厚生労働科学研究費補助金

がん臨床研究事業

オピオイド治療効果に対する実測可能な薬理学的効果予測システムORPSの開発

平成23年度　総括研究報告書

研究代表者　中　川　和　彦

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研究成果の刊行に関する一覧表

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厚生労働科学研究費補助金

がん臨床研究事業

オピオイド治療効果に対する実測可能な薬理学的効果予測ｼｽﾃﾑORPSの開発

平成２３年度　総括研究報告書

研究代表者　中川　和彦

平成２４（２０１２）年　３月

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別紙３

厚生労働科学研究費補助金（がん臨床研究事業）
総合研究報告書

オピオイド治療効果に対する実測可能な薬理学的効果予測ｼｽﾃﾑORPSの開発

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研究要旨　本研究は、がん性疼痛へのオピオイド治療効果に対する実測可能な薬理学的効果予測システムORPS（Opioid treatment Response Prediction System)の開発を目的とする。平成23年度（2年目）は、前向き臨床試験の続行および集積した50例の臨床検体に対して薬力学的バイオマーカーの各種測定を行なった。モルヒネ治療に対する有望な治療効果規定因子と考えられる血中サイトカイン、遺伝子発現変化、SNPを特定し、報告した。

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Ａ．研究目的

がん性疼痛へのオピオイド治療に対して、治療効果の指標およびモニタリングできる実測可能な薬理学的バイオマーカーの開発し、実測可能な薬理学的効果予測システムORPS（Opioid treatment Response Prediction System)の開発を通じて、がん性疼痛の定量化システムに相補的に寄与することを目的とする。　前向き臨床試験においてがん性疼痛へのオピオイド治療を受ける患者を対象に臨床的・定量的エンドポイントと各種薬理学的バイオマーカー候補分子との相関を統合的に検討し、実測可能な薬理学的バイオマーカーを得る。

Ｂ．研究方法

＜臨床試験の続行＞

前向き臨床試験において、速放性モルヒネ製剤によるタイトレーションを行った後、定期投与としてモルヒネ必要用量を投与する。オピオイド治療は通常の治療指針に従って行う。モルヒネ治療前、治療後1日目、治療後8日目に採血、NRS（Numeric Rating Scale)、心理テストおよびQOL評価尺度などを施行する。末梢血は血漿分離およびDNA・RNA用に専用採血管で保存する。

収集する臨床情報は、次の項目である（年齢、性別、PS、疼痛部位、癌種、TNM分類、投薬内容、NSAIDsの種類、量、モルヒネ投与量、オピオイドと相互作用を起こす薬剤の投与の有無、除痛に関連し得る鎮痛補助薬の種類、量、モルヒネの必要用量、治療抵抗性の有無）。

＜臨床検体の測定＞

薬理学的バイオマーカーとしては、①マイクロアレイを用いた薬力学的効果関連遺伝子の特定、②モルヒネ関連代謝酵素の遺伝子多型、③モルヒネ血中濃度、④血中サイトカイン濃度、⑤血中糖鎖解析を実施する。モルヒネ関連遺伝子の遺伝子多型は、ゲノムDNAを試料として測定する。通常使用されるdirect sequence法を用い、PCR法で当該遺伝子の任意のDNA配列を増幅し、シークエンス機器で塩基配列を同定する。マイクロアレイは、末梢血白血球を対象にオピオイド治療前後で変動する遺伝子および、治療抵抗性に関連する遺伝子を特定する際に用いる。Affymetrix 社製のGeneChip HG-U133 Plus2.0 array を用いる。血中サイトカイン測定はBioplex system を用いて測定する。糖鎖解析は、N型糖鎖は薬剤の活性に影響を与えることが知られているため血漿中のN型糖鎖を、糖鎖ビーズを用いて遊離、回収し、MALDI-TOF-MSで解析して検討する。モルヒネ血中濃度測定は、ボンドエルートC18カートリッジカラム、高速液体クロマトグラフィーを用いて血漿中のモルヒネ濃度を測定する。

［研究体制］

研究代表者は研究の統括・計画・測定・解析を実施する。研究分担者は近畿大学医学部腫瘍内科･近畿大学医学部堺病院の2施設において症例集積を行う。バイオマーカーの測定は近畿大学医学部ゲノム生物学教室が行なう。近畿大学総合社会学部心理学科は、心理テストについての評価を行う。大阪府立大学看護学部は、QOL調査票についての評価を行う。解析は九州がんセンター腫瘍統計学部門が行う。研究実施環境については研究施設・研究資料・研究フィールド・現在の研究環境の状況等整備されており問題はない。

（倫理面への配慮）
本研究による身体的な危険性は採血のみでありきわめて少ない。本研究に用いるゲノムDNA遺伝子多型の検出はモルヒネの代謝および薬理作用に関連した遺伝子に制限して解析を行う。本研究では、検体提供者に登録前に同意説明文書・同意書に基づき、本研究の意義、目的、方法、予測される結果や不利益について説明し、文書により自由意思による検体提供者の同意を得る。
本研究のプロトコール「研究名：がん性疼痛へのモルヒネ治療に対する治療効果および薬力学的効果に関する探索的研究」は近畿大学医学部・近畿大学医学部堺病院の２施設の倫理委員会で承認を得ている（平成21年6月5日承認）。
個人情報は個人情報管理者により連結可能匿名化され、厳重に管理される。連結した遺伝子情報が第三者に渡ることはない。本研究では、３省合同「ヒトゲノム・遺伝子解析研究に関する倫理指針」を遵守する。各臨床試験の実施にあたっては「ヘルシンキ宣言」「臨床試験に関する倫理指針」「個人情報保護法」「ヒトゲノム・遺伝子解析研究に関する倫理指針」など関連の指針や法律・省令・告示等に従う。

Ｃ．研究結果
【臨床試験の続行】
検証を含めた最終目標症例数の100例に、予定より早く到達した（H24年度5月現在）。平成23年度・2年目は、前期臨床試験の症例50例に対して以下の解析を行った。
【血中サイトカイン解析】モルヒネ治療前後の血漿サイトカインの変動に対する検討では、MIP-1αの血漿濃度はモルヒネ治療後に有意に減少していた。一方、モルヒネ高用量必要群（治療1日後に判定）においてモルヒネ治療前のIL-8、IL-12（p40）、MIP-1αは有意に低く、モルヒネ高用量必要群（治療8日後に判定）ではモルヒネ治療前のeotaxinは有意に低い濃度であった。最後に、モルヒネ治療前のIL-12（p40）、IL-12（p70）、MIP-1α、MIP-1β濃度は、モルヒネ治療耐性群（治療1日後に判定）では有意に低く、モルヒネ治療前のeotaxinは、モルヒネ治療耐性群（治療8日後に判定）で有意に低い濃度であった。モルヒネ治療前のある種のサイトカイン濃度はモルヒネ治療の有効性と関連し、モルヒネ治療効果を予測するバイオマーカーとなり得ることを初めて報告した（Makimura C, et al. Anticancer Res. 2012）。
【マイクロアレイ解析】
白血球を試料としたマイクロアレイ解析においては、オピオイド受容体シグナル伝達経路関連遺伝子に対して解析を行い、モルヒネ治療によりArrestin beta1（ARRB1）、OPRS、GRK5、RGS9遺伝子の発現が有意に低下することが観察された。独立サンプルに対してRealtime RT-PCR法で解析したところ、ARRB1の発現低下が再現性をもって確認された。ARRB1の発現変化は、血漿中モルヒネ濃度と逆相関することが観察された(Matsuoka H, et al. Oncol Rep. 2012)。
【SNP解析】OPRM1の遺伝子多型とモルヒネ治療の間には相関は認められなかった。しかしながら、COMTについては、A/A遺伝子型群ではモルヒネの血漿中濃度が有意に低く、またモルヒネ必要投与量も低いことが観察された（Matsuoka H, et al. Oncol Rep. 2012)。1,936個の主要薬物代謝マーカーのSNP解析については近日中に解析が終了する見込みである。

Ｄ．考察
H22年度～H23年度で得られたバイオマーカーのうち再現性が得られた分子については、前半50例のデータを用いて予測マーカーとしての閾値を設定する。次に現在集積中の後半50例の各種測定データを用いて予測の有用性を検証していく。具体的にはモルヒネ治療に関連する臨床情報（必要用量・治療抵抗性・NRSなど）の臨床的エンドポイントに対して、上記で特定したバイオマーカーを組み合わせて実測可能な薬理学的効果予測システムORPSを構築する。解析およびORPSの構築は生物統計家によりすべてのデータを動員し開発を行う。また、心理テストとQOL評価表についてもデータを集積しており検討する。

Ｅ．結論
本研究では、３年間で薬理学的バイオマーカーの測定および特定から、がん性疼痛の定量化システムに相補的に寄与可能な分子の選定およびプロトタイプの「薬理学的バイオマーカーによるオピオイド治療効果予測システム」を構築するところまで予定している。

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G. 知的財産権の出願・登録状況

1. 特許取得　なし
2. 実用新案登録　なし
3. その他　　なし

別紙４

研究成果の刊行に関する一覧表レイアウト

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ORIGINAL ARTICLE

High-dose dexamethasone plus antihistamine prevents colorectal cancer patients treated with modified FOLFOX6 from hypersensitivity reactions induced by oxaliplatin

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Abstract
Background Oxaliplatin is a third-generation platinum compound and a key agent for the management of colorectal cancer. Patients treated with oxaliplatin are at risk for hypersensitivity reactions. We designed a modified premedication regimen to prevent oxaliplatin-related hypersensitivity reactions and assessed if this approach is effective.
Methods A retrospective cohort study of patients with advanced colorectal cancer who received modified FOLFOX6 (mFOLFOX6) was performed. Patients received routine premedication with dexamethasone 8 mg and granisetron 3 mg for the first five cycles of mFOLFOX6. From the sixth cycle onward, cohort 1 received the same premedication, and cohort 2 received modified premedication (diphenhydramine 50 mg orally, followed by dexamethasone 20 mg, granisetron 3 mg, and famotidine 20 mg). We compared the incidence of hypersensitivity reactions, duration of treatment, and reasons for treatment withdrawal between the two cohorts.
Results A total of 181 patients were studied (cohort 1, 81; cohort 2, 100). Hypersensitivity reactions developed in 16 patients (20%) in cohort 1 and 7 (7.0%) in cohort 2 ($P = 0.0153$). The median number of cycles increased from 9 in cohort 1 to 12 in cohort 2. Apart from progressive disease, neurotoxicity was the reason for discontinuing treatment in 20% of the patients in cohort 1, as compared with 53% in cohort 2.
Conclusion Increased doses of dexamethasone and antihistamine significantly reduced oxaliplatin-related hypersensitivity reactions. This effective approach should be considered for all patients who receive FOLFOX, allowing treatment to be completed as planned.

Keywords Colorectal cancer · FOLFOX · Hypersensitivity reaction · Oxaliplatin · Premedication

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Introduction

Oxaliplatin, a third-generation platinum derivative, in combination with fluorouracil and leucovorin (FOLFOX) is among the most effective chemotherapies for metastatic colorectal cancer. The increasing use of oxaliplatin for chemotherapy has led to an increased incidence of oxaliplatin-related hypersensitivity reactions. The MOSAIC trial, in which more than 1,100 patients with colorectal cancer received 5-fluorouracil with oxaliplatin in an adjuvant setting, reported a 10.3% incidence of hypersensitivity reactions, which were one of the major reasons for discontinuing treatment [1].

Hypersensitivity is defined as an unexpected reaction inconsistent with a drug's usual toxicity profile. Such reactions usually occur during or immediately after treatment. Once sensitized, patients have recurrent hypersensitivity reactions on subsequent exposure to oxaliplatin. Desensitization protocols have been designed to prevent hypersensitivity reactions. Such protocols have allowed successful rechallenge with oxaliplatin [2, 3]. However, clinical criteria for rechallenge with oxaliplatin remain a matter of debate. Reliable methods for predicting the risk of severe hypersensitivity reactions to oxaliplatin have not been established. The potential risks of rechallenge with oxaliplatin after severe anaphylaxis should be weighed against the expected benefits according to the specific clinical situation.

Hypersensitivity reactions to platinum salts (cisplatin, carboplatin) are classically type I (i.e., immediate) reactions [4], the incidence of which increases with multiple cycles of therapy [5]. The symptoms can resolve after treatment with antihistamines and steroids. More recent series have documented a considerably higher incidence of hypersensitivity reactions, ranging between 8% and 19% [6–10]. Besides these reports, studies assessing the preventative effect of premedication on oxaliplatin-related hypersensitivity are scant.

We have designed a modified premedication regimen, which includes a higher dose of dexamethasone (20 mg) plus an antihistamine. This dose of dexamethasone has been shown to be safe and effective for the prophylaxis of paclitaxel-associated hypersensitivity reactions [11]. Dexamethasone (20 mg) can be administered intravenously for desensitization against oxaliplatin hypersensitivity [3, 12]. These findings suggested that the prophylactic use of dexamethasone (20 mg) would reduce the incidence or severity of hypersensitivity reactions. We gave our modified regimen for premedication to patients with advanced colorectal cancer after they had received five cycles of a modified regimen of FOLFOX6 (mFOLFOX6) with standard premedication. We retrospectively compared the frequencies of hypersensitivity reactions between patients who received this modified premedication regimen with those who received standard premedication for the duration of FOLFOX treatment to determine whether our regimen was effective.

Patients and methods

Patient selection

This investigation was a retrospective cohort study of patients with advanced colorectal cancer who received modified FOLFOX6 (mFOLFOX6: oxaliplatin 85 mg/m^2 plus concurrent leucovorin 400 mg/m^2 as a 2-h intravenous infusion on day 1, followed by a bolus injection of 5-fluorouracil 400 mg/m^2 and by a 46-h continuous intravenous infusion of 5-fluorouracil 2,400 mg/m^2, repeated every 2 weeks) at Kinki University Hospital from September 2005 through September 2009. Eligible patients had to have adenocarcinoma of the colon or rectum; unresectable metastases; adequate bone marrow, liver, and kidney functions; a World Health Organization performance status of 0–2; and an age of $\geq$18 years. Patients who received five cycles of mFOLFOX6 without any allergic reactions were eligible. Patients with central nervous system metastases, only bone metastases, second malignancies, bowel obstruction, peripheral neuropathy of grade 3 or higher, symptomatic angina pectoris, or disease confined to previous radiation fields were excluded.

Chemotherapy and premedication

The patients were divided into two cohorts. In cohort 1, patients received routine premedication for the first five and subsequent cycles of mFOLFOX6 from September 2005 through September 2007. In cohort 2, treated between October 2007 and September 2009, patients similarly received routine premedication for the first five cycles. The premedication included routine antiemetic prophylaxis with dexamethasone 8 mg and granisetron 3 mg in 50 ml 0.9% saline, given intravenously 15 min before oxaliplatin. To reduce the risk of hypersensitivity reactions associated with continued treatment, from the sixth cycle onward all patients in cohort 2 received a modified premedication regimen, consisting of diphenhydramine 50 mg given orally 30 min before oxaliplatin, followed by dexamethasone 20 mg, granisetron 3 mg, and famotidine 20 mg in 50 ml saline, given intravenously 15 min before oxaliplatin.

Definition of allergic reactions

A hypersensitivity reaction to oxaliplatin was defined as the development of at least one of the following signs or symptoms after treatment with oxaliplatin: palmar erythema, pruritus, urticaria, diffuse erythroderma, tachycardia, angina, wheezing, facial or tongue edema, dyspnea, hypertension, hypotension, respiratory arrest, anaphylaxis, seizure, or death. Clinically significant respiratory compromise (wheezing associated with hypoxia or hypercarbia, and respiratory arrest), clinically significant cardiovascular compromise (angina, symptomatic hypotension or hypertension, and cardiovascular collapse), anaphylaxis, seizure, and death were all considered manifestations of a severe allergic reaction.

Study objectives and outcome measures

The primary objective of this study was to evaluate whether the modified premedication regimen reduced the incidence of hypersensitivity reactions. The primary outcome measure was the reduction in such reactions as compared with routine premedication. Secondary objectives were to evaluate the safety of the modified premedication regimen and to compare the duration of treatment with mFOLFOX6 and the reasons for treatment discontinuation between the two cohorts. Progressive disease was excluded from the analysis of reasons for treatment discontinuation.

Statistical analysis

A primary analysis was performed to compare cohorts 1 and 2. To assess the effect of premedication on hypersensitivity reactions to oxaliplatin in cohorts 1 and 2, we calculated risk ratios and 95% confidence intervals (95% CI). In addition, we calculated adjusted risk ratios with 95% CI for covariates (age, sex, diagnosis, prior treatment) by performing a Poisson regression analysis. To assess the effect of treatment exposure to the premedication on hypersensitivity reactions to oxaliplatin in cohorts 1 and 2, we compared the number of cycles between the cohorts with the use of the Wilcoxon test. All tests were two-sided with a significance level ≤ 0.05.

Results

Patient characteristics

The characteristics of the 181 eligible patients are listed in Table 1 (81 in cohort 1 and 100 in cohort 2). The patients' characteristics were well balanced between the cohorts, except for bevacizumab, because bevacizumab was approved in July 2007 in Japan. In 2007, bevacizumab was introduced to Japan; we therefore assessed the number of cycles administered for mFOLFOX6 alone in cohort 1 ($n = 81$) and for mFOLFOX6 alone ($n = 49$) and mFOLFOX6 plus bevacizumab ($n = 51$) in cohort 2. No patient in cohort 1 received bevacizumab, whereas nearly half the patients in cohort 2 received bevacizumab. No patient had a known history of allergy to a platinum salt. Five patients had a history of drug allergy.

Table 1 Patient characteristics

	Routine premedication (cohort 1)	Modified premedication (cohort 2)
No. of patients	81	100
Median age, years (range)	62 (29–82)	62 (34–84)
Sex		
Male/female	53/28	66/34
Diagnosis		
Colon	44	51
Rectum	37	49
Line of therapy		
First-line therapy	43	50
Second-line therapy	27	42
Third-line or subsequent therapy	11	8
mFOLFOX6 + bevacizumab	0	51
Median cumulative oxaliplatin dose for the first five cycles (mg/m^2)	414	419

FOLFOX6 chemotherapy with oxaliplatin plus fluorouracil and leucovorin

Incidence of hypersensitivity reactions to oxaliplatin

In cohort 1, hypersensitivity reactions developed in 16 (20%) of 81 patients who received routine premedication (Table 2). Six of these patients (7.4%) had manifestations of severe allergic reactions. In cohort 2, hypersensitivity reactions occurred in 7 (7.0%) of 100 patients who received modified premedication (Table 2). Three of these patients (3.0%) had manifestations of severe allergic reactions. The incidence of hypersensitivity reactions differed significantly between the cohorts (risk ratio, 0.3544; 95% CI, 0.1532–0.8196; $P = 0.0153$). Poisson regression analysis yielded a risk ratio of 0.3581 (95% CI, 0.1541–0.8324; $P = 0.0170$) (Table 2). None of the patients with a history of drug allergy had hypersensitivity reactions.

Treatment exposure

The 81 patients in cohort 1 received a total of 382 cycles of mFOLFOX6 (Table 2). The median number of cycles of mFOLFOX6 was 9 (9 as first-line therapy, 9 as second-line or subsequent therapy) (Table 3). The 100 patients in cohort 2 received a total of 781 cycles (Table 2). The median number of cycles of mFOLFOX6 was 12 overall (Table 2). The number of cycles differed significantly between the cohorts on the Wilcoxon test ($P < 0.0001$) (Table 2). In cohort 2, the median number of cycles of mFOLFOX6 without bevacizumab was 11 (10 as first-line therapy, 11 as second-line or subsequent therapy) (Table 3). The median number of cycles of mFOLFOX6 plus bevacizumab was 12 (12 as first-line therapy, 12 as second-line or subsequent therapy) (Table 3). The number of cycles in patients who additionally received bevacizumab did not differ significantly on the Wilcoxon test. The reasons for treatment

Table 2 Effect of premedication on incidence of hypersensitivity reactions to oxaliplatin

	Incidence of hypersensitivity reactions/ total patients (%)	Risk ratio (95% CI) (*P* value)	Adjusted risk ratio (95% CI) (*P* value)	Incidence of hypersensitivity reactions/total cycles (%)	Median cycles	*P* value
Routine premedication (cohort 1)	16/81 (20)	0.3544 (0.1532–0.8196) ($P = 0.0153$)	0.3581 (0.1541–0.8324) ($P = 0.0170$)	16/382 (4.2)	9	<0.0001
Modified premedication (cohort 2)	7/100 (7.0)			7/781 (0.90)	12	

CI confidence interval

Table 3 Effect of modified premedication on median number of treatment cycles

Cohort	Regimen	Line of therapy	Median cycles of mFOLFOX6 (range)	No. of patients
Routine premedication (cohort 1)	mFOLFOX6	First-line therapy	9 (6–17)	43
		Second-line or subsequent therapy	9 (6–22)	38
Modified premedication (cohort 2)	mFOLFOX6	First-line therapy	10 (6–28)	27
		Second-line or subsequent therapy	11 (6–29)	22
	mFOLFOX6 + bevacizumab	First-line therapy	12 (7–31)	23
		Second-line or subsequent therapy	12 (7–31)	28

discontinuation differed between the cohorts (Table 4). The main reason for treatment discontinuation in cohort 1 was hypersensitivity reactions (53%). Hypersensitivity was the second reason for discontinuing treatment in 11% of the patients in cohort 2. The main reason for treatment discontinuation in cohort 2 was neurotoxicity (53%). Neurotoxicity was the second reason for discontinuing treatment in 20% of the patients in cohort 1.

Table 4 Reasons for treatment discontinuation

Reasons for discontinuation	Routine premedication (cohort 1) ($n = 30$)		Modified premedication (cohort 2) ($n = 62$)	
	No. of patients	%	No. of patients	%
Neurotoxicity	6	20	33	53
Hypersensitivity reactions	16	53	7	11
Fatigue	0	0	3	4.8
Vomiting	0	0	2	3.2
Thrombocytopenia	0	0	1	1.6
Febrile neutropenia	2	6.7	4	6.5
Liver dysfunction	2	6.7	0	0
Thrombosis	0	0	1	1.6
Diarrhea	0	0	1	1.6
Others	4	13	10	16

Safety

Modified premedication did not increase the incidence of adverse effects related to the high dose of dexamethasone, such as exacerbation of diabetes, osteoporosis, and compression fracture. Diphenhydramine was associated with mild somnolence in two patients, but this symptom resolved promptly.

Discussion

The incidence of hypersensitivity reactions in cohort 1 was similar to that in previous studies. Allergic reactions usually develop after several infusions of oxaliplatin [13]. In cohort 2 of our study, the use of modified premedication decreased the incidence of hypersensitivity reactions to 7.0%. Modified premedication with increased doses of dexamethasone and antihistamines thus reduced the incidence of hypersensitivity reactions by 14 percentage points as compared with cohort 1, treated with routine premedication. Gowda et al. [9] evaluated the incidence of hypersensitivity reactions to oxaliplatin and reported 32 hypersensitivity reactions in 169 patients (incidence, 18.9%) who received oxaliplatin preceded by dexamethasone (10 mg) and ondansetron (Zofran, 8 mg). Brandi et al. [7] reported that hypersensitivity reactions occurred in 18.1% of patients who received oxaliplatin preceded by ondansetron. Other than these reports, studies assessing the

preventative effect of premedication on oxaliplatin-related hypersensitivity are scant.

In our study, all patients received mFOLFOX6. Kim et al. retrospectively investigated 247 patients given oxaliplatin-containing regimens and reported that the incidences of hypersensitivity reactions did not depend on the oxaliplatin-containing regimen employed [6]. The modified premedication regimen used in the present study might thus be useful for the management of hypersensitivity reactions to other oxaliplatin-containing regimens.

The patient characteristics were well balanced between the cohorts. The median number of cycles increased from 9 to 12 when modified premedication was used instead of routine premedication. This three-cycle increase in the median number of cycles administered to patients who received modified premedication is particularly important, because prolonged therapy might contribute to improved survival. In cohort 2, patients could receive mFOLFOX6 plus bevacizumab, newly approved in Japan. The addition of bevacizumab to oxaliplatin-based, first-line chemotherapy has been shown to significantly improve progression-free survival in patients with metastatic colorectal cancer [14, 15]. We therefore examined if increasing the number of treatment cycles was associated with the inclusion of bevacizumab. The median number of cycles in patients who additionally received bevacizumab was similar to that in patients treated with mFOLFOX6 without bevacizumab. We found no association between bevacizumab and the number of cycles administered to cohort 2. Bevacizumab thus apparently did not contribute to a longer duration of treatment. Kim et al. [6] reported that anti-vascular epithelial growth factor (anti-VEGF) monoclonal antibody bevacizumab was not associated with hypersensitivity reactions when given with combination chemotherapy regimens. Consistent with their results, we found no difference in the frequency of hypersensitivity reactions according to the presence or absence of bevacizumab.

The major reasons for discontinuing treatment with mFOLFOX6 were neurotoxicity and hypersensitivity reactions. Neurotoxicity was the most remarkable as well as the most common dose-limiting factor. Treatment withdrawal was based on the highest grade adverse effects occurring during the previous cycle. Sensory neuropathy was treatment limiting in patients who received FOLFOX4 (85 mg/m^2 oxaliplatin) because it generally occurred after 8–10 cycles [16]. Tournigand et al. [17] reported that oxaliplatin was associated with grade 3 neuropathy in 20% of patients who received FOLFOX6 (100 mg/m^2 oxaliplatin) and in 34% of patients after 12 cycles. In our study, neurotoxicity was the reason for discontinuing treatment in 20% of the patients in cohort 1, as compared with 53% of those in cohort 2. These reports supported our results that a decreased frequency of hypersensitivity reactions was associated with an increased rate of treatment discontinuation caused by neurotoxicity.

If treatment is discontinued because of neurotoxicity, oxaliplatin-based therapy may be able to be resumed after this adverse effect resolves. This strategy enables treatment for longer periods. When oxaliplatin is used in an adjuvant setting, in which the median number of courses of treatment ranges from 10 to 12, it is important to note that the use of modified premedication reduced the frequency of hypersensitivity reactions from 20% to 7.0%, allowing treatment to be completed as planned. Completion of adjuvant treatment by our strategy may reduce the relapse rate, thereby contributing to improved survival.

The exact mechanism responsible for platinum-related hypersensitivity reactions is unknown, but several mechanisms may be involved. Hypersensitivity reactions have been linked to the release of histamine and other vasoactive substances and ascribed to type I hypersensitivity IgE-mediated reactions [9, 18]. Hypersensitivity reactions usually develop after multiple infusions of oxaliplatin (7 on average) [19], clearly showing that repeated exposure to the drug is prerequisite to the induction of an allergic immune response.

The optimal strategy for resuming treatment after discontinuation caused by an episode of hypersensitivity remains controversial. Because resumption of treatment can be fatal, several preventive procedures have been proposed. Patient desensitization is of interest because of its consistent efficacy but has been studied in only a small number of subjects [19]. Moreover, desensitization is cumbersome to implement. The prick test, using a concentration of 1 mg/ml oxaliplatin, appears not to be very sensitive. Skin tests are useful for detecting IgE-mediated reactions, but their sensitivity is not high enough. When hypersensitivity reactions to oxaliplatin do occur, symptoms generally subside on discontinuation of treatment and administration of steroids and antihistamines. Mild sensitivity reactions to oxaliplatin can be controlled by treatment with antihistamines, steroids, or both. Interestingly, all the patients in cohort 1 of our study received premedication with dexamethasone 8 mg and granisetron 3 mg as a part of a "standard antiemetic" regimen before the infusion of oxaliplatin. In cohort 2, we confirmed that modified premedication with an increased dose of dexamethasone plus an antihistamine effectively decreased hypersensitivity reactions. Premedication was not associated with any side effects. In particular, adverse events potentially associated with a high dose of dexamethasone, such as exacerbation of diabetes, osteoporosis, and compression fractures, did not occur.

In conclusion, our study showed that modified premedication with an increased dose of dexamethasone plus an antihistamine from the sixth cycle of mFOLFOX6

greatly reduced the frequency of hypersensitivity reactions, an important dose-limiting toxic effect of oxaliplatin. A reduced incidence of hypersensitivity reactions to oxaliplatin enhances the effectiveness of mFOLFOX6 by allowing treatment to be prolonged. Our results were statistically significant, although the study was performed in a single institution. We therefore recommend our modified premedication regimen to reduce hypersensitivity reactions in clinical practice. Phase III prospective studies are highly warranted to confirm the effectiveness of modified premedication.

Conflict of interest No author has any conflict of interest.

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ORIGINAL REPORT

Randomized Phase III Placebo-Controlled Trial of Carboplatin and Paclitaxel With or Without the Vascular Disrupting Agent Vadimezan (ASA404) in Advanced Non–Small-Cell Lung Cancer

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Clinical Trials repository link available on JCO.org.

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ABSTRACT

Purpose
This phase III trial was conducted to test whether the novel vascular disrupting agent ASA404 (vadimezan), when combined with first-line platinum-based chemotherapy, improves survival in patients with advanced non–small-cell lung cancer (NSCLC) versus chemotherapy alone.

Patients and Methods
Patients with advanced stage IIIB or IV NSCLC, stratified by sex and tumor histology, were randomly assigned 1:1 to paclitaxel (200 mg/m^2) and carboplatin (area under the curve, 6.0) with or without ASA404 (1,800 mg m^2), given intravenously once every 3 weeks for six cycles followed by maintenance ASA404 or placebo. Primary end point was overall survival (OS); secondary end points included overall response rate (ORR) and progression-free survival (PFS).

Results
One thousand two hundred ninety-nine patients were randomly assigned. The trial was stopped for futility at interim analysis. At final analysis, there was no difference in OS seen between ASA404 (n = 649) and placebo (n = 650) arms: median OS was 13.4 and 12.7 months respectively (hazard ratio [HR], 1.01; 95% CI, 0.85 to 1.19; P = .535). Similarly, no OS difference was seen in the histologic (squamous or nonsquamous) and sex (male or female) strata. Median PFS was 5.5 months in both arms (HR, 1.04; P = .727), while ORR was 25% in both arms (P = 1.0). Overall rate of adverse events (AEs) was comparable between the ASA404 and placebo arms. Grade 4 neutropenia (27% *v* 19%) and infusion site pain (10% *v* 0.5%) were reported more frequently in the ASA404 arm.

Conclusion
The addition of ASA404 to carboplatin and paclitaxel, although generally well tolerated, failed to improve frontline efficacy in advanced NSCLC.

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INTRODUCTION

Vascular disruption of existing tumor blood vessels represents a novel antineoplastic strategy. In preclinical models, tumor vascular disrupting agents (VDAs) have been shown to selectively affect endothelial cells of established tumor blood vessels, resulting in ischemia in the central component of tumor masses, but with persistence of a viable layer of cancer cells in the periphery.[1-3] Because tumor VDAs predominantly target the tumor core—a hypoxic region in which cells are known to harbor resistance to traditional DNA-damaging chemotherapy—drug development has evolved to combine VDAs (targeting the core) with cytotoxic agents (targeting the viable rim) to achieve synergistic tumor kill.[4]

Among the tumor VDAs furthest along in development is ASA404 (vadimezan, 5,6-dimethylxanthenone-4-acetic acid), an analog of flavone acetic acid. Although the actual molecular target of ASA404 is unknown, its pharmacologic effects have been well described in preclinical models.[5] It has been shown to promote apoptosis of endothelial cells of tumor blood vessels, causing the release of von Willebrand's factor which then leads to blood clotting and vessel occlusion.

ASA404 has also been shown to trigger a local cascade of cytokines including serotonin and tumor necrosis factor. The direct and indirect effects of ASA404 culminate in the breakdown of vasculature and hemorrhagic tumor necrosis. ASA404 has also shown to have either additive or synergistic antitumor effects when combined with several cytotoxic chemotherapeutic agents, including paclitaxel.[6]

A randomized phase II trial of carboplatin (area under the curve [AUC], 6) and paclitaxel (175 mg/m^2) with or without ASA404 (at 1,200 mg/m^2) was conducted in 73 patients with advanced non–small-cell lung cancer (NSCLC),[7] a population in which standard platinum-based chemotherapy has traditionally yielded marginal outcomes, such as overall response rates (ORR) of lower than 30% and median overall survival (OS) times of approximately 8 to 10 months.[8,9] In that trial, ASA404 plus chemotherapy appeared to improve efficacy over chemotherapy alone in terms of ORR (31.3% *v* 22.2%), median time to progression (TTP, 5.4 *v* 4.4 months), and median OS (14.0 *v* 8.8 months). To further verify those results and to explore a dose-response relationship, a single-arm phase II extension trial of 31 patients with advanced NSCLC was performed to evaluate ASA404 at a higher dose of 1,800 mg/m^2, again in combination with carboplatin and paclitaxel. Tumor ORR was 37.9%, median TTP was 5.5 months, and median OS was 14.9 months.[10] In both studies, efficacy appeared to be improved with ASA404 regardless of tumor histology (squamous *v* nonsquamous), and there was no overt increase in serious adverse events.

These results led to this global, randomized, double-blind, placebo-controlled trial (Antivascular Targeted Therapy: Researching ASA404 in Cancer Treatment [ATTRACT-1]) of ASA404 plus carboplatin and paclitaxel versus placebo plus carboplatin and paclitaxel in patients with stage IIIB/IV NSCLC who had not previously received systemic therapy for metastatic disease. This trial was conducted at more than 200 sites in 20 countries.

PATIENTS AND METHODS

Patients

Eligible patients were ≥ 18 years of age with histologically confirmed NSCLC and WHO performance status 0 or 1 who had either newly-diagnosed stage IIIb disease (malignant pleural effusion or pericardial effusion) or stage IV disease.[11] No prior systemic antineoplastic treatment for advanced NSCLC was allowed; however, prior neoadjuvant or adjuvant chemotherapy for earlier stage I/II NSCLC was allowed if the last dose was 12 months or more before the baseline visit. Patients must have measurable or nonmeasurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) and acceptable hematologic, renal, and hepatic end-organ function. Patients must have recovered from all prior anticancer therapies, including radiotherapy and major surgery.

Patients with symptomatic or uncontrolled central nervous metastases were excluded, as were those with a history of another primary malignancy ≤ 5 years, with the exception of nonmelanoma skin cancer or cervical cancer in situ. Prior exposure to tumor VDAs or other antiangiogenic agents was not allowed. Patients with uncontrolled hypertension (systolic blood pressure [BP] > 160 mmHg and/or diastolic BP > 90 mmHg), hemoptysis (> 1 teaspoon in a single episode within 4 weeks), or concurrent severe and/or uncontrolled medical, neurologic, or psychiatric disease were excluded. Because of the uncertain effects of protocol therapy on the developing fetus or nursing infant, pregnant or breast feeding females were excluded. Patients with pre-existing QT prolongation or relevant cardiac rhythm disorders at baseline were also excluded.

The study protocol was approved by the independent ethics committee or institutional review board of all participating study centers, and all patients gave written informed consent before any study-related procedures were performed. A list of all participating investigators and their countries of origin is provided in Appendix Table A1 (online only).

Study Design and Treatment Schedule

Patients received a 3-hour intravenous infusion of paclitaxel every 3 weeks. To be consistent with contemporary studies of paclitaxel-based therapy in NSCLC, paclitaxel dose was set at 200 mg/m^2 instead of 175 mg/m^2. Paclitaxel was followed by a 30- to 60-minute infusion of carboplatin AUC 6.0 on day 1. Calvert's formula using AUC and calculated glomerular filtration rate (Cockroft and Gault formula) was used to determine carboplatin dose. Patients also received an intravenous infusion of ASA404 1800 mg/m^2 or matched placebo (both with identical amber colored cover and tubing for ASA404 light sensitivity) over 20 minutes after the administration of chemotherapy on day 1. Any dose reduction or dose delay in chemotherapy was based on the severity of a related toxicity, as graded by National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0. Patients requiring a delay in study treatment for longer than 3 weeks or who had more than two dose reductions were discontinued from study treatment.

Study treatment was to be administered for 6 treatment cycles. Patients who completed the 6 cycles of study treatment without progressive disease (PD) continued to receive blinded study drug, either ASA404 1,800 mg/m^2 or placebo, as maintenance treatment until progression. Patients who discontinued study treatment before completing all 6 cycles were not eligible to continue on maintenance treatment but were observed until documented PD and then for survival.

Tumor response was evaluated according to the RECIST using computed tomography scans (or magnetic resonance imaging) with contrast of the chest and abdomen. All the patients were assessed radiographically every 6 weeks ± 3 days from the date of random assignment until PD. Patients who discontinued study treatment for reasons other than documented PD continued to have tumor assessments every 6 weeks until documented PD. All patients were followed every 6 weeks for survival following treatment discontinuation, or documented PD until either death or the data cutoff date was reached.

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 questionnaire was used to evaluate the patient's symptoms, function, and quality of life. Questionnaires were administered before patients being assessed for response or informed about their disease status. Questionnaires were completed by the patient on day 1 of each odd cycle and at the end of treatment visit. Safety assessments consisted of monitoring and recording all AEs and serious AEs, with their severity and relationship to study drug, and regular monitoring of hematology, blood chemistry, urine, EKGs, vital signs, physical condition, and body weight.

Statistical Analysis

Random assignment was stratified by sex (male *v* female) and histology (squamous *v* nonsquamous). Institutional balancing was used to ensure that approximately the same numbers of patients were assigned to each treatment arm within the center. Sample size calculation was based on a two-look group sequential design with an overall type I error of $\alpha = .025$ (one sided) and a study power $1 - \beta = 90\%$ using the log-rank test. Assuming an hazard ratio (HR) of 0.80 (corresponding to a median OS of 9 months for the placebo plus carboplatin/paclitaxel arm and 11.25 months for the ASA404 plus carboplatin/paclitaxel arm), a 1:1 random assignment to ASA404 versus placebo and a preplanned interim analysis with 25% of the total number of deaths, a total of 950 deaths were required in the final analysis of OS. Assuming a recruitment time of 18 months and an additional follow-up of approximately 15 months, 1,200 patients were required. One interim analysis of OS was planned after the occurrence of 238 deaths (25% of the total deaths). The trial was to be stopped for futility if an observed HR (ASA404 *v* placebo) was greater than 0.9985, where a HR of lower than 1 meant better survival in the experimental arm than in the control arm. At the preplanned interim analysis conducted in March 2010, and the independent data safety monitoring committee recommended stopping the trial for futility.

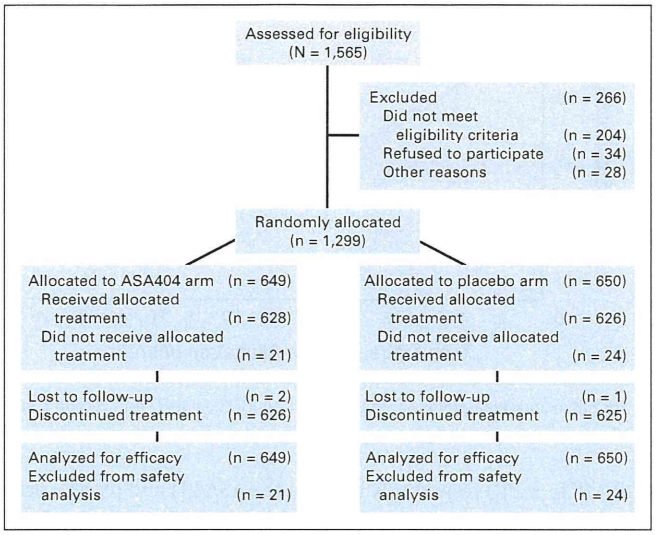

Fig 1. CONSORT diagram.

RESULTS

Patients

From April 2008 to October 2009, 1,299 patients were randomly assigned, 649 to the ASA404 arm and 650 to the placebo arm. Figure 1 summarizes the disposition of patients entered into the trial. Baseline demographics and disease characteristics are summarized in Table 1. The ASA404 and placebo treatment arms were well-balanced with regard to the demographic characteristics. The median age was 61 years, and the majority of the patients were white (approximately 72%). Most patients had nonsquamous tumor histology (75%), with adenocarcinoma (approximately 67%) being the most common subtype. The vast majority of patients (91%) had stage IV disease. The time from initial diagnosis to random assignment was ≤ 6 months for 92% of patients. There were no apparent differences between the arms in the proportion and type of subsequent systemic therapies after completion of protocol treatment, as summarized in Table 2.

Efficacy

Overall survival outcomes for all randomly assigned patients are summarized in Figure 2. The median OS for the ASA404 and placebo arms was 13.4 months (95% CI, 11.4 to 16.6) and 12.7 months (95% CI, 11.3 to 14.4), respectively. There was no statistically significant difference in OS between the two treatment arms, HR of 1.01 (95% CI, 0.85 to 1.19; one-sided $P = .535$). There were also no differences in OS between the two treatment arms with regards the primary stratification factors of histology and sex. Specifically, HRs for OS for the strata were as follows: patients with nonsquamous NSCLC (HR, 0.98; 95% CI, 0.80 to 1.19); squamous NSCLC patients (HR, 1.10; 95% CI, 0.79 to 1.52); male patients (HR, 1.02; 95% CI, 0.83 to 1.25); and female patients (HR, 0.98; 95% CI, 0.72 to 1.34).

Table 1. Patient Demographics and Disease Characteristics

Demographic or Characteristic	ASA404 + Carboplatin/Paclitaxel		Placebo + Carboplatin/Paclitaxel		All Patients	
	No.	%	No.	%	No.	%
No. of patients	649		650		1,299	
Age, years						
Median	62		61		61	
Range	29-87		23-85		23-87	
Sex						
Male	403	62.1	405	62.3	808	62.2
Race						
White	464	71.5	465	71.5	929	71.5
Asian	162	25.0	164	25.2	326	25.1
Other	23	3.5	21	3.3	44	3.4
Performance status						
0	266	41.0	258	39.7	524	40.3
1	381	58.7	384	59.1	765	58.9
Missing	2	0.3	8	1.2	10	0.8
Histology						
Squamous	132	20.3	133	20.5	265	20.4
Nonsquamous	494	76.1	484	74.5	978	75.3
Adenocarcinoma	432	66.5	436	67.1	868	66.8
Undifferentiated carcinoma	24	3.7	20	3.1	44	3.4
Adenosquamous cell carcinoma	7	1.1	4	0.6	11	0.8
Large-cell carcinoma	29	4.5	23	3.5	52	4.0
Other (mixed carcinoma or missing)	25	3.8	34	5.3	59	4.5
Stage						
IIIB	53	8.2	56	8.6	109	8.4
IV	596	91.8	591	90.9	1,187	91.4
Missing	0	0.0	3	0.5	3	0.2

Table 2. Systemic Antineoplastic Therapies Since Discontinuation of Study Treatment

Line of Treatment	ASA404 + Carboplatin/ Paclitaxel		Placebo + Carboplatin/ Paclitaxel	
	No.	%	No.	%
No. of patients	649		650	
Second line				
Any	364	56.1	368	56.6
Pemetrexed	115	17.7	113	17.4
Erlotinib	70	10.8	75	11.5
Carboplatin	64	9.9	56	8.6
Paclitaxel	42	6.5	41	6.3
Cisplatin	36	5.5	25	3.8
Docetaxel	35	5.4	44	6.8
Gemcitabine	34	5.2	38	5.9
Gefitinib	26	4.0	27	4.2
Investigational drug	22	3.4	28	4.3
Vinorelbine	20	3.1	16	2.5
Bevacizumab	9	1.4	9	1.4
Paclitaxel with carboplatin	4	0.6	2	0.3
Other cytotoxic chemotherapy	5	0.5	9	1.4
Other biologics	3	0.5	1	0.2
Third line				
Any	99	15.3	106	16.3
Erlotinib	35	5.4	31	4.8
Pemetrexed	28	4.3	29	4.5
Vinorelbine	9	1.4	7	1.1
Gemcitabine	7	1.1	5	0.8
Cisplatin	6	0.9	5	0.8
Docetaxel	6	0.9	16	2.5
Gemcitabine	6	0.9	2	0.3
Investigational drug	5	0.8	2	0.3
Bevacizumab	4	0.6	3	0.5
Carboplatin	3	0.5	1	0.2
Gefitinib	2	0.3	6	0.9
Other cytotoxic chemotherapy	5	0.8	6	0.9
Other biologics (cetuximab)	1	0.2	0	
Fourth line				
Any	31	4.8	28	4.3
Fifth line				
Any	6	0.9	5	0.8

Progression-free survival (as assessed by investigators) for all patients is summarized in Figure 3. The estimated rates of PFS at 12 months were 6.7% and 6.9% in the ASA404 and placebo arms, respectively. The median PFS was 5.5 months (95% CI, 5.2 to 5.6) for the ASA404 arm, and 5.5 months (95% CI, 5.4 to 5.6) for the placebo arm. The two treatments arms did not show a statistically significant difference in PFS (HR, 1.04; 95% CI, 0.91 to 1.19; one-sided $P = .727$). As with the OS analysis, none of the prespecified strata demonstrated any significant differences in PFS between the treatment arms (data not shown).

Overall response rate as per RECIST based on investigators' assessment demonstrated complete response (CR) in 2 (0.3%) and 3 (0.5%) patients and partial response (PR) in 158 (24.3%) and 157 (24.2%) in the ASA404 and placebo arms, respectively. Disease stabilization (39.6% *v* 39.5%) and PD (15.7% *v* 15.8%) were observed at similar rates between the ASA404 and placebo arms, respectively. The

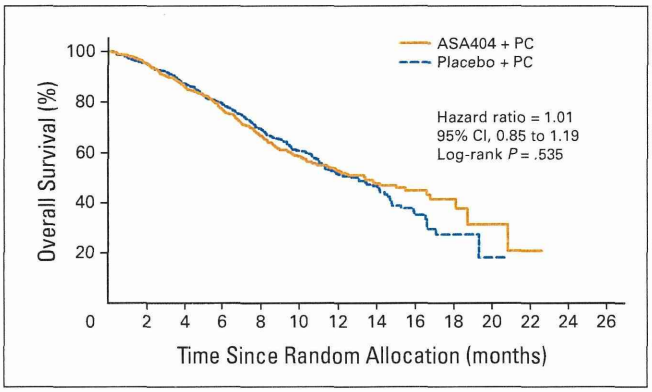

Fig 2. Kaplan-Meier curves for overall survival. PC, paclitaxel and carboplatin.

ORR (CR + PR) respectively between the ASA404 and placebo arms were 24.7% (95% CI, 21.4 to 28.2) and 24.6% (95% CI, 21.3 to 28.1).

Safety and Tolerability

The median number of cycles delivered for the combination treatment was 5 (range, 1 to 6) in both treatment arms. The median number of cycles for maintenance treatment was 3 (range, 1 to 17) and four (range, 1 to 16) in the ASA404 and placebo arms, respectively. Overall, there were no major variations between the two arms in the number of patients in each treatment cycle. Similarly, dose reductions and delays were comparable between both the treatment arms. The most common reasons for dose reduction were AEs (36.9% in the ASA404 arm *v* 31% in the placebo arm) and lab test abnormalities (21.6% *v* 20.8%), whereas the most common reasons for dose delay were AEs (23.5% *v* 22.2%) and scheduling conflicts (25.6% *v* 26.1%). Median cumulative dose, median dose intensity, and median relative dose intensity were also comparable between the ASA404 and placebo treatment arms (data not shown).

The incidence of AEs was similar between the arms and the majority of AEs were of grade 1 to 2 severity. Neutropenia, alopecia, nausea, and fatigue were the most frequently reported AEs, occurring with comparable incidence in both arms. Incidence of grade 4 neutropenia was higher in the ASA404 arm than the placebo arm (26.6% and 19%, respectively). Infusion site pain was also reported at a higher incidence in the ASA404 arm compared with the placebo arm (10.5%

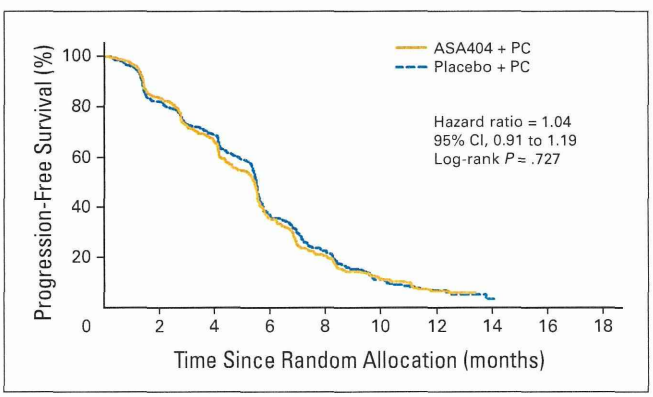

Fig 3. Kaplan-Meier curves for progression-free survival (investigator assessment). PC, paclitaxel and carboplatin.

Table 3. Adverse Events, Regardless of Study Drug Relationship, With at Least 10% Incidence of Any Grade Events in Either Arm by Preferred Term, Maximum Grade, and Treatment

	Treatment by Grade											
	ASA404 + PC (n = 629)						Placebo + PC (n = 62)					
	All		3		4		All		3		4	
Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Neutropenia	357	56.8	158	25.1	167	26.6	317	50.7	148	23.7	119	19.0
Alopecia	297	47.2	10	1.6	3	0.5	303	48.5	6	1.0	0	0.0
Nausea	250	39.7	14	2.2	1	0.2	251	40.2	13	2.1	0	0.0
Fatigue	224	35.6	22	3.5	1	0.2	219	35.0	21	3.4	0	0.0
Decreased appetite	195	31.0	13	2.1	0	0.0	166	26.6	12	1.9	0	0.0
Constipation	166	26.4	7	1.1	1	0.2	161	25.8	5	0.8	0	0.0
Anemia	155	24.6	29	4.6	5	0.8	156	25.0	28	4.5	2	0.3
Diarrhea	154	24.5	15	2.4	1	0.2	128	20.5	6	1.0	1	0.2
Arthralgia	153	24.3	7	1.1	0	0.0	146	23.4	13	2.1	2	0.3
Dyspnea	131	20.8	32	5.1	5	0.8	131	21.0	26	4.2	4	0.6
Myalgia	131	20.8	5	0.8	0	0.0	12	20.3	10	1.6	0	0.0
Vomiting	131	20.8	9	1.4	0	0.0	146	23.4	13	2.1	0	0.0
Peripheral neuropathy	115	18.3	8	1.3	2	0.3	124	19.8	10	1.6	1	0.2
Cough	104	16.5	11	1.7	0	0.0	106	17.0	7	1.1	0	0.0
Peripheral sensory neuropathy	100	15.9	6	1.0	1	0.2	99	15.8	8	1.3	1	0.2
Pain in extremity	93	14.8	9	1.4	1	0.2	69	11.0	4	0.6	1	0.2
Dizziness	92	14.6	1	0.2	0	0.0	67	10.7	0	0.0	0	0.0
Leucopenia	91	14.5	40	6.4	2	0.3	74	11.8	21	3.4	3	0.5
Insomnia	86	13.7	2	0.3	0	0.0	99	15.8	3	0.5	0	0.0
Pyrexia	86	13.7	1	0.2	0	0.0	92	14.7	5	0.8	0	0.0
Thrombocytopenia	85	13.5	22	3.5	6	1.0	84	13.4	22	3.5	4	0.6
Asthenia	83	13.2	8	1.3	0	0.0	76	12.2	6	1.0	1	0.2
Rash	76	12.1	0	0.0	0	0.0	79	12.6	2	0.3	0	0.0
Infusion site pain	66	10.5	3	0.5	0	0.0	7	1.1	0	0.0	0	0.0
Back pain	61	9.7	14	2.2	0	0.0	70	11.2	13	2.1	2	0.3
Paresthesia	60	9.5	3	0.5	0	0.0	69	11.0	2	0.3	0	0.0
Noncardiac chest pain	48	7.6	5	0.8	1	0.2	74	11.8	11	1.8	2	0.3

NOTE. Preferred terms are sorted by descending frequency of all grades in the ASA404 + PC arm. Adverse events occurring more than 28 days after last date of study treatment are not summarized.
Abbreviation: PC, paclitaxel and carboplatin.

and 1.1%, respectively). The other AEs reported with a slightly higher incidence in the ASA404 arm compared to placebo were dysgeusia, visual impairment, decreased appetite, pain in extremity, and dizziness. There was no overt increase in AEs relevant to VDAs, such as hemoptysis or cardiac toxicity. For example, hemoptysis (all grades) was observed in 6.4% in the ASA404 arm versus 6.2% in the placebo arm. Only one patient in each arm had grade 4 hemoptysis. A summary of AEs by treatment arm is presented in Table 3.

Overall, a similar number of on-treatment deaths were reported between the ASA404 and placebo treatment arms (28 patients and 25 patients, respectively). Three deaths were considered to be related to the study drug, one in the ASA404 arm (myocardial infarction) and two in the placebo arm (cerebrovascular accident in one and unknown in the other). There was no clustering of any specific type of events leading to death in any treatment arm. Notably, there was no evidence for enhanced vascular toxicities, such as bleeding or thrombosis with ASA404, even in the squamous cell cancer subset, in contrast to that seen with angiogenesis inhibitors such as bevacizumab.

Quality of Life

Summary of the changes in patient reported outcome scores assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 questionnaire by time point and treatment are presented in the Appendix Table A2 (online only). There was a decrease in the physical functioning domain across both treatment arms at the end of treatment. However, for the global health status/quality of life domain there was no change observed between the treatment arms over time.

DISCUSSION

This large randomized trial failed to demonstrate any efficacy advantage to the addition of the tumor VDA ASA404 to standard platinum-based chemotherapy for the first-line treatment of advanced NSCLC. As a result, further clinical development of this agent has been halted. This trial thus joins a long list of many like-designed negative studies that have tested the paradigm of chemotherapy with or without a novel targeted agent. Of the dozens of failed randomized phase III trials that employed this strategy in the recent past, only trials of bevacizumab plus carboplatin/paclitaxel (Eastern Cooperative Oncology Group trial 4599)[12] and arguably, cetuximab plus cisplatin/vinorelbine,[13] have yielded improvements in OS, albeit modest, in favor of the experimental arm. The ATTRACT-1 trial has now clearly demonstrated that the purported synergistic vascular disrupting activity of

ASA404 was insufficient to improve any of the efficacy measures in unselected patients. This was in contrast to the trends for improvement in efficacy variables of the preceding randomized phase II trial.

Why was there a disconnect between the encouraging results of the randomized phase II trial of carboplatin/paclitaxel with or without ASA404 and the negative results of this subsequent randomized phase III trial? The most likely explanation is that the smaller sample size of the phase II trial simply overestimated the treatment effect; the small number of events wrongly influenced the shape of the survival curves in favor of the experimental arm. This so-called random high yielded a false-positive signal that could only have been refuted by a larger clinical trial such as ATTRACT-1.[14] The lack of a placebo control and investigator/patient blinding in the preceding phase II trial may also have introduced biases that favored the experimental arm.

Surprisingly, the control arm of this phase III trial yielded a median survival time of 12.7 months, well above the a priori assumption of 9 months that was used in the ATTRACT-1 sample size and power calculations. In fact, the numerical median OS achieved in the control arm of this trial is higher than the median OS achieved with the bevacizumab plus carboplatin/paclitaxel regimen in the pivotal ECOG 4599 trial, which was 12.3 months.[12] The reason for this temporal upward drift in OS is unclear, but may be related to stage migration, the higher accrued proportion of Asian patients (25%) who typically have better outcomes compared to Western populations, and/or overall improvements in subsequent therapies for advanced NSCLC beyond initial platinum-based therapy.[15,16] For example, in Eastern Cooperative Oncology Group trial 4599, subsequent therapy was reported in 46% of patients in the bevacizumab arm and in 43% in the control arm, contrasting with the 56% rate in both arms of the current study. It must also be noted that a slightly higher dose of paclitaxel was used in ATTRACT 1 (200 mg/m^2) as compared with the predecessor phase II study where 175 mg/m^2 was used. Whether this change contributed to the higher than expected OS in the control arm is uncertain. Nevertheless, the a priori assumptions of the ATTRACT 1 trial may have confounded the expectations of benefit in both treatment arms.

It is notable that clinical evaluation of nonflavonoid (ie, tubulin directed) VDAs are still in progress. These agents include fosbretabulin, ABT-751, and NPI-2358, among others.[17] Interestingly, preliminary results of a randomized phase II trial of carboplatin, paclitaxel, and bevacizumab with or without fosbretabulin in advanced NSCLC demonstated enhanced OS in the fosbretabulin-containing arm.[18] However, it remains to be seen whether tubulin-directed VDAs in combination with chemotherapy and/or angiogenesis inhibitors will improve outcomes in the phase III context.

Finally, it is worth emphasizing that the precise molecular target of ASA404 remains elusive. This lack of understanding of the basic mechanisms of ASA404 drug action have hampered a more defined and ideal approach to clinical trial design wherein only patients with a high likelihood of benefiting from VDA therapy, as identified by some putative biomarker, are selectively accrued to a phase III randomized experiment. Molecular correlative studies on tumor and blood specimens collected from patients in this trial are ongoing and will be reported in a separate publication. If further development of this class of agents were to prosper, identification and validation of predictive biomarkers for VDA benefit are warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Xiaolin Fan, Novartis (C); Abderrahim Fandi, Novartis (C) **Consultant or Advisory Role:** Primo N. Lara Jr, Novartis (C); Jean-Yves Douillard, Novartis (C); Joachim von Pawel, Novartis (C), Antisoma (C); Mark J. McKeage, Novartis (C), Antisoma (C); Martin Reck, Hoffman-La Roche (C), Pfizer (C), Bristol-Myers Squibb (C), Eli Lilly (C), AstraZeneca (C) **Stock Ownership:** None **Honoraria:** Primo N. Lara Jr, Novartis; Jean-Yves Douillard, Novartis; Kazuhiko Nakagawa, Chugai, Daiichi Sankyo, Abbott Japan; Joachim von Pawel, Novartis; Mark J. McKeage, Novartis, Antisoma; Martin Reck, Hoffmann-La Roche, Eli Lilly, AstraZeneca; Giorgio Scagliotti, Eli Lilly, Roche, AstraZeneca **Research Funding:** Primo N. Lara Jr, Novartis; Mark J. McKeage, Novartis, Antisoma **Expert Testimony:** None **Other Remuneration:** None

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