α-1-Acid Glycoprotein As an Independent Predictor for Treatment Effects and a Prognostic Factor of Survival in Patients with Non-small Cell Lung Cancer Treated with Docetaxel

René Bruno, Robert Olivares, Jocelyne Berille, Philip Chaikin, Nicole Vivier, Luz Hammershaimb, Gerald R. Rhodes, and James R. Rigas


ABSTRACT

Purpose: To identify predictors of treatment outcome and survival in patients with non-small cell lung cancer (NSCLC) treated with docetaxel.

Experimental design: The data were collected from 180 NSCLC patients enrolled in six docetaxel Phase II studies at a dose of 100 mg/m2. Clinical end points for this study were safety reported as the first course adverse events requiring dose reduction, and efficacy was measured by response rate and survival. The independent variables included docetaxel dose, individual estimates of clearance, area under the plasma concentration time curve, extent of previous treatment, and covariables related to the patient's demographics, extent of disease, and performance status. The data were analyzed using a logistic regression model for response and severe adverse events and a Cox multivariate regression model for survival.

Results: Docetaxel exposure as measured by the area under the plasma concentration time curve was the only significant predictor (P < 0.0001) of severe toxicity during the first course of therapy. Baseline α1-acid glycoprotein (AAG) was the only significant predictor of response with an odds ratio of 0.44 for changes in AAG from 1.11 to 1.85 grams/liter (P = 0.0039). Cumulative dose, AAG, and extent of disease were independent predictors of survival (P < 0.005). The median survival varied from 15.6 months for patients with a low AAG (AAG ≤ 1.11 grams/liter) to 5.5 months for patients with a high AAG (AAG ≥ 1.85 grams/liter).

Conclusion: AAG appears to be an independent predictor of response and a major objective prognostic factor of survival in patients with NSCLC treated with docetaxel chemotherapy.

INTRODUCTION

Population PK/PD7 of docetaxel (Taxotere, RP 56976; Rhone-Poulenc Rorer, Antony, France) has been studied extensively during the early clinical development of this novel chemotherapeutic agent (1–3). Multivariate models have been derived to assess the independent predictors of docetaxel CL (2) and clinical outcomes, including safety and efficacy (3). From this large data set of 640 patients with advanced solid tumors enrolled in 24 Phase II studies of docetaxel, the first cycle pharmacokinetic parameters of systemic CL or AUC and baseline AAG level were found to be significant independent predictors of hematologic adverse events (grade 4 neutropenia and febrile neutropenia). In addition, docetaxel exposure, as measured by the first-dose AUC, and baseline AAG were also predictors of time to progression of disease in NSCLC patients (3). AAG appears to be an important modulator of docetaxel pharmacokinetics and pharmacodynamics.

The biological functions of AAG are poorly understood; it is an acute phase protein, and its plasma level increase as a response to inflammation is triggered by cytokines (e.g., interleukin 6; Ref. 4). As a consequence, AAG levels vary in many physiological states (i.e., age and pregnancy) and pathological conditions (i.e., liver cirrhosis, renal disease, and cancer; Refs. 5 and 6). Under physiological conditions, the plasma level of AAG varies from 0.36 to 1.46 grams/liter (6). Increased levels have been reported in all of the pathological conditions already mentioned and, in particular, in NSCLC patients (5). Acute-phase proteins and AAG in particular have long been associated with poor prognostics in many conditions, including cancer. Many reports of AAG as a “marker of disease” have been published in the 1970s and 1980s (7–10). Significant elevations of AAG were found in patients with active lung and gastrointestinal cancers compared with patients with inactive disease. Moreover, in patients with colorectal cancer treated with...
5-fluorouracil, AAG correlated with a response to therapy, with lower AAG levels in responding patients and higher AAG levels in patients with progressive disease (8). In another study (9), AAG has been shown to be highly sensitive and specific in the detection of lung cancer. In this study, the normalization of AAG during chemotherapy correlated with a prolonged relapse-free survival.

Increased AAG levels associated with advanced tumors limited the efficacy of STI571, a tyrosine kinase inhibitor, in a mouse model of leukemia (11). This effect has been proposed as a mechanism of resistance to this agent. However, these findings could not be confirmed in another study (12). The binding of UCN-01, another protein kinase inhibitor, to AAG modulated the PK and effects of this agent (13). Similar observations have been made with protease inhibitors used in the treatment of human immunodeficiency virus (14, 15).

AAG binds a wide variety of basic, neutral, and acidic drugs (5). Erythromycin competes with STI571 for AAG binding and can therefore modulate the activity of this agent (11). Docetaxel is highly bound to plasma protein. Its high-affinity binding to AAG is responsible for a decrease in free fraction with high AAG levels (16).

The goal of this study was to further assess the effect of AAG on the clinical response and survival in patients with NSCLC treated with docetaxel.

PATIENTS AND METHODS

Patients/Treatment

The data for this study were prospectively collected from 22 Phase II open label, nonrandomized studies of docetaxel in patients with NSCLC. Detailed information and clinical trial results for these studies have been published previously (17–22). Briefly, the criteria for eligibility included confirmation of NSCLC, one or more bidimensionally measurable lesions, adequate bone marrow (absolute neutrophil count > 2000/μl), renal (normal creatinine), and hepatic function (total bilirubin < 1.25 × upper limit of normal; alanine aminotransferase ≤ 2 × upper limit of normal). According to the study design, patients may have received previous treatment. The initial docetaxel dose for most patients was 100 mg/m² given as a 1-h infusion every 3 weeks. Dose reduction of 25% or delay of subsequent courses of therapy was permitted, based on the grade of toxicity observed. These studies were part of the 22 Phase II studies reported in a previous PK/PD analysis of docetaxel. The studies were conducted at multiple centers in Europe and the United States (3). These clinical trials were approved by local ethics committees or institutional review boards.

Pharmacokinetic Data

Pharmacokinetic assessment was performed at the first cycle of treatment. The design of the sampling strategy has been published previously by Bruno et al. (3). In brief, the sampling strategy consisted of four different sampling schedules of three sampling times, which were assigned randomly to patients on study entry. Docetaxel was assayed in plasma samples using high-performance liquid chromatography and UV detection after solid-phase extraction (23).

From the population pharmacokinetic parameters (2), Bayesian methods were used to estimate each individual’s pharmacokinetic parameters from the patient’s plasma concentrations (24). The NONMEM computer program was used for these studies (version IV, level 2.0; Ref. 25). The PK model used a three-compartment structural model with first-order elimination, and the PK parameters considered for this analysis were CL (obtained using the Bayesian estimation) and AUC (calculated from CL).

Clinical End Points

The following clinical end points were considered for this analysis.

Safety. Febrile neutropenia, infections, grade 3/4 stomatitis, grade 3/4 diarrhea, and severe asthenia reported during the first course of therapy were considered as safety end points. These end points of acute toxicity were only considered at first course because we wanted to study the drug exposure effects, and pharmacokinetic data were only collected at the first course of treatment. These parameters were selected as they typically require dose reduction or treatment delay. Stomatitis and diarrhea were defined and graded using the Common Toxicity Criteria of United States National Cancer Institute, whereas COSTART classification was used for asthenia. Febrile neutropenia was defined as body temperature > 38°C with concomitant National Cancer Institute grade 4 neutropenia (neutrophil count < 500/μl) requiring antibiotics and/or hospitalization.

Because of the few patients and low incidence of severe adverse events, these safety end points were pooled for analysis.

Response Rate. Response was assessed every 2 weeks during treatment. The patients were considered to be responders when they experienced either a partial or complete response using standard criteria. Patients with minor responses (<50% reduction in tumor size), stable disease, and patients with disease progression were considered as nonresponders. Responses had to be confirmed after a minimum of 4 weeks and were reviewed by an independent panel.

Survival. Survival was calculated from the date of the first docetaxel infusion to the date of death, last contact for patients lost to follow-up, or a cutoff date for patients alive at the time of closure of the data set.

Data Analysis

Three categories of independent variables thought to affect survival in NSCLC were considered for this analysis: (a) docetaxel exposure, assessed by the cumulative dose, or CL and AUC at first course of therapy; (b) the patient characteristics age, gender, performance status, AAG, lactate dehydrogenase, baseline neutrophil count, time from initial diagnosis of NSCLC, number of disease sites, visceral cancer involvement, and hepatic and bone metastasis; and (c) the extent of previous treatment (e.g., number of previous chemotherapy regimens, cisplatin, and radiotherapy).

A logistic regression analysis was used to relate binary end points, such as the incidence of severe adverse events and response rate, to the independent variables, whereas a Cox regression was used for the survival analysis. Cumulative docetaxel dose was the only time-dependent covariate used in the
Cox model. Univariate and multivariate analyses were conducted. The multivariate model involved a stepwise selection of covariates starting from the null model. Significance levels for variable entry or removal at each step in the development of the multivariate model were \( P < 0.1 \) and \( < 0.05 \), respectively. The median survival was estimated using the Kaplan-Meier method. Analyses were carried out using the SAS software (SAS version 6.12; SAS Institute, Inc., Cary, NC).

**RESULTS**

**Patient Characteristics at Baseline.** Overall, 189 of the 269 NSCLC patients entered in the six Phase II docetaxel studies (70%) had pharmacokinetic data available for analysis. Nine patients received 75 mg/m\(^2\) docetaxel as their initial dose, and all other patients \((n = 180)\) received 100 mg/m\(^2\). This analysis was restricted to the patients treated with 100 mg/m\(^2\) docetaxel. Among these patients, 143 were evaluable for response; however, the analysis was conducted on the intent-to-treat population of 180 patients. Some models were reassessed on the evaluable patient population as a sensitivity analysis. The patient characteristics are summarized in Table 1. Median age for this population of NSCLC patients was 61 years, two-thirds were male, and 82% of the patients had a WHO performance status of 0–1. Most of the patients were chemotherapy naive (71%) and had metastatic disease (77%).

**Table 1 Patient characteristics and docetaxel exposure \((n = 180)\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
<th>Median</th>
<th>5–95% percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61</td>
<td>61</td>
<td>43–72</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>118 (66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>62 (34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>35 (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>113 (63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>32 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAG (grams/liter)</td>
<td>1.42</td>
<td>0.84–2.71</td>
<td></td>
</tr>
<tr>
<td>Time from diagnosis (month)</td>
<td>4.7</td>
<td>0.6–39</td>
<td></td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of disease sites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>48 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>70 (39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>42 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>20 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>34 (19)</td>
<td></td>
<td></td>
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<tr>
<td>Prior treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>52 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of prior regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>128 (71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>34 (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>18 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous platinum</td>
<td>43 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>70 (39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL (liters/h)</td>
<td>35.7</td>
<td>17.8–58.8</td>
<td></td>
</tr>
<tr>
<td>AUC (µg/h/ml)</td>
<td>4.98</td>
<td>3.24–9.76</td>
<td></td>
</tr>
</tbody>
</table>

**Individual PK Parameter Estimates.** Individual estimates of PK and exposure parameters are summarized in Table 1. In this NSCLC patient population, the median CL was 35.7 liters/h varying from 17.8 to 58.8 liters/h (5–95% percentile range). This CL distribution was very similar to that of the larger population of patients with various tumor types with a median of 36.3 liters/h (3). The observed median AUC was 4.98 µg/h/ml with a 5–95% percentile range of 3.24–9.76 µg/h/ml.

**PK/PD**

**Severe Adverse Events.** Twenty-five patients (13.9%) experienced at least one severe adverse event during the first cycle of therapy (TOX; Table 2). Docetaxel exposure as measured by the AUC was the only significant predictor of these adverse events \((P < 0.0001)\). A high AUC was associated with increased probability of experiencing any of the severe toxicities. Subsets of associated toxicities were also analyzed for their correlative significance. In all subsets, docetaxel exposure as measured by AUC was the only significant predictor of these severe adverse events. In one subset (TOX1) that included febrile neutropenia, infection, or diarrhea \((n = 23)\), AAG reached borderline significance \((P = 0.0505)\) in addition to AUC.

The odds ratio for the logistic regression models calculated for the relevant covariates changes from the 25th to the 75th percentiles is presented in Table 3. According to the logistic model, the odds of experiencing a severe adverse reaction was −2-fold greater for a change in AUC from 4.2 to 6.5 µg/h/ml. An increase in AAG from 1.11 to 1.85 grams/liter resulted in a −50% reduction in the odds of experiencing one toxicity event.

**Response Rate.** The overall response rate was 25% in both intent-to-treat and evaluable populations. Baseline AAG was the only significant predictor of response rate \((P = 0.0039)\) with an odds ratio of 0.44 for a change in AAG from 1.11 to 1.85 grams/liter. An increase in the baseline AAG level was associated with a 56% decrease in the odds of response (Table 4). The response rate was 41.3% \((95\% \text{ CI: 27–56.8})\%\) for patients with a low AAG \((\text{AAG} \leq 1.11 \text{ grams/liter}, n = 46)\) and 15.9% \((95\% \text{ CI: 6.7–30.1})\%\) for patients with a high AAG \((\text{AAG} \geq 1.85 \text{ grams/liter}, n = 44)\).
In the univariate analyses, in addition to baseline AAG levels, trends were observed for a lower odds of response in patients with metastatic disease \((P = 0.054)\), in patients who received radiotherapy before docetaxel treatment \((P = 0.055)\), in younger patients \((P = 0.08)\), and in patients with a poor performance status \((P = 0.08)\). However, when baseline AAG was included in the multivariate analysis, none of these covariates entered the model even at a significance level of \(P < 0.1\). Similar findings were obtained for the patients with evaluable disease.

**Survival.** The most significant univariate predictors of survival were cumulative dose, baseline AAG, and number of sites of disease \((P < 0.0001)\). CL or AUC, previous radiotherapy, gender, and performance status were also significant predictors of survival \((P < 0.05)\). The risk of death decreased as the cumulative dose of docetaxel increased. However, an increased risk of death was observed for patients with higher baseline AAG, two or more sites of disease, low CL or high AUC at first cycle, poor performance status, female gender, and for patients having received previous therapy.

Only cumulative dose, AAG, and two or more disease sites remained significant in the multivariate analysis (Table 5). The risk of death decreased by 20% for each additional cycle of treatment and roughly doubled in patients with a high AAG (1.85 grams/liter) compared with patients with a low AAG (1.11 grams/liter) and in patients with two or more sites of disease.

When baseline AAG was not considered in the stepwise multivariate analysis, it was replaced by performance status \((P = 0.0053)\), gender \((P = 0.025)\), and previous radiotherapy \((P = 0.045)\). Therefore, the pretreatment AAG level appeared to be a more important predictor of survival in NSCLC patients treated with docetaxel than several other known prognostic factors. The median survival (Table 6 and Fig. 1) varied from 15.6 months in low AAG patients \((AAG \leq 1.11 \text{ grams/liter}, n = 46)\) to 5.5 months in high AAG patients \((AAG \geq 1.85 \text{ grams/liter}, n = 44)\). Patients with intermediate AAG values \((n = 90)\) had a median survival time of 9.2 months (Fig. 1).

**DISCUSSION**

Performance status has been the most important prognostic factor in lung cancer for 5 decades (26). In this data set of 189 patients with NSCLC, patients with a high baseline AAG had a lower response rate (14%) compared with 44% in patients with a low AAG and a markedly shorter survival (median of 5.5 months compared with 15.6 months in patients with a low AAG). Large-scale population PK/PD assessment of docetaxel was performed previously in 640 patients with various solid tumor types (3). Baseline AAG was found to be a significant predictor of several clinical end points. In particular, high AAG patients were at decreased risk of hematological toxicity and febrile neutropenia. Moreover, AAG was a risk factor for disease progression in NSCLC patients treated with docetaxel. The identification of predictors of treatment outcomes and survival may be the basis for further treatment optimization.

In our patient population, with a median AAG of 1.42 mg/liter, roughly half of the patients had a level exceeding the maximum seen in healthy subjects. The finding that, during docetaxel treatment of patients with advanced NSCLC, high baseline AAG levels are associated with a lower response rate and disease progression (3), and shorter survival is consistent with the findings of previous studies where high levels of AAG have been reported to modulate the biological activity of several drugs. High AAG levels are associated with a decrease of the free fraction (fu) of docetaxel (16). This effect may result in a restriction of free docetaxel distribution in patients with high

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**Table 4** Logistic regression model for response

<table>
<thead>
<tr>
<th>Predictor</th>
<th>(P)</th>
<th>Odds ratio(^b) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAG (1.11–1.85 grams/liter)</td>
<td>0.0039</td>
<td>0.44 (0.25–0.77)</td>
</tr>
</tbody>
</table>

\(^a\) Intent-to-treat population, response rate = 25%.

\(^b\) Odds ratio for AAG change from 25\(^b\) to 75\(^b\) percentiles.

**Table 5** Cox regression model for survival

<table>
<thead>
<tr>
<th>Predictor</th>
<th>(P)</th>
<th>Risk ratio(^b) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative dose(^a) (100 mg/m(^2))</td>
<td>&lt;0.0001</td>
<td>0.82 (0.74–0.90)</td>
</tr>
<tr>
<td>AAG (1.11–1.85 grams/liter)</td>
<td>&lt;0.0001</td>
<td>1.76 (1.40–2.21)</td>
</tr>
<tr>
<td>Nb disease sites (&lt;2 to ≥2)</td>
<td>0.0049</td>
<td>1.96 (1.23–3.12)</td>
</tr>
</tbody>
</table>

\(^a\) Death occurred in 70.5% of the patients (127 of 180 patients).

\(^b\) Risk ratio for change of covariates given in brackets.

**Table 6** Survival as a function of AAG baseline level

<table>
<thead>
<tr>
<th>AAG (grams/liter)</th>
<th>(n)</th>
<th>(95%) Cl</th>
<th>Log-rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.11(^b)</td>
<td>46</td>
<td>(11.8–20.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1.12–1.84</td>
<td>90</td>
<td>(6.4–11.4)</td>
<td></td>
</tr>
<tr>
<td>≥1.85(^b)</td>
<td>44</td>
<td>(4.1–7.5)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) 25% quartile of AAG distribution.

\(^b\) 75% quartile of AAG distribution.

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**Fig. 1.** Survival curves in NSCLC patients with low (≤1.11 grams/liter, —), intermediate (1.12–1.84 grams/liter, —), and high (≥1.85 grams/liter, – –) baseline AAG (censored observation).
AAG levels. This pharmacokinetic effect may be an important predictor of safety end points, particularly those related to hematological adverse events. This pharmacokinetic effect may also play an important role in decreasing the overall pharmacologic activity of docetaxel (including tumor shrinkage). These effects of AAG on docetaxel pharmacokinetics and pharmacodynamics may also contribute to the shorter survival observed in this study for patients with high baseline AAG. However, the shorter survival is very likely to be related to the poor prognosis of patients with high AAG (5, 7–9). Several factors have limited the usefulness of AAG as a prognostic factor in cancer. Primarily, levels of this protein are associated with a high frequency of nonspecific changes (5). In addition, AAG is a heterogeneous glycoprotein with up to four glycoforms, each of which may have a different pathophysiological meaning (27).

Overall, the observation that patients with high AAG levels demonstrate decreased docetaxel treatment effects both in toxicity and efficacy and shorter survival is of interest. A clinical trial simulation was conducted recently to determine whether patients with high AAG levels might tolerate a higher dose of docetaxel (125 mg/m² versus 100 mg/m²) and benefit by achieving improved efficacy and longer survival (28). This simulation, however, did not show a benefit in any of the clinically relevant parameters of efficacy (time to progression) and survival for the patients receiving 125 mg/m². The predicted median time to progression in this patient population with high AAG was only 8.5 weeks; therefore, these patients could only be treated for a median of three cycles and did not benefit from the dose intensification.

AAG is one covariate in NSCLC that appears to impact on time to disease progression, survival, and response to docetaxel chemotherapy. These observations are likely related to the high-affinity protein binding effects of this drug to AAG and the different prognosis of patients with various levels of AAG. A more complete understanding of the PK/PD interactions between drugs and AAG warrants additional studies.

REFERENCES


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