, which also apply to the following data. [e]Patients with wild-type or mutant BRAF. [f]Subtype of ER(+)/HER-2(-), HER-2(+) and triple negative breast cancer. [g]Subtype of mutant EGFR, mutant KRAS and wild-type EGFR or KRAS. [h]Patients of chemotherapy-naïve or docetaxel-treated. SCT, stem cell transplant; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; EGFR, epidermal growth factor receptor: ER, estrogen receptor; HER, human epidermal growth factor receptor; GIST, gastrointestinal stromal tumors; TKIs, tyrosine kinase inhibitors; IVD, intravenous dose; NA, not available.

Table II. Treatment administration and clinical outcomes of the studies that used Hsp90 inhibitor.

		Treatment administration			Clinical outcomes						
Trial	Cancer type	Drug	Dose regime	Median cycles	PR	CR	OR	ORR	SD	PD	Others (median)
1	Breast	17-AAG	220 mg/m^2 IVD on days 1, 4, 8 and 11 of a 21-day cycle	2	0	0	0	0	3	4	PFS: 1 month OS: 10 months
2	Breast	17-AAG + Trastuzumab	450 mg/m^2 iv. + 2 mg/kg iv. weekly (intial dose of 4 mg/kg was >21 days prior to the present study	NA	6	0	6	0.22	10	11	PFS: 6 months OS: 17 months DR: 147 days
3	Breast	Ganetespib	200 mg/m^2 IVD days 1, 8 and 15 of a 28-day cycle	NA	0/2/0[e]	0/0/0	0/2/0	0.09	0/6/1	NA	PFS: 7 weeks OS: 46 week
4	Breast	IPI-504 Trastuzumab	300 mg/m^2 iv. weekly plus trastuzumab 6 mg/kg iv. every 3 weeks (intial dose of 8 mg/kg for patients whose last trastuzumab therapy was >4 weeks prior to study entry)	3[g]	0	0	0	0	16	NA	NA
5	Ovarian Peritoneal	17-AAG + Gemcitabine	154 mg/m^2 iv. on days 1 and 8, days 1 and 9 of subsequent cycles + 750 mg/m^2 iv. gemcitabine on day 7 (days 1 and 8 of subsequent cycles) of a 21-day cycle	4/3.5[a]	0/1	0/0	0/1	0.04	4/2	7/11	OS: 11.5/18.3 months TTP: 2.7/1.6 months
6	Multiple myeloma	17-AAG + Bortezomib	340/175/50 mg/m^2 iv. plus bortezomib + 1.3 mg/m^2 on days 1, 4, 8 and 11 of a 21-day cycle	NA	2	0	3[b]	0.14	10	NA	NA
7	Renal	17-AAG	220 mg/m^2 IVD days 1, 4, 8 and 11 of a 21-day cycle	NA	0	0	0	0	9/5[c]	NA	TTP: 3.3/1.6 months
8	Prostate	17-AAG	300 mg/m^2 IVD days 1, 8 and 15 of a 28-day cycle	2	0	0	0	0	1	13	TTP: 1.8 months 6-month OS: 71%
9	Prostate	IPI-504	400 mg/m^2 IVD days 1, 4, 8 and 11 of a 21-day cycle[h]	2	0	0	0	0	1	NA	NA
10	Melanoma	17-AAG	450 mg/m^2 IVD weekly (6/8-week cycle)	5 dose	0	0	0	0	1	14	NA
11	Melanoma	17-AAG	450 mg/m^2 IVD weekly	10	0	0	0	0	3	8	OS: 232 days
12	Colorectal	Ganetespib	200 mg/m^2 IVD days 1, 8 and 15 of a 28-day cycle	NA	0	0	0	0	2[d]	NA	PFS: 1.6 months OS: 5.1 months 6-month OS: 71%
13	Lung (NSCLC)	Ganetespib	200 mg/m^2 IVD days 1, 8 and 15 of a 28-day cycle	NA	0/0/4[f]	0/0/0	0/0/4	0.04	6/6/26	7/7/26	PFS: 1.9/1.9/1.8 months OS: 7.1/11.0/8.8 months PFS rate at 16 weeks: 13.3/5.9/19.7%

Table II. Continued.

Trial	Cancer type	Treatment administration			Clinical outcomes						
		Drug	Dose regime	Median cycles	PR	CR	OR	ORR	SD	PD	Others (median)
14	Lung (NSCLC)	IPI-504	400 mg/m^2 IVD days 1, 4, 8 and 11 of a 21-day cycle[i]	2	5[j]	0	5	0.07	18	NA	PFS: 2.86 months DR: 120 days
15	GIST	BIIB021	12 patients: 600 mg p.o. twice a week of a 28-day cycle 11 patients: 400 mg p.o. three times a week of a 28-day cycle	NA	3[k]/2	0	5	0.12	4/2[l] 6/4	NA	DR:25-138 days

[a]Patients enrolled in two groups whether exposure to gemcitabine or not, which also apply to the following data. [b]One patient of minimal response in the 340 mg/m^2 dose group and two patients of PR in the 175 mg/m^2 dose group. [c]Nine patients from the clear-cell RCC cohort and five patients from the papillary RCC cohort, which also apply to the following data. [d]Patients with KRAS G12V mutations. [e]Subtype of ER(+)/HER-2(-), HER-2(+) and TNBC, which also apply to the following data. [f]Subtype of mutant EGFR, mutant KRAS and no EGFR or KRAS mutations, which also apply to the following data. [g]Cycle 1 was defined receiving at least two doses of IPI-504. [h]A reduced dose of 300 mg/m^2 due to two mortalities were assessed by the investigator. [i]Due to hepatotoxicities observed at the 400 mg/m^2 dose in a separate trial of IPI-504 in patients with GI stromal tumors, the last enrolled patient started at a dose of 225 mg/m^2. [j]For EGFR status, four patients had EGFR wild-type and one patient had EGFR mutations; for KRAS status, three patients had KRAS wild-type; for ALK status, two patients had ALK rearrangement and one patient had ALK wild-type; [k]evaluated by FDG-PET criteria; [l]evaluated by RECIST and Choi criteria. PFS, progression-free survival; OS, overall survival; TTP, time to progress; NA, not available; DR, response of duration; NSCLC, non-small cell lung cancer; GIST, gastrointestinal stromal tumors; IVD, intravenous dose; RCC, renal cell carcinoma; ER, estrogen receptor; HER, human epidermal growth factor receptor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, objective response; ORR, objective response rate; 17-AAG, 17-allylamino-17-demthoxygeldanamycin; IPL-504, retaspimycin HCl; ALK, anaplastic lymphoma kinase.

Table III. HSP90 inhibitor used in tumors harboring genomic alteration.

Trial	Drug	Cancer status	Genotype	Prior therapy[a]	Total	Response[a]				
						CR	PR	SD	PD	Others ([c])
1	17-AGG	Locally advanced or metastatic breast cancer	TNBC (n=6); HER2(+) (n=0)	Chemotherapy (all); hormonal (all); bevacizumab (n=1); lapatinib (n=1)	11(7[b])	0	0	3	4	PFS: 1 month OS: 10 months
2	17-AGG + Trastuzumab	Advanced trastuzumab-refractory breast cancer	HER2(+) (all)	Chemotherapy (n=25); trastuzumab (all)	31(27[b])	0	6	10	11	PFS: 6 months OS: 17 months DR: 147 days
5	17-AGG	Metastatic melanoma	Wild-type BRAF (n=6); V600E BRAF (n=9)	Chemotherapy (n=5/9)	15	0	0	1	14	NA
6	Ganetespib	Stage IIIB/IV NSCLC	Mutant EGFR (n=15); mutant KRAS (n=17); no EGFR or KRAS mutations (n=66)	Systemic therapy (all); TKI (mutant EGFR, n=14)	98	0/0/0	0/0/4[c]	6/6/26	7/7/26	PFS: 1.9/1.9/1.8 months PFS rate at 16 weeks: 13.3/5.9/19.7%
7	Ganetespib	Metastatic breast cancer	ER(+)/HER2(-) (n=6); HER2(+) (n=13); TNBC (n=3)	Chemotherapy (all); trastuzumab (HER2(+), n=12)	22	0/0/0	0/2/0	0/6/1	NA	PFS: 7 weeks OS: 46 weeks
8	Ganetespib	Metastatic colorectal cancer	KRAS wild (n=6); KRAS mutant (n=10)	Chemotherapy (all); anti-EGFR therapy (KRAS wild-type)	17	0/0	0/0	0/2	NA	PFS: 1.6 months 6-month OS: 41% OS: 5.1 months
10	IPI-504	Advanced or metastatic breast cancer	HER2(+) (all)	Chemotherapy (all); trastuzumab (all)	26	0	0	16	NA	NA
11	IPI-504	Stage IIIB/IV NSCLC	EGFR (wild/mutant) (n=40/28); KRAS (wild/mutant) (n=26/12); ALK (wild/rearranged) (n=12/3)	Systemic therapy (all); TKI (all)	76	0/0 0/00 /0	4/13/ 01/2	10/64 /53/3	NA NA	PFS: 2.86/2.76 months 2.86/3.91 months 2.86 months/NA
12	BIIB021	GIST refractory to imatinib and sunit-inib	KIT exon 11 mutation (n=7); KIT exon 9 mutation (n=1); no detected PDGFRA or KIT mutation (n=1); unknown mutation status (n=14)	Imatinib (all); sunitinib sorafenib (n=14); nilotinib (n=2)	23	0	5	10	NA	

[a]The data separated by separator according to genotype sequence. [b]Median: data are median values. [c]Patients with ALK rearrangement. PFS, progression-free survival; OS, overall survival; TTP, time to progress; NA, not available; DR, response of duration; NSCLC, non-small cell lung cancer; GIST, gastrointestinal stromal tumors; ER, estrogen receptor; HER, human epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, objective response; ORR, objective response rate; 17-AAG, 17-allylamino-17-demthoxygeldanamycin; IPL-504, retaspimycin HCl; PDGFRA, Platelet-derived growth factor receptor α; ALK, Anaplastic lymphoma kinase.

resistance to receptor-specific targeted treatments. The results are shown in Table III.

Additionally, trials that failed to achieve OR are also summarized in Table II. The lack of efficacy of Hsp90 inhibitors in these initial phase II studies may be due to treatment-associated toxicity limitations, accounting for insufficient dose of drug or infrequent schedule of administration, which leads to the lack of adequate inhibition of target proteins.

Discussion

Hsp90 is a chaperone for a wide variety of signaling proteins, many of which serve an important role in tumorigenesis, including HER2, EGFR, Akt, c-RAF, BRAF and re-arranged ALK (28-33). Loss of Hsp90 function leads to ubiquitination and degradation of these proteins, causing cell growth inhibition, apoptosis of tumor cells and antitumor activity in preclinical models (8-12). These preclinical observations have prompted the clinical assessment of Hsp90 inhibitors in various tumor types.

The present review summarized 15 phase II clinical trials of different types of tumor and found that the Hsp90 inhibitor may be a potential agent against tumors via the inhibition of intended client proteins. Modi *et al* (14) and Socinski *et al* (15) have proved the antitumor activity of 17-AAG and ganetespib, respectively, for patients with HER2-positive MBC which progressed following trastuzumab administration. Notably, p95HER2 is an Hsp90 target that is degraded by Hsp90 inhibitors (28). Furthermore, trastuzumab-resistant models with overexpression of p95HER2 are sensitive to Hsp90 inhibitors. Sustained loss of HER2 and p95HER2 expression, and inhibition of AKT activation with regulatory administration of Hsp90 inhibitors resulted in apoptosis of cancer cells and inhibition of tumor growth. Data from previous studies of NSCLC show that lower concentrations of Hsp90 inhibitors may be required to inhibit the expression of echinoderm microtubule associated protein like 4-ALK compared with mutant EGFR, all of which had previously received and acquired resistance to lines of chemotherapy or EGFR TKIs, respectively (25,26). Additionally, induction of small cell histological changes or epithelial-mesenchymal transition may have been present in certain cases and may have contributed to the lack of durable clinical activity for patients with EGFR mutations with Hsp90 inhibitors (29).

Tillotson *et al* (30) revealed that Hsp70 may be a biomarker for predicting the antitumor activity of Hsp90 inhibitors (30). Furthermore, the authors demonstrated that response to Hsp90 inhibitors is correlated to the extent of downregulation of client proteins, which relies on occupancy of Hsp90 (30-33). Inhibition of Hsp90 may induce bortezomib-triggered apoptosis, even in drug-resistant multiple myeloma cells, due to upregulation of plasma Hsp70 and downregulation of proteasomal activity (18). Although partial downregulation of Chk1 was observed after 17-AAG administration, the 17-AAG/gemcitabine combination showed limited anticancer activity in patients with advanced epithelial ovarian and primary peritoneal carcinoma, probably attributed to insufficient downregulation of client proteins, including HER2, insulin-like growth factor 1 receptor, insulin receptor, Akt and c-Raf, at currently used doses (17). Accumulating evidence has suggested that the interaction of client proteins with the Hsp90 chaperone is a multifaceted process, with certain kinases forming stable heterocomplexes with the chaperone machinery and others forming more dynamic complexes that are more readily disassembled, and in which the client is more modestly ubiquitinated (34). These differences may contribute to the hierarchy of sensitivity of clients to degradation.

The lack of efficacy of Hsp90 inhibitors in these initial phase II studies may be due to the treatment-associated toxicity limitation accounting for insufficient dose of drug or infrequent schedule of administration, which leads to the lack of adequate inhibition of target proteins. Although overexpression of Hsp72 and low expression of Hsp90 were detected, the client proteins, including HER2 and cyclin-dependent kinase (CDK)4 depletion were not consistently detected in patients with metastatic melanoma (23). The lack of objective tumor responses is consistent with what has been reported in hormone-refractory prostate cancer (20) and in renal cell carcinoma (19) using lower doses of 17-AAG. No significant changes in interleukin (IL)-6, IL-8 and maspin in metastatic, hormone-refractory prostate cancer with 17-AAG may lead to failure of prostate-specific antigen response (20). Preclinical studies have demonstrated that both suppression of client proteins within 24-72 h and sufficient administration of Hsp90 inhibitors are required to induce antitumor effects (35). At the time of the posttreatment biopsy (median, 44 h after dose 1), an increase in Hsp70 levels and a decrease in cyclin D1 levels were detected (22). These findings, together with the observation of changes in RAF-1 and CDK4 at 24 h in another study (32), suggested that transient decreases in raf kinases, phosphorylated-extracellular signal-regulated kinase-1 and CDK4 may have occurred. However, these changes in the components of the mitogen-activated protein kinase pathway were not sufficient to cause tumor shrinkage. Clinically, frequent dosing schedules have been restricted by the toxicity observed in patients. The death of two patients with castration-resistant prostate cancer, treated with IPI-504 at a dose of 400 mg/m^2 on days 1, 4, 8 and 11 of a 21-day cycle, was a result of drug-related events of hepatic failure and ketoacidosis, respectively (21).

In conclusion, only tumor types driven by client proteins that are hypersensitive to Hsp90 inhibition will be susceptible to the effects of Hsp90 inhibitors at the currently doses and schedules. The present review summarized 15 phase II clinical trials using Hsp90 inhibitors and found that Hsp90 inhibitors may be a potential cancer therapy against a variety of oncogene-addicted cancer types, including those developing resistance to specific receptors.

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