### Evaluation of Plasma Insulin-like Growth Factor Binding Protein 2 and Her-2 Extracellular Domain as Biomarkers for 17-Allylamino-17-Demethoxygeldanamycin Treatment of Adult Patients with Advanced Solid Tumors

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#### Abstract

**Purpose:** Interaction of 17-allylamino-17-demethoxygeldanamycin (17-AAG) with heat shock protein 90 results in proteasomal degradation of many proteins, including Her-2-neu, with subsequent decreased expression of insulin-like growth factor binding protein-2 (IGFBP-2). Concentrations of both IGFBP-2 and Her-2 extracellular domain (Her-2 ECD) in sera of mice bearing BT474 human breast cancer xenografts decrease after 17-AAG treatment. We investigated whether this phenomenon occurred in patients.

**Materials and Methods:** Eight to 15 plasma samples were obtained between 0 and 72 h from 27 patients treated with single-agent 17-AAG at doses between 10 and 307 mg/m² and 18 patients treated with 17-AAG at doses between 220 and 450 mg/m² combined with 70 to 75 mg/m² of docetaxel. Pretreatment plasma samples were also obtained from 12 healthy volunteers. Plasma IGFBP-2 and Her-2 ECD concentrations were quantitated by ELISA.

**Results:** Pretreatment plasma IGFBP-2 concentrations in patients (171 ± 116 ng/mL) were 2-fold higher than those in healthy volunteers (85 ± 44 ng/mL; P < 0.05). Following 17-AAG treatment, there were no consistent dose-dependent or time-dependent changes in plasma IGFBP-2 and Her-2 ECD concentrations. IGFBP-2 concentrations decreased by ≥40% in 8 patients, increased 2- to 5-fold in 8 patients, and remained essentially unchanged in 29 patients. Her-2 ECD concentrations decreased by ≥40% in 10 patients, increased 1.5- to 5-fold in 2 patients, and remained essentially unchanged in 25 patients.

**Conclusions:** As previously reported, IGFBP-2 concentrations in plasma of cancer patients are significantly higher than those in healthy volunteers. In contrast to a mouse model, 17-AAG treatment was not consistently associated with decreases in IGFBP-2 or Her-2 ECD concentrations in patient plasma.

The insulin-like growth factors (IGF) are a family of growth factors that have mitogenic effects and are involved in tissue growth, differentiation, and apoptosis (1). IGFs are regulated by a family of IGF binding proteins (IGFBP), of which six have been identified (2). IGFBP-2, the second most abundant IGFBP, exerts an inhibitory effect on cell growth and proliferation in the majority of normal tissues as a result of its ability to sequester IGFs (1, 2). In contrast to its inhibitory effects in normal tissues, IGFBP-2 is associated with an increase in cell proliferation in cancer cell lines (3). Further, IGFBP-2 is expressed by many malignancies and often reflects an increasingly malignant tumor phenotype (3, 4). Increased serum IGFBP-2 concentrations have been reported in adult patients with liver (5), lung (6), colon (7), prostate (8), ovarian (9), adrenal (10), or non–islet cell pancreatic malignancies (11), and in children with central nervous system tumors (12) or acute lymphoblastic leukemia (12–14).

The Her-2 oncogene (c-erbB2/c-neu) encodes a 185-kDa transmembrane glycoprotein (p185) that has intrinsic tyrosine kinase activity and shares close sequence homology with the...
epidermal growth factor receptor (15). Dimerization of Her-2 with an activated epidermal growth factor receptor molecule leads to a signal transduction cascade that is associated with subsequent increases in cell proliferation, angiogenesis, and metastatic potential, as well as a decrease in apoptosis. Her-2 overexpression has been observed in 25% to 30% of human breast cancers (15–19) and is also overexpressed in many ovarian (16, 20), lung (21, 22), endometrial (23), gastric (24), oral (25, 26), and prostate carcinomas (27). Clinical studies indicate that Her-2 overexpression is associated with poor response to conventional therapy and shorter relapse-free and overall survival (20, 21, 23, 26, 28). The Her-2 extracellular domain (Her-2 ECD) can be shed from the cell surface, resulting in a 105-kDa protein fragment (p105) that can be detected in the serum, effusion, and saliva of many cancer patients (29–31).

Heat shock protein 90 (Hsp90) plays a key role in the conformational maturation of important cell signaling proteins, including Her-2, Akt, and Raf-1 (32). Because inhibition of Hsp90 function leads to improper folding of these proteins and to their degradation in a proteasome-dependent manner, Hsp90 has been proposed as a potential target for antitumor drug development (32–34). 17-Allylamino-17-demethoxygeldanamycin (17-AAG) is the first Hsp90 inhibitor to be tested clinically (35–41). A recent study showed that concentrations of IGFBP-2 and Her-2 ECD in sera of mice bearing BT474 human breast tumor xenografts decreased as early as 6 h after 17-AAG treatment and remained so for at least 72 h, which suggested that these proteins could be useful biomarkers in clinical trials of 17-AAG and other Hsp90 inhibitors (42). Therefore, we assessed concentrations of IGFBP-2 and Her-2 ECD in plasma of patients before and after treatment with 17-AAG.

**Materials and Methods**

**Patients and samples**

Serial, heparinized plasma samples that had been obtained for pharmacokinetic and pharmacodynamic studies of 17-AAG (35, 36, 38) and stored at −80°C were used for these analyses. Samples had been obtained at multiple times between 0 and 72 h after administration of the first dose of 17-AAG (Division of Developmental Therapeutics, National Cancer Institute, Rockville, MD) to 45 patients with advanced solid tumors (35, 36). Twenty-seven patients had been treated with 17-AAG as a single agent at doses between 10 and 307 mg/m² (35, 38), and 18 patients had been treated with 17-AAG at doses between 220 and 450 mg/m² combined with 70 to 75 mg/m² of docetaxel (Sanofi-Aventis, Bridgewater, NJ; ref. 36; Table 1). Plasma samples had been thawed once for pharmacokinetic analysis before being assayed for IGFBP-2 and at least twice before being assayed for Her-2 ECD. Samples from all 45 patients were evaluated for IGFBP-2 concentrations, whereas plasma samples from 37 patients were evaluated for concentrations of Her-2 ECD. Pretreatment heparinized plasma samples from six male and six female healthy volunteers, participating in pharmacokinetic and pharmacodynamic studies, were handled and assayed for IGFBP-2 in a manner identical to that for patient samples. Although these samples were obtained at approximately the same time of day at which patient pretreatment samples were obtained, the healthy volunteers were not age matched with patients. Before enrollment in studies for which blood sampling was done, all patients and healthy volunteers gave written, informed consent in accordance with institutional and federal guidelines.

**Sample analysis**

**IGFBP-2.** IGFBP-2 concentrations in plasma were determined with IGFBP-2 DuoSet ELISA Development kits and microplates (R&D Systems, Inc. Minneapolis, MN) according to the manufacturer’s instructions. Briefly, plasma samples were diluted 1:200 with the sample buffer provided with the kit and were analyzed in duplicate. One hundred microliters of sample or IGFBP-2 standard were incubated for 2 h in ELISA plates that had been precoated with capture antibody (murine anti-human IGFBP-2). IGFBP-2 was detected by addition of detection antibody (biotinylated goat anti-human IGFBP-2) and streptavidin-horseradish peroxidase conjugate.

**Her-2 ECD.** Her-2 ECD concentrations in plasma were measured with Her-2 ELISA kits (EMD Biosciences, Inc., San Diego, CA) according to the manufacturer’s instructions. Briefly, plasma samples were diluted 1:10 with the sample buffer provided with the kit and were analyzed in duplicate. One hundred microliters of sample or Her-2 ECD standard were added to ELISA plates that had been precoated with capture antibody (c-erbB2/c-neu antibody). Her-2 ECD was detected by addition of detection antibody (biotinylated monoclonal anti-human c-erbB2/c-neu antibody) and streptavidin-horseradish peroxidase conjugate.

**Assay color development.** Color for each ELISA assay was developed according to manufacturer’s instructions, and absorbance was measured on an MRX Revelation Microplate Reader (Dynex Technologies, Chantilly, VA) at 450 nm with reference at 570 nm. Concentrations of IGFBP-2 and Her-2 ECD were calculated from concomitantly prepared standard curves. The percentage coefficient of variation for analyses of multiple aliquots of the same sample and repeated analyses of given samples was 20%. Samples from one patient (predose, 1 h, 4 h, 24 h, 48 h, 72 h, predose cycle 2, and 4 h cycle 2) were processed in duplicate after thawing and after two additional freeze-thaw cycles. The concentrations of both IGFBP-2 and Her-2 ECD were similar after the

<table>
<thead>
<tr>
<th>17-AAG dose (mg/m²)</th>
<th>Docetaxel dose (mg/m²)</th>
<th>No. patients</th>
<th>IGFBP-2</th>
<th>Her-2 ECD</th>
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<td>Yes</td>
<td>(38)</td>
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<tr>
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<td>(38)</td>
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two additional freeze-thaw cycles to the concentrations that were obtained after only the initial thaw. There was a 20% difference between repeats of the same samples but no consistent decrease in concentration of either IGFBP2 or Her-2 ECD. An additional series of samples were run after 1 month and again the values were within 20% of the initial values obtained using either ELISA.

**Statistics**

Dunnett’s test, as implemented in Minitab software (Minitab, State College, PA), was used to compare IGFBP-2 concentrations in pretreatment plasma from patients with those in plasma of healthy volunteers, and \( P < 0.05 \) was set as the threshold for statistical significance. Changes in concentrations of IGFBP-2 and Her-2 ECD in plasma of individual patients were evaluated by normalizing each patient’s pretreatment concentrations of IGFBP-2 or Her-2 ECD to the concentrations of the respective proteins in the patient’s pretreatment plasma sample. Normalized concentrations were considered to be unchanged if the posttreatment concentration did not differ from pretreatment concentration by >40%, which represented twice the percentage coefficient of variation of the ELISA assays used (±20%).

**Results**

**Pretreatment plasma IGFBP-2 concentrations.** The pretreatment plasma IGFBP-2 concentrations for the 12 healthy volunteers and the 45 patients studied were 85 ± 44 and 171 ± 116 ng/mL, respectively (\( P < 0.05 \); Fig. 1). However, there was marked interindividual variation within each group and overlap in values between the groups (Fig. 1).

**Changes in plasma IGFBP-2 and Her-2 ECD concentrations after 17-AAG treatment.** The actual concentrations of IGFBP-2 in plasma from patients varied between 10 and 653 ng/mL before treatment and between 48 and 785 ng/mL following 17-AAG treatment (Fig. 1). There were no consistent dose- or time-dependent changes in plasma IGFBP-2 concentrations following 17-AAG treatment. When each patient’s IGFBP-2 concentration following 17-AAG treatment was normalized to the patient’s pretreatment IGFBP-2 concentration, posttreatment IGFBP-2 concentrations decreased by >40% in 8 patients, increased 2- to 5-fold in 8 patients, and remained essentially unchanged in 29 patients. This lack of consistency was also observed when the change in plasma IGFBP-2 after 17-AAG treatment was evaluated in patients from the top and bottom quartiles of pretreatment plasma IGFBP-2 concentrations (Table 2). In the 11 patients with pretreatment IGFBP-2 concentrations between 214 and 653 ng/mL, 4 had decreases and 7 had no change in plasma IGFBP-2 after 17-AAG treatment. In the 11 patients with pretreatment IGFBP-2 concentrations between 10 and 77 ng/mL, 4 had increases and 7 had no change in plasma IGFBP-2 after 17-AAG treatment. As far as

<table>
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<th>Pretreatment [IGFBP-2] (ng/mL)</th>
<th>Change after 17-AAG</th>
<th>17-AAG dose (mg/m²)</th>
<th>Docetaxel dose (mg/m²)</th>
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<tr>
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<td>70</td>
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<tr>
<td>10</td>
<td>No change</td>
<td>307</td>
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could be evaluated, there was also no obvious relationship between tumor type and change in IGFBP-2 concentration. Among 15 patients with prostate carcinomas, IGFBP-2 concentrations increased in 2, decreased in 3, and were unchanged in 10. Among 6 patients with non–small cell lung cancer, IGFBP-2 concentrations decreased in 1 and were unchanged in 5. Among 5 patients with colorectal carcinomas, IGFBP-2 concentrations increased in 3, decreased in 1, and were unchanged in 1. IGFBP-2 concentrations decreased in the plasma of the only patient with breast cancer whose plasma was studied. The changes in IGFBP-2 in individual patients receiving 10 or 295 mg/m² 17-AAG are presented in Fig. 2A and B, respectively.

Her-2 ECD concentrations were measured in serial plasma samples from 37 patients, none of whom received the lowest dose of 17-AAG (10 mg/m²). Her-2 ECD concentrations in plasma, which were much lower than those of IGFBP-2, were between 1.3 and 9.9 ng/mL in pretreatment plasma samples and between 0.5 and 10.4 ng/mL following 17-AAG treatment. As with IGFBP-2, there were no consistent dose- or time-dependent changes in plasma Her-2 ECD concentrations following 17-AAG treatment. When normalized to pretreatment concentrations, posttreatment Her-2 ECD concentrations decreased by ≥40% in 10 patients, increased 1.5- to 5-fold in 2 patients, and remained essentially unchanged in 25 patients. Normalized Her-2 ECD data for patients receiving 220 mg/m² of single-agent 17-AAG are shown in Fig. 3A and data for patients receiving 300 mg/m² of 17-AAG in combination with 75 mg/m² of docetaxel are shown in Fig. 3B. There was no concordance between the change in concentrations of IGFBP-2 and Her-2 ECD in the plasma of the 37 patients for whom both proteins were evaluated (Table 3).

![Fig. 2. Changes in plasma concentrations of IGFBP-2 after treatment with 10 mg/m² (A) or 295 mg/m² (B) of 17-AAG. Each set of symbols and line represents data from an individual patient. The doses represent low and high doses of single-agent 17-AAG.](image)

![Fig. 3. Changes in plasma concentrations of Her-2 ECD after treatment with 220 mg/m² of single-agent 17-AAG (A) or 300 mg/m² of 17-AAG in combination with 70 mg/m² of docetaxel (B). Each set of symbols and line represents data from an individual patient.](image)
Table 3. Concordance in changes in plasma IGFBP-2 and Her-2 ECD of individual patients after 17-AAG treatment

<table>
<thead>
<tr>
<th>IGFBP-2</th>
<th>n*</th>
<th>Her-2 ECD</th>
<th>Increase</th>
<th>No change</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
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<td>24</td>
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<td>16</td>
<td>6</td>
<td></td>
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<tr>
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<td>16</td>
<td>0</td>
<td>13</td>
<td>3</td>
<td></td>
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</table>

*Number of patients.

Discussion

Biomarkers are widely used in drug development because they can contribute to increased productivity and improve patient care across a wide spectrum of drug development activities. Biomarker measurements can help explain the results of clinical trials by relating the effect of interventions on molecular and cellular pathways to clinical response. Therefore, the development and validation of biomarkers is very important.

Because of its central role in the conformational maturation of many key proteins associated with cell signaling, growth, and survival, Hsp90 has been proposed as a potentially attractive target for antitumor drug development (32–34). Of the various chemical platforms that are being evaluated as potential Hsp90-interacting agents (32–34), the group of benzoquinone-containing ansamycins related to herbimycin and geldanamycin has undergone the most extensive study. Despite extensive preclinical and clinical evaluation, which has included monitoring Hsp90, Hsp70, and a number of Hsp90 client proteins in peripheral mononuclear cells, the clinical activity of 17-AAG and related compounds has not been frequently reported. The availability of a validated biomarker of interference with Hsp90 function in tumor tissue could greatly enhance the development of 17-AAG and related compounds because it would facilitate identifying and addressing problems such as the use of suboptimal dosing schedules. Unfortunately, development of a biomarker for cancer treatment is likely to involve addressing important logistical problems such as (a) timing of the sample or samples; (b) acquisition of relevant tissue, which is likely to be tumor and not an easily acquired normal tissue; (c) sample handling, which may involve rapid freezing before transport to a laboratory for analysis. We evaluated plasma IGFBP-2 and Her-2 ECD as potential biomarkers in patients after they had received 17-AAG treatment because preclinical data indicated that those proteins were decreased after 17-AAG treatment (42) and because of the attractive nature of using plasma instead of a cellular matrix in which to measure a potential biomarker.

Our observation that concentrations of IGFBP-2 in plasma of cancer patients were higher than those in plasma of healthy volunteers is consistent with multiple previous reports (5–14). Moreover, the absolute values and degree of variability for IGFBP-2 measured in plasma of healthy volunteers and cancer patients in our study are very consistent with those in the literature (42–45), including 5 “normals” and 20 cancer patients reported in the article describing the murine studies that prompted our study (42). Furthermore, the absolute values that we measured for HER-2 ECD in plasma and our observation that Her-2 ECD concentrations were much lower than the IGFBP-2 concentrations in the plasma of each patient agree well with the patient data included in the aforementioned article (42).

In contrast, our observations that concentrations of IGFBP-2 and Her-2 ECD in patient plasma did not consistently or concordantly decrease after treatment with 17-AAG do not agree with the preclinical observations (42), although both studies used identical IGFBP-2 and Her-2 ECD ELISA kits to quantitate each protein, and each kit was indicated by its respective manufacturer as being suitable for use with serum or plasma. Despite this discordance, there are a number of factors that support the validity of the clinical data generated. Because the doses of 17-AAG given to patients were between 10 mg/m² and the maximum tolerated dose, it seems unlikely that all doses of 17-AAG were insufficient to produce the decreases in IGFBP2 and Her-2 ECD described in the mice. Thus, changes in IGFBP2 and Her-2 ECD were not observed during the first 72 h after treatment of patients with clinically relevant doses of 17-AAG. Furthermore, the doses used in mouse studies (42) were between 10 and 90 mg/kg, which translate to human doses between 30 and 300 mg/m², and those doses are very consistent with the range of doses given to the patients that we studied. Although the half-life of IGFBP-2 in humans is not known, it has been shown to be 150 min in rats (46). Moreover, decreased concentrations of IGFBP-2 and Her-2 ECD in sera of mice were obvious by 6 h and remained so for at least 72 h after 17-AAG administration (42). Therefore, the fact that each patient’s plasma concentrations of IGFBP-2 and Her-2 ECD were evaluated at multiple times between 30 min and 24 h, and in some cases as late as 72 h, after 17-AAG dosing makes it less likely that a consistent decrease in IGFBP-2 or Her-2 ECD would have been missed due to an inadequate sampling strategy. In addition, the fact that peripheral blood mononuclear cell concentrations of Hsp70 have been consistently observed by 4 h after 17-AAG doses of 100 to 250 mg/m² (47) indicates that 17-AAG produces some pharmacodynamic responses by that time. The failure to observe changes in plasma IGFBP-2 compatible with those reported in mice when such changes were sought only in the upper and lower quartiles of patients based on pretreatment IGFBP-2 concentrations makes it less likely that changes were obscured by data from subsets of patients with pretreatment values so low that a further decrease might not be detected by the assay used or so high as to possibly represent tumors for which 17-AAG-induced changes might not be expected. The fact that all samples evaluated had been handled in a similar fashion, which included being stored at –80°C in a common freezer, being handled in a central reference pharmacokinetic laboratory, and being thawed only once for pharmacokinetic analysis before being assayed for IGFBP-2 and, most commonly, twice before being assayed for Her-2 ECD, reduces the likelihood that the variability observed in IGFBP-2 and Her-2 ECD response after 17-AAG treatment could be an artifact related to sample storage and handling.

There are several possible explanations for the different IGFBP-2 and Her-2 ECD behaviors observed after 17-AAG treatment of mice bearing human BT474 breast cancer xenografts and patients with various malignancies. The fact that the
antibodies used in each ELISA are specific for human IGFBP-2 and Her-2 ECD means that the only IGFBP-2 and Her-2 ECD detected in mouse serum would be those derived from the BT474 human breast cancer xenograft. Another possible explanation for the discordance between murine and clinical studies is that a tumor of 1 to 2 g in a mouse represents 5% to 10% of the mouse’s body weight whereas a tumor of <1 kg in a human represents <1.5% of the patient’s body weight. Therefore, there may be much lower concentrations of tumor-derived IGFBP-2 and Her-2 ECD released into the patient’s plasma than would be released into murine plasma from a proportionally much larger tumor. Another obvious difference between murine and human studies is that all mice studied carried a Her-2 – expressing human tumor xenograft, whereas patients studied had a variety of malignancies and were not screened for Her-2 status before, or as a requirement for, being treated with 17-AAG.

A heterogeneous response of a biomarker of drug treatment is not necessarily a negative characteristic and may actually be desirable if the variability in biomarker response can be related to drug dose, some pharmacokinetic variable, tumor type, or, ideally, a qualitative or quantitative therapeutic or toxic response. Unfortunately, none of those potential correlations was observed when IGFBP-2 and Her-2 ECD were quantitated in the plasma of patients treated with 17-AAG, which implies that neither protein is likely to be clinically useful as biomarker for 17-AAG treatment. Nevertheless, questions remain about (a) whether a prospectively done study similar to ours might produce data more compatible with the murine data that prompted our retrospective analysis of plasma IGFBP-2 and Her-2 ECD (42), and (b) how generalizable our data are and whether HSP90 inhibitors with structures not related to geldanamycin (32) might produce clinical data compatible with the 17-AAG–associated decreases in concentrations of IGFBP-2 and Her-2 ECD in sera of mice bearing human BT474 breast cancer xenografts (42).

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References


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