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Phase I Trial of Arginine Deprivation Therapy with ADI-PEG 20 Plus Docetaxel in Patients with Advanced Malignant Solid Tumors

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Abstract

Purpose: This phase I study examined the toxicity and tolerability of pegylated arginine deiminase (ADI-PEG 20) in combination with docetaxel in patients with advanced solid malignancies.

Experimental Design: Eligible patients had histologically proven advanced solid malignancies, with any number of prior therapies, Zubrod performance status 0–2, and adequate organ function. Patients received ADI-PEG 20 weekly intramuscular injection ranging from 4.5 to 36 mg/m^2 and up to 10 doses of docetaxel (75 mg/m^2) every 3 weeks. Primary endpoints were safety, toxicity, and a recommended phase II dose. Circulating arginine levels were measured before each cycle. Tumor response was measured as a secondary endpoint every 6 weeks on study.

Results: Eighteen patients received a total of 116 cycles of therapy through four dose levels of ADI-PEG 20. A single dose-limiting toxicity (grade 3 urticarial rash) was observed at the 1st dose level, with no additional dose-limiting toxicities observed. Hematologic toxicities were common with 14 patients experiencing at least one grade 3 to 4 leukopenia. Fatigue was the most prevalent toxicity reported by 16 patients. Arginine was variably suppressed with 10 patients achieving at least a 50% reduction in baseline values. In 14 patients with evaluable disease, four partial responses (including 2 patients with PSA response) were documented, and 7 patients had stable disease.

Conclusions: ADI-PEG 20 demonstrated reasonable toxicity in combination with docetaxel. Promising clinical activity was noted, and expansion cohorts are now accruing for both castrate-resistant prostate cancer and non–small cell lung cancer at a recommended phase II dose of 36 mg/m^2. *Clin Cancer Res; 21(11); 2480–6. ©2015 AACR.*

Introduction

Modulation of amino acid metabolism has been shown to have antineoplastic activity. For example, the use of the enzyme L-asparaginase to enhance hydrolysis of the amino acid asparagine to aspartic acid has clinically meaningful activity against childhood acute lymphoblastic leukemia (1). Arginine represents yet another amino acid that can be exploited in cancer drug development. Specifically, the enzyme arginine deiminase (ADI) has been shown to degrade dietary arginine and result in enhanced cell kill in select tumor cells that lack argininosuccinate synthetase (ASS), the rate-limiting step in the synthesis of arginine from citrulline. Cancer cells variably express ASS, which can be evaluated by immunohistochemistry (2). Cells lacking ASS become dependent on exogenous arginine. Deprivation of arginine has been shown to decrease cancer cell survival, and can induce autophagy and later cell death via caspase-independent apoptosis (3, 4).

ADI is a recombinant protein originally derived from *Mycoplasma* bacteria and is present in other infectious organisms. As a result of its origins, it is highly immunogenic as a free molecule leading to antibody formation and concern for allergic reactions that could limit its clinical utility. Holtsberg and colleagues demonstrated that pegylation of ADI with 20,000 molecular weight polyethylene glycol (ADI-PEG 20) resulted in a longer half-life with reduced immunogenicity in animal models (5). Further studies confirmed that ADI-PEG 20 inhibits cancer growth both *in vivo* and *in vitro* (6, 7). Human studies have shown a reasonable safety profile for ADI-PEG 20. The most common adverse events related to the study drug have been local injection reactions, rashes, and fatigue. Myelosuppression rates appear to be minimal; grade 3 and 4 events were rare. Anaphylactic reactions have also been rare (8). Prior clinical experience has been primarily in patients with hepatocellular carcinoma (HCC) and melanoma, and clinical benefit has been observed in both tumor types, with some correlation of response with absence of ASS noted in melanoma cells (8–14). Feun and colleagues (8) was able to demonstrate correlation of response with absence of ASS noted in melanoma cells.

As a result, development of ADI-PEG 20 has focused on potentially ASS-deficient tumors. Dillon and colleagues (2) demonstrated that 100% of examined prostate cancer cells

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Translational Relevance

Arginine deprivation is a new therapeutic strategy for cancer treatment. It promotes autophagy and caspase-dependent apoptosis in susceptible tumor cells—particular those lacking arginine succinyl synthetase. The bacterial enzyme arginine deiminase pegylated with 20,000 molecular weight polyethylene glycol (ADI-PEG 20) has clinical single-agent activity in several tumor types. Preclinical work has demonstrated that arginine deprivation in combination with cytotoxic chemotherapy has synergistic antineoplastic activity in *in vitro* and *in vivo* models. In this work, we demonstrate the safety and tolerability of ADI-PEG 20 in combination with docetaxel in patients with advanced solid tumors, and offer insights into future strategies to further develop this promising new anticancer agent.

lines were deficient in ASS, but also found a small percentage of many tumor types are also deficient. Kim and colleagues (4) further confirmed *in vitro* that prostate cancer cells that experienced arginine deprivation by ADI-PEG 20 underwent autophagy and cell death. Their work further evaluated ADI-PEG 20 plus docetaxel in ASS-deficient prostate cancer mouse models, demonstrating synergistic cell kill. Thus, arginine deprivation in combination with cytotoxic therapy appears to be a rational antineoplastic strategy.

Based on this preclinical work, we conducted a phase I trial to assess the safety and feasibility of ADI-PEG 20 in combination with docetaxel in patients with advanced solid tumors.

Materials and Methods

This study was designed as a single-center, open-label, phase I dose-escalation study to determine the dose-limiting toxicity (DLT) and MTD of ADI-PEG 20 in combination with docetaxel to patients with advanced solid tumors. The primary endpoint was safety and toxicity to determine an appropriate phase II dose of ADI-PEG 20 in combination with docetaxel. Secondary endpoints include assessment of tumor response and biologic correlates of arginine suppression, immunogenicity.

Patient selection

Eligible patients were 18 years or older with cytologically or histologically proven advanced solid malignancy. Patients were required to have a Zubrod performance status of 0–2 with a life expectancy greater than 3 months. Any number of prior systemic therapies was permitted, but must have been completed 4 weeks before start of study medications. Adequate renal, liver, and bone marrow function was required, defined by creatinine clearance of at least 45 mL/min, aspartate aminotransferase and alanine aminotransferase less than 2.5 × the upper limit of normal, platelets greater than 100,000 cells/mm^3, and absolute neutrophil count (ANC) of 1,500 cells/mm^3. There was no limit to number of prior therapies. Patients with asymptomatic metastatic disease to the brain were allowed to participate if they had received treatment to metastases and were neurologically stable. All patients completed a written informed consent process according to federal and institutional standards.

Treatment and dose-escalation scheme

ADI-PEG 20 (Polaris Pharmaceuticals) was given intramuscularly once weekly during treatment. Docetaxel was dosed at 75 mg/m^2 and administered 1 hour after ADI-PEG 20 administration on day 1, with a cycle length of 3 weeks. Prednisone (10 mg) by mouth daily was given to patients with castrate-resistant prostate cancer (CRPC), but not to other forms of solid tumors. Hematopoietic growth factors were permitted at the discretion of the treating physician. ADI-PEG 20 was dose escalated according to a standard 3 × 3 phase I design from a starting dose of 4.5 mg/m^2 to a maximum possible dose of 36 mg/m^2 over four dose levels (full dose-escalation schema available in Supplementary Table S1). Dose levels were developed from results of MTD and optimal biologic dosing (OBD) from prior ADI-PEG 20 monotherapy studies. Early phase I studies reported an OBD of 160 IU/m^2 (or 18 mg/m^2) based on arginine suppression, though MTDs exceeded this (13). OBD was further elucidated by a phase II study in HCC that demonstrated consistently higher citrulline levels with 320 IU/m^2 (36 mg/m^2; ref. 12). Three patients were recruited at each dose level. If no DLT was observed, 3 patients were treated at the next level. If one DLT occurred, 3 additional patients were recruited at that dose level. If no further DLTs were observed, the dose could be escalated. DLTs in 2 or more patients at any dose level would result in the MTD to be considered the lower dose (15, 16). Dose escalation was not permitted within individual patients.

History and physical examination along with confirmation of performance status were performed before every cycle; laboratory analysis, including complete blood count (CBC), electrolytes, blood urea nitrogen (BUN) and creatinine, and liver enzymes were analyzed before every cycle. Uric acid was checked weekly for 8 weeks. Pharmacodynamic and immunogenicity sampling were done before each cycle. Radiographic tumor response as defined by RECIST 1.1 was monitored every two cycles. Patients with CRPC had PSA checked every cycle; a PSA partial response was considered a 50% reduction or greater in the baseline PSA without additional evidence of progression.

Docetaxel was permitted to be continued up to 10 cycles. ADI-PEG 20 was permitted to continue for up to one year. Patients were removed from study at the time of disease progression, unacceptable toxicity, or withdrawal of consent.

Dose-limiting toxicity

DLTs were defined as any of the following occurring during the first cycle: hematologic toxicities of grade 4 thrombocytopenia, grade 3 thrombocytopenia with bleeding, febrile neutropenia (ANC < 1,000 cells/mm^3), or ANC < 1.0 with a documented infection. Nonhematologic DLTs were defined as any ≥ grade 3 toxicity attributable to study drug, except for alopecia and hypersensitivity reactions to docetaxel. The description of hematologic toxicity was originally defined as toxicities attributable to either single agent, but during recruitment of patients at the 36 mg/m^2 dose level, the protocol was amended under FDA guidance to attribute all hematologic toxicities to both drugs. All toxicities were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Dose modifications

Dose modifications of both docetaxel and ADI-PEG 20 for grade 3 and 4 toxicities occurring beyond the first cycle were permitted for non-DLTs. Specific guidelines for toxicities for

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docetaxel were provided. In general, grade 3 or higher toxicities required holding of all treatment until toxicity reduced to grade 1. Exceptions included hypersensitivity reactions, where no dose adjustment was required, but the reaction was immediately managed. A grade 4 reaction required removal from protocol. The other exception was fluid retention, where initial management with diuretics was recommended. For grade 3 and above toxicities attributed to ADI-PEG 20, the medication was held and then reintroduced at a lower dose level after improvement to grade 1 or less. A delay of treatment by 3 weeks necessitated removal from the protocol.

Pharmacodynamics and immunogenicity

Pharmacodynamics were assessed by measurements of plasma arginine and citrulline levels by high-performance liquid chromatography–mass spectrometry as previously described (6). Immunogenicity was assessed by ELISA assay of anti-ADI antibodies as previously described (6).

Results

Patient demographics

A total of 18 patients were recruited over four dose levels: 6 patients at the 4.5 mg/m^2 dose level, three at 9 mg/m^2, three at 18 mg/m^2, and six at 36 mg/m^2. Patients had variable tumor types: nine had non–small cell lung cancer (NSCLC), three had CRPC, two had squamous cell carcinoma of the head and neck, whereas the remaining constituted a variety of tumor types (small cell lung cancer, gastric cancer, colorectal cancer, and thymic cancer). All 3 prostate cancer patients had received two or more forms of hormone therapy and had not been treated with cytotoxic chemotherapy. Of the remaining 15 patients, 13 (86.7%) had two or more prior systemic treatments and 8 (53.3%) had received three systemic therapies. Patients with tumors not typically sensitive to docetaxel had exhausted approved therapy options.

Safety and tolerability

One DLT occurred in dose level 1. This was a grade 3 urticarial rash attributed to ADI-PEG 20, necessitating expansion of dose level 1 to 6 patients. No further DLTs were observed through the remaining dose levels. A total of 116 cycles of chemotherapy were administered, which included 99 cycles of ADI-PEG 20 in combination with docetaxel. The median number of cycles completed for both ADI-PEG 20 and docetaxel was 3, with a range of 0 to 22 cycles for ADI-PEG 20 and 1 to 10 cycles for docetaxel. Two patients completed 10 cycles of docetaxel and continued onto ADI-PEG 20 alone. One patient with lung cancer treated at the 4.5 mg/m^2 dose level was treated for 67 weeks, including 12 cycles of ADI-PEG 20, and 1 patient with CRPC treated at the 36 mg/m^2 dose level was still receiving treatment after completing docetaxel with 5 cycles of single-agent ADI-PEG 20. No DLTs were observed at 36 mg/m^2, including after expansion of this group to 6 patients. Serious adverse events occurred 21 times on study. The majority of these were hematologic—six episodes of grade 4 neutropenia and two of lymphopenia. Two grade 4 anemia events were recorded. One of these was attributed to the combination therapy, but the second was from gastrointestinal bleeding due to peptic ulcer disease, which was assessed to be unrelated to the study drug. There were two deaths on study, and another person had decline in performance status that necessitated removal from trial. These three events were attributed to disease progression and not toxicity. Two patients were removed from study for ADI-PEG 20–related toxicity: one for the previously mentioned DLT and the other withdrew due to injection site pain. One patient was removed for intolerable dizziness, which was attributed to docetaxel. Five patients had dose reductions as a result of toxicity: 3 patients had dose reductions in docetaxel and 2 patients had dose reductions in ADI-PEG20.

Hematologic toxicity

Leukopenia events were documented 67 times on study, with neutropenia documented along with leukopenia 51 times. Of 67 leukopenia events, 58% were at least grade 3 in severity. Of 51 neutropenia events, 80% were at least grade 3. Fourteen patients, or 78%, experienced at least one episode of grade 3 to 4 leukopenia or neutropenia. There were 87 events of grade 3 to 4 lymphopenia (including two grade 4 events). There were three episodes of febrile neutropenia, but none occurring within the first cycle, and all were successfully treated. Thrombocytopenia was relatively common, but there were no grade 3 to 4 events. The number of patients who experienced a hematologic toxicity is summarized in Table 1.

Nonhematologic toxicity

Two patients experienced injection site reactions, generally described as pain at the site of injection. Observed skin and subcutaneous tissue toxicities were varied. Five instances of rash, three instances of palmar-plantar erythrodysaesthesia, and one instance of urticarial rash were observed. Of these skin reactions, only two were grade 3 or higher, including the aforementioned DLT. Fatigue was the most prevalent nonhematologic toxicity, with 16 patients reporting at least one instance. Laboratory abnormalities were common, but were usually grades 1 to 2 in severity. The most common with 29 observed events was

Table 1. Hematologic toxicities; number of patients with at least one instance of different toxicities through the 1st cycle and through all cycles; the worst grade toxicity recorded is reported

	Dose level 1 (4.5 mg/m^2—6 patients) 1st cycle (all cycles)		Dose level 2 (9 mg/m^2—3 patients) 1st cycle (all cycles)		Dose level 3 (18 mg/m^2—3 patients) 1st cycle (all cycles)		Dose level 4 (36 mg/m^2—6 patients) 1st cycle (all cycles)	
	G1 and G2	G3 and G4	G1 and G2	G3 and G4	G1 and G2	G3 and G4	G1 and G2	G3 and G4
Leukopenia	1 (1)	3 (5)	1 (1)	2 (2)	1 (1)	1 (2)	1 (2)	5 (5)
Neutropenia	0 (0)	2 (4)	0 (0)	3 (3)	0 (0)	1 (2)	0 (0)	4 (4)
Lymphopenia	1 (1)	3 (5)	2 (2)	1 (1)	1 (1)	0 (2)	2 (1)	3 (4)
Anemia	3 (3)	0 (0)	1 (1)	1 (2)	1 (1)	0 (1)	3 (3)	0 (1)
Thrombocytopenia	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (1)	0 (0)

NOTE: Number outside of parentheses is toxicities occurring in cycle 1 only. Number in parentheses is toxicities occurring in all cycles.
Abbreviations: G1, grade 1; G2, grade 2; G3, grade 3; G4, grade 4.

Table 2. Most prevalent nonhematologic toxicities; number of patients with at least one instance of listed toxicities through the 1st cycle and through all cycles; the worst grade toxicity is reported

	Dose level 1 (4.5 mg/m²—6 patients)1st cycle (all cycles)		Dose level 2 (9 mg/m²—3 patients)1st cycle (all cycles)		Dose level 3 (18 mg/m²—3 patients)1st cycle (all cycles)		Dose level 4 (36 mg/m²—6 patients)1st cycle (all cycles)	
Toxicity	**G1 and G2**	**G3 and G4**	**G1 and G2**	**G3 and G4**	**G1 and G2**	**G3 and G4**	**G1 and G2**	**G3 and G4**
General								
Fatigue	2 (5)	0 (0)	0 (1)	0 (0)	3 (3)	0 (0)	4 (5)	1 (1)
Edema	1 (1)	0 (0)	0 (1)	0 (0)	0 (1)	0 (0)	1 (1)	0 (0)
Generalized weakness	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (4)	0 (0)
Skin disorders								
Alopecia or nail disorder	1 (2)	0 (0)	1 (1)	0 (0)	0 (1)	0 (0)	2 (3)	0 (0)
Rash, urticaria, pruritus	3 (3)	1 (1)	0 (1)	0 (0)	1 (1)	0 (0)	0 (1)	0 (0)
Respiratory								
Cough	2 (3)	0 (0)	1 (1)	0 (0)	0 (1)	0 (0)	1 (5)	0 (0)
Dyspnea	2 (1)	0 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)
Nasal congestion	0 (2)	0 (0)	0 (0)	0 (0)	0 (1)	0 (0)	0 (1)	0 (0)
Gastrointestinal								
Nausea and vomiting	1 (1)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)	0 (1)	0 (0)
Diarrhea	2 (3)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition								
Anorexia	0 (1)	0 (0)	0 (0)	0 (0)	0 (1)	0 (0)	0 (0)	0 (0)
Nervous system								
Dizziness	0 (1)	0 (0)	0 (1)	0 (0)	0 (0)	0 (1)	0 (0)	1 (1)

NOTE: Number outside of parentheses is toxicities occurring in cycle 1 only. Number in parentheses is toxicities occurring in all cycles.
Abbreviations: G1, grade 1; G2, grade 2; G3, grade 3; G4, grade 4.

hypoalbuminemia. Among laboratory abnormalities, only liver function test (LFT) elevations and hyperuricemia were attributed to ADI-PEG 20 by investigators. A total of six grade 3 to 4 laboratory values were observed. Only one of these higher grade laboratory measurements, a grade 3 elevation of alkaline phosphatase, was felt possibly related to ADI-PEG 20. The most frequently observed nonhematologic toxicities are presented in Table 2, with laboratory abnormalities presented in Table 3.

Other toxicities

Three patients experienced hypersensitivity reactions on treatment, only one was grade 3 or higher. These were attributed to docetaxel and were manageable.

Pharmacodynamics and immunogenicity

For all four dose cohorts, the mean plasma arginine levels demonstrated an initial decrease followed by a gradual return to baseline values with extended time of treatment. The mean plasma arginine values measured at approximately the end of each month of treatment are presented in Fig. 1. Data for the 9 mg/m² cohort was limited by patient withdrawal from study before collection of arginine and citrulline levels at the end of the second month. The longest individual sustained duration of arginine suppression was 20 weeks, occurring in 1 patient at the 36 mg/m² dose level. Suppression of plasma arginine was not detected for every patient. However, it should be noted that the first postdose arginine and citrulline levels were obtained 4 to 5 weeks after the first administration of ADI-PEG 20 and thus do not capture any decrease in arginine levels that would have occurred during the first month of treatment. The shortest duration of mean plasma arginine suppression occurred in the lowest dose cohort. The remaining three dose cohorts displayed similar duration of mean plasma arginine suppression. The change in mean plasma arginine levels was expectedly accompanied by a reciprocal change in mean plasma citrulline levels (Fig. 2). The two highest dose cohorts displayed similar absolute increases in mean plasma citrulline levels, with the 36 mg/m² dose cohort displaying the longest sustained increase in mean plasma citrulline level. It should also be noted that all reported plasma arginine and citrulline levels were obtained 1 week after the immediate prior administration of ADI-PEG 20 and thus may not accurately reflect the maximal decrease in arginine or

Table 3. Most prevalent laboratory toxicities; number of patients with at least one instance of different toxicities through the 1st cycle and through all cycles; the worst grade toxicity is reported

	Dose level 1 (4.5 mg/m²—6 patients) 1st cycle (all cycles)		Dose level 2 (9 mg/m²—3 patients) 1st cycle (all cycles)		Dose level 3 (18 mg/m²—3 patients) 1st cycle (all cycles)		Dose level 4 (36 mg/m²—6 patients) 1st cycle (all cycles)	
Toxicity	**G1 and G2**	**G3 and G4**	**G1 and G2**	**G3 and G4**	**G1 and G2**	**G3 and G4**	**G1 and G2**	**G3 and G4**
Laboratory abnormalities								
Hypoalbuminemia	1 (1)	0 (0)	2 (3)	0 (0)	1 (1)	0 (1)	3 (5)	0 (0)
Hyponatremia	1 (2)	0 (0)	1 (2)	1 (1)	1 (2)	0 (0)	3 (4)	0 (0)
Elevated LFTs	1 (2)	0 (0)	0 (0)	0 (0)	0 (1)	0 (0)	1(1)	0 (0)
Elevated clotting times	0 (0)	0 (0)	0 (0)	1 (1)	0 (1)	0 (0)	0 (1)	0 (0)
Hypocalcemia	0 (0)	0 (0)	0 (1)	0 (0)	0 (1)	0 (0)	0 (1)	0 (0)
Hypokalemia	0 (0)	0 (0)	0 (1)	0 (0)	0 (1)	0 (0)	0 (0)	0 (0)
Hyperkalemia	0 (0)	0 (0)	1 (1)	0 (0)	0 (1)	0 (0)	0 (0)	0 (0)

NOTE: Number outside of parentheses is toxicities occurring in cycle 1 only. Number in parentheses is toxicities occurring in all cycles.
Abbreviations: G1, grade 1; G2, grade 2; G3, grade 3; G4, grade 4.

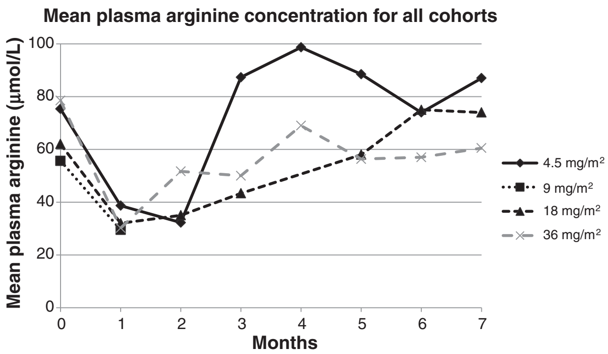

Figure 1.
Changes in mean plasma arginine levels for all cohorts of ADI-PEG 20 dose levels.

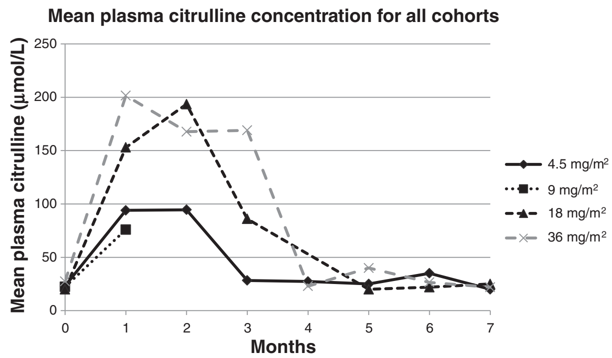

Figure 2.
Changes in mean plasma citrulline levels for all cohorts of ADI-PEG 20 dose levels.

increase in citrulline. Antibodies were detected by the start of the second cycle and generally reached a plateau by about the fourth month on treatment. The return to baseline of plasma arginine closely correlated with increase in antibody titer (Fig. 3). Complete pharmacodynamic results are available in Supplementary Table S2.

Efficacy

Fourteen patients had evaluable disease. Best response included four documented partial responses and 7 patients with stable disease. Two of the partial responses were by PSA level, 1 patient with a decline from a baseline of 49.9 ng/mL to a nadir of 21.8 ng/mL, and another from a baseline of 83.9 ng/mL to a nadir of 2.2 ng/mL. Patients with response included 1 patient with NSCLC, and another with squamous cell cancer of the head and neck. The 2 patients with PSA response had stable disease on imaging. The overall disease control rate in evaluable disease was 85%, including 4 of 6 patients with NSCLC. Best response listed against tumor type for evaluable patients is available in Supplementary Table S3.

Discussion

The combination of amino acid deprivation and chemotherapy is well established for some hematologic tumors, particularly childhood acute lymphoblastic leukemia (1). The potential value of arginine deprivation therapy with ADI-PEG 20 has been well documented in preclinical models; work is progressing in clinical trials for several tumor types, particularly HCC, malignant mesothelioma, and melanoma (3, 17). Several phase I and II trials have been completed. Phase I to II studies of ADI-PEG 20 as a single agent for HCC in the United States, Taiwan, and Italy have evaluated over 180 subjects and demonstrated disease control rates ranging from 31% to 63% (9–12). A phase III trial of ADI-PEG 20 in advanced HCC is now accruing (17). Phase I and II trials for melanoma have completed in the United States and Italy, and both partial response and stable disease have been observed (8, 13, 14). Results from a randomized phase II study in mesothelioma have been presented showing improved progression-free survival compared with best supportive care with ADI-PEG 20 (18). To our knowledge, ours is the first reported study of ADI-PEG 20 in combination with cytotoxic chemotherapy in humans.

Although there were high rates of hematologic toxicity, the severity and degree of neutropenia was similar to known historical rates of neutropenia with docetaxel alone. Phase I trials of single-agent docetaxel in heavily pretreated patients showed that grade 3 and 4 neutropenia was experienced by up to 80% of patients (19). In the TAX 317 trial of previously treated NSCLC patients randomized to docetaxel versus best supportive care, 76% of patients treated with docetaxel experienced grade 3 or 4 neutropenia (20). Even in patients without prior chemotherapy exposure, the grade 3 and 4 neutropenia rate has historically been reportedly high. In the TAX 327 trial of CRPC patients, >30% of patients experienced significant neutropenia (21).

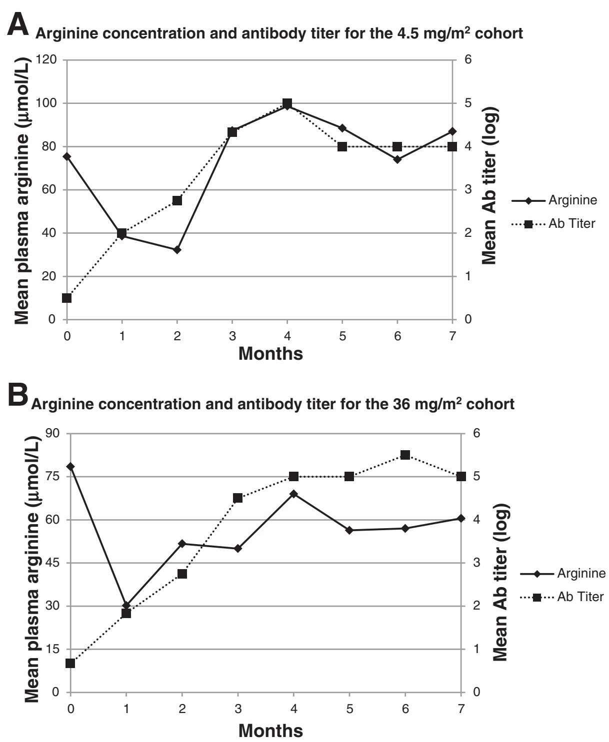

Figure 3.
A, mean plasma arginine levels and ADI-PEG 20 antibody titer for the 4.5 mg/m^2 cohort. B, mean plasma arginine levels and ADI-PEG 20 antibody titer for the 36 mg/m^2 cohort.

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Thus, our observed rate of 78% of patients (many of whom are heavily pretreated) who developed a grade 3 or 4 leukopenia or neutropenia is in line with known toxic effects of this drug. Hematologic toxicities were generally reversible and manageable as well. Additional nonhematologic toxicities were generally manageable. Many of the toxicities were laboratory abnormalities, and it did not appear there were any significant clinical sequelae to these. Although FDA guidance led to late hematologic toxicities being consistently attributed to both drugs, this study suggests the combination has predictable and acceptable toxicity.

Exploratory analysis included pharmacodynamic studies. The data suggest that trends in biomarker levels observed here were similar to pharmacodynamic data from prior studies (10, 11, 13). Arginine was variably suppressed at the end of the first cycle of treatment for different patients, with longer suppression obtained at higher doses. Prior pharmacokinetic and pharmacodynamics studies demonstrated peak enzyme activity of ADI-PEG 20 6 to 7 days after intramuscular administration, and that arginine suppression is continuous when measured daily. At doses of 18 to 36 mg/m^2 of ADI-PEG 20, plasma arginine concentrations tended to be completely depleted early during treatment and then rose slowly after the first month (11, 13). Although the precise duration of arginine suppression after each dose was not known as pharmacodynamics analysis was only performed once per cycle, these earlier studies demonstrate that a monthly sampling is likely adequate to measure suppression. The average measured duration of suppression is encouraging, as data from Yang and colleagues suggested that patients with HCC treated with ADI-PEG 20 as a single agent may have improved overall survival with arginine suppression of at least 4 weeks (12). This study also demonstrated that antibody formation to ADI-PEG 20 was usually detectable by the 2nd cycle of chemotherapy. This is also in line with prior experience with ADI-PEG 20.

In this phase I trial, tumor response rate was a secondary endpoint. However, response was observed in several types of malignancies, and the disease control rate is promising, though most of the tumors treated are known to have some sensitivity to docetaxel alone. Docetaxel is the current first-line chemotherapy option for metastatic CRPC, though it remains an incurable disease (21, 22). The same drug is a widely accepted second-line agent for platinum refractory NSCLC with phase III data demonstrating superiority over vinorelbine and ifosfamide (23). In addition, phase II studies note a response rate near 30% for head and neck tumors exposed to single-agent docetaxel in the second-line setting (24, 25). Suppression of arginine was not required to see clinical benefit, as 3 patients with stable disease did not demonstrate decreased arginine concentrations. Nevertheless, neither patient with progressive disease had documented arginine reduced 50% from baseline. In the 8 patients who had both evaluable disease and suppressed arginine, the disease control rate was 100%. Successful arginine suppression as a predictor of response warrants evaluation in future studies.

In conclusion, ADI-PEG 20 demonstrated reasonable toxicity in combination with docetaxel. The recommended phase II dose is 36 mg/m^2. An expansion cohort of patients with CRPC was preplanned based on the preclinical data with the hope of further evaluating the synergy of docetaxel and ADI-PEG 20 as well as any correlation of efficacy with ASS expression. An expansion cohort for patient with NSCLC was developed given the promising phase I efficacy. Both of these cohorts are now accruing.

Disclosure of Potential Conflicts of Interest

J.A. Thomson has ownership interest (including patents) in Polaris Pharmaceuticals, Inc. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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