Phase II Study of Tirapazamine, Cisplatin, and Etoposide and Concurrent Thoracic Radiotherapy for Limited-Stage Small-Cell Lung Cancer: SWOG 0222

Quynh-Thu X. Le, James Moon, Mary Redman, Stephen K. Williamson, Primo N. Lara Jr, Zelanna Goldberg, Laurie E. Gaspar, John J. Crowley, Dennis F. Moore Jr, and David R. Gandara

From the Stanford University, Stanford; University of California, Davis Cancer Center, Sacramento, CA; Southwest Oncology Group Statistical Center, Seattle, WA; University of Kansas Medical Center, Kansas City; Wichita CCOP, Wichita, KS; and University of Colorado Denver, Aurora, CO.

Submitted December 2, 2008; accepted January 13, 2009; published online ahead of print at www.jco.org on April 13, 2009.

Presented in part at the 44th Annual Meeting of the American Society of Clinical Oncology Annual Meeting, Chicago, IL, May 31 to June 3, 2008.

Supported in part by the following PHS Cooperative Agreement Grants No. CA32102, CA38926, CA35431, CA35090, CA35261, CA45808, CA20319, CA67575, CA35281, CA22433, CA52654, CA12644, CA45368, CA46282, CA45560, CA35128, CA11083, CA37981, CA58658, CA76462, CA13612, CA42777, CA27057, CA14028, and CA118582 from the National Cancer Institute, Department of Health and Human Services.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Quynh-Thu X. Le, MD, 875 Blake Wilbur Dr, MC 5847, Stanford, CA 94305-5847; e-mail: Qle@stanford.edu.

© 2009 by American Society of Clinical Oncology

0732-183X/09/2718-3014/\$20.00

DOI: 10.1200/JCO.2008.21.3868

A B S T R A C T

Purpose

A SWOG pilot study (S0004) showed that tirapazamine (TPZ) when combined with concurrent chemoradiotherapy yielded a promising median survival of 22 months in limited-stage small-cell lung cancer (LSCLC). We report results of the phase II study designed to confirm this result.

Patients and Methods

The concurrent phase consisted of two cycles of cisplatin, etoposide, and once-daily radiation to 61 Gy. TPZ was given at 260 mg/m² on days 1, 29, and at 160 mg/m² on days 8, 10, 12, 36, 38, and 40. Consolidation consisted of two cycles of cisplatin and etoposide. Complete responders received prophylactic cranial irradiation. Results were considered promising if the median survival time was at least 21 months and of no further interest if ≤ 14 months.

Results

S0222 was closed early due to a report of excess toxicity for TPZ in a head and neck cancer trial elsewhere. Of planned 85 patients, 69 were accrued. In 68 assessable patients, 17 (25%) had grade 3 to 4 esophagitis and eight (12%) had grade 3 febrile neutropenia during the concurrent phase. There were three possible treatment-related deaths, two in concurrent phase (one progressive disease not otherwise specified within 30 days, one pericardial effusion) and one in consolidation phase (esophageal hemorrhage). At a median follow-up of 35 months, median progression-free survival was 11 months (95% CI, 10 to 13 months) and median overall survival was 21 months (95% CI, 17 to 33 months).

Conclusion

S0222 showed acceptable levels of toxicity and similar promising median survival as S0004. Further study of hypoxia-targeted therapy is warranted in LSCLC.

J Clin Oncol 27:3014-3019. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Although significant progress has been made for non-small-cell lung cancers (NSCLC), very little progress has been achieved for small-cell lung cancer (SCLC). Clinical studies have indicated that concurrent administration of chemotherapy and thoracic radiotherapy (TRT) is superior to sequential treatment, that early TRT delivery is superior to late delivery and that cisplatin and etoposide (PE) continue to be the core chemotherapy regimen for limited-stage SCLC (LSCLC) in this country.¹ The only noticeable advancement was the intergroup trial (INT-0096), which showed accelerated TRT (1.5 Gy twice-daily to 45 Gy) yielded superior survival compared to conventional TRT (1.8 Gy once-daily to 45 Gy).² However, the accelerated arm was associated with a higher rate of grade 3 to 4 acute

toxicity, in particular esophagitis. The increased adverse effects coupled with the inconvenience of twice-daily TRT resulted in a low adoption rate of this approach by community practitioners.³

Tumor hypoxia (low tumor oxygen) has been shown to adversely impact treatment outcomes in several solid tumors, including NSCLC.⁴⁻⁷ More recently, it has been demonstrated to enhance tumor invasion and metastasis in addition to treatment resistance as a result of gene expression changes and selection for tumor clones with more genetic mutations.⁸⁻¹⁰ Studies using computed tomography (SPECT) and ¹²³I-iodine-radiolabeled iodoazomycin arabinoside (IAZA) as a hypoxia-specific radio-tracer suggested that hypoxia exists in 60% (nine of 15) of SCLC patients.^{11,12} In addition, the use of a hypoxic cell radiosensitizer enhanced radiation efficacy in human SCLC xenografts.¹³

Tirapazamine (TPZ; Tirazone; SRI International, Menlo Park, CA) is a benzotriazine di-N-oxide with selective cytotoxicity for hypoxic cells.¹⁴ It has been shown to increase the antitumor effect of fractionated radiotherapy (RT) when given concurrently.¹⁴ Clinically, the combination of TPZ, RT, and cisplatin has been found promising in several phase II trials.^{15,16} We have previously reported on a pilot study using concurrent TPZ, PE, and high-dose once-daily TRT in LSCLC patients, S0004.¹⁷ We found that that the maximally tolerated dose for TPZ when delivered with TRT and PE was 260 mg/m². We also noted a promising median survival of 22 months in this pilot study. These results prompted a phase II study, S0222, to test the efficacy of this regimen in LSCLC patients. Herein, we report the results of this phase II study.

PATIENTS AND METHODS

Patients

The study was approved by the Clinical Trial Evaluation Program (CTEP) of the National Cancer Institute (NCI), the SWOG Clinical Trial Review Committee, and local institutional review board (IRB) of participating institutions. All patients gave informed consent. Definition of limited stage disease, eligibility criteria, pretreatment evaluations, and criteria for removal were similar to those of S0004.¹⁷ Positron emission tomography scans were not required for staging, restaging, or radiation treatment planning.

Concurrent Chemoradiotherapy

The treatment schema is shown in Figure 1. Initial chemotherapy consisted of intravenously (IV) cisplatin 50 mg/m²/d on days 1, 8, 29, and 36 and etoposide 50 mg/m²/d IV on day 1 through 5 and 29 to 33, administered concurrently with TRT. TPZ, 260 mg/m², was administered on days 1 and 29, 1 to 2 hours before cisplatin and 1 to 3 hours before TRT. In addition, TPZ at 160 mg/m² was administered on days 8, 10, 12, 36, 38, and 40, 1 to 3 hours before TRT. Premedication with dexamethasone and a 5-HT agonist were recommended to minimize the emetogenic effect of TPZ. Chemotherapy was held 1 week if the absolute neutrophil count was lower than 1,000/ μ L or the platelet count was lower than 100,000/ μ L. If blood counts did not return to acceptable levels, the dose of cisplatin, etoposide, and TPZ were reduced by 12% to 50% as specified in the protocol. Cisplatin dose was decreased 50% for any grade 2 neurotoxicity; both cisplatin and TPZ were held for any grade ≥ 3 neurotoxicity or ototoxicity until symptom resolution. Cisplatin was dose reduced 50% for serum creatinine between 1.5 to 2 mg/dL and creatinine clearance higher than 50 mL/min and terminated for serum creatinine higher than 2 mg/dL and creatinine clearance lower than 50 mL/min.

TRT began on day 1 and was administered once daily for 6.5 weeks. Three-dimensional conformal RT was required and participating centers had to complete a benchmark through the Quality Assurance Review Center. The clinical target volume, covering the primary tumor, ipsilateral hilum, and mediastinum with a 1.5 to 2 cm margins above and below any known gross disease, received 45 Gy at 1.8 Gy/fraction/d. The planning target volume was not used. Supraclavicular and inferior mediastinal nodes were treated only if they were directly involved. Inclusion of the contralateral mediastinum at the levels of involved ipsilateral mediastinum was at the discretion of treating physicians as long as normal tissue constraints were met. A 16 Gy boost was delivered in 8 fractions of 2 Gy daily to the gross target volume (gross tumor volume), defined as the tumor and clinically involved nodes (nodes > 1 cm in short axis on CT or biopsy proven positive) plus a 1.5 cm margin. Target doses were prescribed to the isocenter and the doses within the target volumes were kept within 10% of the prescribed doses. Homogeneity correction was not used. The protocol recommended that the volume of total lung receiving more than 20 Gy (V20) be $\leq 35\%$. The maximum spinal cord dose was limited to 50 Gy.

Rapid review of the RT plan within 3 days of starting TRT was instituted through Quality Assurance Review Center to ensure protocol compliance. Radiation interruption or delays were discouraged and were allowed only for febrile neutropenia, any grade 4 hematologic toxicity, or grade ≥ 3 esophagitis or pneumonitis.

Consolidation Chemotherapy

Patients were required to reregister for consolidation chemotherapy. Only patients with stable or responding disease and with adequate hematologic function proceeded to consolidation consisting of cisplatin 60 mg/m² on day 1 and etoposide 120 mg/m² on days 1 through 3 of weeks 11 and 14. Similar treatment delay and dose modification criteria as in the concurrent phase were applied.

Prophylactic Cranial Irradiation

Patients with a complete response after consolidation chemotherapy were recommended to receive prophylactic cranial irradiation (PCI) to 30 Gy in 15 fractions over 3 weeks. PCI was administered within 6 weeks of hematologic recovery from the last cycle of chemotherapy. Repeat brain imaging before PCI was recommended but not required. Twenty-two patients received PCI on protocol.

Response and Toxicity Criteria

Treatment-related toxicities were classified according to the NCI Common Toxicity Criteria version 3.0. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors.¹⁸

Study Design and Statistical Analysis

This study was designed to test the efficacy of adding TPZ to concurrent PE and TRT followed by PE consolidation. Based on the estimated 18-month median survival in S8269, it was assumed that this regimen would be considered promising if the true median survival was at least 21 months and of no further interest if it was ≤ 14 months. It was estimated that 85 patients, accrued over 17 months and followed for 18 months, would yield a 0.81 power of a one-sided .05 level test of 14 months versus 21 months median survival. An observed median survival of at least 19 months would be considered sufficient evidence that this regimen warrants further study. In addition, 85 patients would be sufficient to estimate response and toxicity rates to within 11%.

This study was closely monitored for toxicity. Early stopping rules were set to close the study if more than three deaths occurred within the first 30 patients enrolled, or if at any time, grade 4 esophagitis exceeded 10% or grade ≥ 3 infection exceeded 40%. Survival estimates were derived using the Kaplan-Meier method.¹⁹

Fig 1. S0222 treatment schema. TPZ, tirapazamine; TRT, thoracic radiotherapy; PCI, prophylactic cranial irradiation; Ex, fraction.

RESULTS

Patient Characteristics

Between September 2003 and July 2006, 72 of planned 85 LSCLC patients from 26 institutions were enrolled. The study was closed early

Table 1. Comparison of Patient Characteristics Between S0004 (phase I) and S0222 (phase II)

Characteristic	Patients			
	S0004		S0222	
	No.	%	No.	%
Total	30		68	
Median age, years	63		63	
Range	40-78		39-86	
Sex				
Male	17	56	30	44
Female	13	43	38	56
Weight loss, %				
< 5	23	77	50	74
≥ 5	7	23	16	24
Unknown			2	3
Performance status				
0	16	53	39	57
1	14	47	29	43

due to a report of excess toxicity for TPZ in a head and neck cancer trial elsewhere. Since the accrual to S0222 was near completion, it was decided that closing the study early would be most prudent to protect patient safety. Three of the enrolled 72 patients were ineligible: one due to bilateral disease, one due to distant metastasis at presentation, and one due to inadequate renal function. In addition, one eligible patient never received any protocol treatment and was not analyzable. Therefore, 68 patients formed the patient cohort for this report. The characteristics of these patients, compared to those in S0004 are presented in Table 1. Pretreatment characteristics between the two studies appear similar.

Treatment-Related Toxicities

Toxicity was scored separately for the concurrent and the consolidation portions. All 68 patients were eligible for toxicity assessment of

the concurrent phase. Principal toxicities during the concurrent phase are summarized in Table 2 and compared to those observed for S0004. Thirty-one patients (46%) experienced grade 4 adverse events, mostly hematologic. The predominant hematologic toxicity was grade 3 to 4 neutropenia ($n = 42$; 62%), with eight patients experiencing grade 3 febrile neutropenia. Predominant nonhematologic toxicities were grade 3 to 4 RT esophagitis ($n = 17$; 25%), grade 3 dehydration ($n = 19$; 28%), and myalgia ($n = 9$; 13%). The toxicity profiles were similar for both trials, with the exception of a higher incidence of myalgia in S0222. This was presumably due to more frequent TPZ delivered at a lower dose in this current study. Twenty-six patients were hospitalized for serious adverse events including 10 for esophagitis, five for nausea/vomiting/dehydration, five for febrile neutropenia, and six for other causes (three infections without neutropenia with known sources, one liver function test elevation with active hepatitis B reactivation, one cerebrovascular accident, and one myocardial infarction in the background of significant atherosclerotic disease). There were two treatment-related deaths, one from a pericardial effusion. The second death was primarily due to disease progression, although the contribution of treatment, TRT in particular, could not be excluded.

Forty eligible patients proceeded to consolidation chemotherapy. One patient was not assessable for toxicity due to delinquent data submission. Table 3 compares consolidation toxicities for the two studies. There was one treatment-related death, due to late esophageal hemorrhage related to a stricture dilation, and 20 additional patients (51%) experienced grade 4 adverse events, primarily hematologic.

Response

Data on response to concurrent chemoradiotherapy was available for 63 assessable patients who had measurable disease at baseline, including 12 patients who could not have their exact response determined due to inadequate disease assessments. These 12 patients were counted as nonresponders. Response details are presented in Table 4.

Table 2. Principal Toxicities During the Concomitant Phase

Toxicity	Grade											
	Phase I (n = 29)						Phase II (n = 68)					
	3		4		5		3		4		5	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Leukopenia	9	31	9	31	0	0	24	35	23	34	0	0
Neutropenia	7	24	9	31	0	0	16	24	26	38	0	0
Thrombocytopenia	3	10	2	7	0	0	10	15	4	6	0	0
Anemia	4	14	1	3	0	0	6	9	0	0	0	0
Febrile neutropenia	2	7	2	7	0	0	8	12	0	0	0	0
Infection	5	17	0	0	1	3	2	3	3	4	0	0
RT esophagitis	7	24	3	10	0	0	15	22	2	3	0	0
Pneumonitis	0	0	0	0	0	0	1	1	0	0	0	0
Vomiting	10	34	0	0	0	0	8	12	0	0	0	0
Dehydration	6	21	1	3	0	0	19	28	0	0	0	0
Diarrhea	0	0	0	0	0	0	2	3	0	0	0	0
Myalgia	1	3	0	0	0	0	9	13	0	0	0	0
Pericardial effusion	—	—	—	—	—	—	0	0	0	0	1	1
Disease progression NOS	—	—	—	—	—	—	0	0	0	0	1	1
Maximum grade any adverse event	12	41	12	41	1	3	29	43	31	46	2	3

Abbreviations: RT, radiation therapy related; NOS, not otherwise specified.

Table 3. Principal Toxicity During the Consolidation Phase

Toxicity	Grade											
	Phase I (n = 18)						Phase II (n = 39)					
	3		4		5		3		4		5	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Leukopenia	4	22	7	39	0	0	10	26	16	41	0	0
Neutropenia	2	11	8	44	0	0	8	21	19	50	0	0
Thrombocytopenia	2	11	1	6	0	0	10	26	3	8	0	0
Anemia	1	6	0	0	0	0	6	15	1	3	0	0
Febrile neutropenia	2	11	1	6	0	0	5	13	1	3	0	0
Infection	3	17	0	0	1	6	1	3	3	8	0	0
Dysphasia/esophagitis	1	6	0	0	0	0	2	5	0	0	0	0
Esophageal hemorrhage	—	—	—	—	—	—	0	0	0	0	1	3
Maximum grade, any adverse event	3	17	10	56	1	6	9	23	20	51	1	3

There were seven complete and 32 partial responses, for a response rate estimate of 63% (95% CI, 49% to 74%).

Survival

The median follow-up among patients known to be alive at last contact was 35 months, (range, 10 to 47 months). The estimated median progression-free survival was 11 months (95% CI, 10 to 13 months) and the estimated median overall survival is 21 months (95% CI, 17 to 33 months). Figure 2 shows progression-free (Fig 2A) and overall survival (Fig 2B) Kaplan-Meier curves for the study.

DISCUSSION

Since the original SWOG trial (S8269) that established concurrent chemoradiotherapy as a standard in LSCLC,²⁰ several subsequent SWOG trials have maintained the core regimen of concurrent PE and once-daily TRT to 45 Gy, while investigating different approaches to consolidation therapy. None of these strategies have improved survival over that observed in S8269.²¹ The latest SWOG phase II trial, S9713, tested higher dose TRT (61 Gy) with concurrent PE chemotherapy followed by carboplatin and paclitaxel consolidation. Although the regimen was well tolerated, the result was disappointing with a median survival of 17 months.²² Thus, the median survival of 22 months observed in S0004 was intriguing, especially for a small phase I dose finding study.¹⁷ Based on this promising result, we proceeded with a larger phase II trial using a similar regimen of TRT, TPZ, and PE to replicate the outcomes of S0004. Although S0222 was terminated

early due to a report of excess toxicity for TPZ in another cancer trial elsewhere, we did not note any obvious increase in toxicity when compared to past SWOG trials for LSCLC, except for grade 3 myalgia, esophagitis, and nausea/vomiting, resulting in hospital admission for 15 patients for either esophagitis or dehydration. Despite the early

Fig 2. (A) Progression-free survival for S0222 patients. (B) Overall survival for S0222 patients. PE, cisplatin and etoposide; XRT, radiotherapy; TPZ, tirapazamine.

Table 4. Response After Concurrent Chemoradiotherapy

Response	No.	%
Complete response	7	11
Partial response	32	51
Stable disease	9	14
Progressive disease	3	5
Assessment inadequate	12	19
Total	63	100

closure, the median survival of 21 months in S0222 duplicated the promising survival noted for S0004 and considered to be a positive result based on our statistical design. Such results suggest that hypoxia targeting is effective in LSCLC and should be explored further.

TPZ has several limitations including poor drug diffusion through hypoxic tissues and activation by less stringent hypoxia, a feature that can cause toxicity in normal but poorly oxygenated tissues. This may explain for a higher rate of esophagitis noted in both S0004 and S0222 as prior immunohistochemic studies have demonstrated strong binding of the hypoxia marker misonidazole to esophageal epithelium, suggesting an oxygen poor environment.^{23,24} Since major acute nonhematologic toxicities in both S0222 and S0004 are esophagitis and dehydration, a better hypoxia targeted drug with a larger therapeutic ratio is needed to improve the efficacy of hypoxia targeting in combination with RT. Therefore, there is strong interest in developing novel hypoxic cell cytotoxins with more specific antitumor activity. Several new compounds have been identified, including the dinitrobenzamide mustards (DNBMs), which constitute a potent class of hypoxic cytotoxins.^{25,26} These compounds have improved properties over TPZ, including activation by more stringent hypoxia and a substantial bystander killing effect. A lead DNBM compound, PR-104, is currently being studied in phase I trials for several solid tumors.^{27,28} These new hypoxic cytotoxins are candidates for future investigation in LSCLC.

Although a systematic review indicated that hypoxia modification can significantly enhanced RT outcomes; at the present time, there is no universally accepted strategy for hypoxia targeting.²⁹ This is due to the lack of an optimal approach for selecting appropriate patients with hypoxic tumors who would benefit from such treatment. Although tumor pO₂ measurement is feasible in superficial tumors, it cannot be carried out for deeply seated tumors such as SCLC.

Imaging with hypoxia specific tracers is promising; however, this technology is not widely available and cannot yet be conducted in a cooperative group setting. The lack of hypoxia imaging or assessment at baseline is a major limitation of this study. However, we have been able to collect pretreatment paraffin embedded tumor tissues and blood from patients for planned hypoxia-related correlative studies. Recently, certain hypoxic cell gene and protein signatures have been compiled and shown to correlate with outcomes in several solid tumors.³⁰⁻³² Certain microRNAs are also induced by hypoxia and their circulating levels can be measured in cancer patients' blood.³³⁻³⁵ As part of S0222, we plan to perform correlative studies to identify patients who would best benefit from hypoxia targeting. Such studies will shed some light on hypoxia targeting in SCLC.

At the completion of S0004, emerging data suggested that TPZ was more efficacious when combined with radiation and chemotherapy rather than with chemotherapy alone. In a phase III randomized study for locally advanced head and neck cancer, there was a trend for better locoregional failure-free survival in patients who did not have major RT deviation, favoring the combination of TPZ, cisplatin, and RT over cisplatin and RT alone.³⁶ In this regimen, TPZ was given at 290 mg/m² before cisplatin in weeks 1, 4, 7, and then alone at 160 mg/m² 3 times a week in week 2 and 3 of RT.³⁷ Therefore, the TPZ schedule in S0222 was modified to deliver TPZ more frequently at lower doses in order to optimize its radiation sensitivity. Despite in the change in the dosing schedule, similar toxicity profiles were noted for S0222 and S0004.

Three treatment-related deaths were observed in S0222, one from pericardial effusion and one from esophageal hemorrhage from a stricture dilation. The cause of death in the last patient was primarily disease progression, although it was considered treatment-related as it occurred soon after TRT termination and thus RT contribution could not be excluded. This rate is consistent with literature reports of a 2% to 6% mortality risk for patients with LSCLC treated with chemoradiotherapy.^{2,38}

The rationale for using once-daily TRT was due to the low adoption rate of accelerated fractionation in the community, despite randomized data showing it to be superior to once-daily TRT to 45 Gy.^{2,3} At the time that we designed the pilot S0004 study, results from a phase I dose escalation trial suggested that the maximum-tolerated dose for TRT in LSCLC was 70 Gy when delivered at 2 Gy/fraction/d concurrently with cisplatin and etoposide.³⁹ A subsequent phase II study from the Cancer and Leukemia Group B (CALGB) also confirmed that it was feasible to deliver 70 Gy at once daily fraction concurrently with carboplatin and etoposide with a promising median survival of 22 months.⁴⁰ However, neither of these studies included a third untested drug such as TPZ. Therefore, for safety purposes, we decided to keep the total TRT dose at 61 Gy, which has been shown to be feasible when given with TPZ in prior phase I studies.^{41,42} In addition, keeping the TRT dose at 61 Gy would allow us to compare the results of S0004 and S0222 to S9713, which employed the same concomitant chemoradiotherapy regimen without TPZ.²² Despite the lower total dose of 61 Gy and the use of once-daily fractionation, we still observed a grade 3 to 4 esophagitis rate of 25%. Such a rate could be substantially higher if we were to employ a higher total TRT dose or accelerated fractionation. A presently ongoing intergroup study will shed some light as to the best and least toxic radiation regimen to use for LSCLC.⁴³

In conclusion, we found that S0222 replicated the promising median survival seen originally in S0004. These findings suggested that further study for hypoxia-targeted therapies should be evaluated in LSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Quynh-Thu X. Le, Stephen K. Williamson, Primo N. Lara Jr, Zelanna Goldberg, Laurie E. Gaspar, John J. Crowley, David R. Gandara

Provision of study materials or patients: Stephen K. Williamson, Primo N. Lara Jr, Zelanna Goldberg, Laurie E. Gaspar, David R. Gandara

Collection and assembly of data: Quynh-Thu X. Le, James Moon, Mary Redman

Data analysis and interpretation: Quynh-Thu X. Le, James Moon, Mary Redman, John J. Crowley

Manuscript writing: Quynh-Thu X. Le, James Moon, Primo N. Lara Jr, Laurie E. Gaspar, David R. Gandara

Final approval of manuscript: Quynh-Thu X. Le, James Moon, Mary Redman, Stephen K. Williamson, Primo N. Lara Jr, Zelanna Goldberg, Laurie E. Gaspar, John J. Crowley, David R. Gandara

REFERENCES

1. Lally BE, Urbanic JJ, Blackstock AW, et al: Small cell lung cancer: Have we made any progress over the last 25 years? *Oncologist* 12:1096-1104, 2007
2. Turrisi AT 3rd, Kim K, Blum R, et al: Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 340:265-271, 1999
3. Movsas B, Moughan J, Komaki R, et al: Radiotherapy patterns of care study in lung carcinoma. *J Clin Oncol* 21: 4553-4559, 2003
4. Nordsmark M, Bentzen SM, Rudat V, et al: Prognostic value of tumor oxygenation in 397 head and neck tumors after primary radiation therapy: An international multi-center study. *Radiother Oncol* 77:18-24, 2005
5. Fyles A, Milosevic M, Hedley D, et al: Tumor hypoxia has independent predictor impact only in patients with node-negative cervix cancer. *J Clin Oncol* 20:680-687, 2002
6. Brizel DM, Scully SP, Harrelson JM, et al: Tumor oxygenation predicts for the likelihood of distant metastases in human soft tissue sarcoma. *Cancer Res* 56:941-943, 1996
7. Le QT, Chen E, Salim A, et al: An evaluation of tumor oxygenation and gene expression in patients with early stage non-small cell lung cancers. *Clin Cancer Res* 12:1507-1514, 2006
8. Le QT, Denko NC, Giaccia AJ: Hypoxic gene expression and metastasis. *Cancer Metastasis Rev* 23:293-310, 2004
9. Denko NC, Fontana LA, Hudson KM, et al: Investigating hypoxic tumor physiology through gene expression patterns. *Oncogene* 22:5907-5914, 2003
10. Graeber TG, Osmanian C, Jacks T, et al: Hypoxia-mediated selection of cells with diminished apoptotic potential in solid tumours. *Nature* 379:88-91, 1996
11. Urtasun RC, Parliament MB, McEwan AJ, et al: Measurement of hypoxia in human tumours by non-invasive spect imaging of iodoazomycin arabinoside. *Br J Cancer* 27:S209-S212, 1996 (suppl)
12. Parliament MB, Chapman JD, Urtasun RC, et al: Non-invasive assessment of human tumour hypoxia with 123I-iodoazomycin arabinoside: Preliminary report of a clinical study. *Br J Cancer* 65:90-95, 1992
13. Suzuki Y, Hasegawa M, Hayakawa K, et al: In vivo study of radiosensitizing effect of hypoxic cell radiosensitizer PR-350 on a human small cell lung cancer. *Anticancer Res* 19:3993-4000, 1999
14. Brown JM, Sim BG: Hypoxia-specific cytotoxins in cancer therapy. *Semin Rad Oncol* 6:22-26, 1996
15. Rischin D, Peters L, Hicks R, et al: Phase I trial of concurrent tirapazamine, cisplatin, and radiotherapy in patients with advanced head and neck cancer. *J Clin Oncol* 19:535-542, 2001
16. Craighead PS, Pearcey R, Stuart G: A phase I/II evaluation of tirapazamine administered intravenously concurrent with cisplatin and radiotherapy in women with locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys* 48:791-795, 2000
17. Le QT, McCoy J, Williamson S, et al: Phase I study of tirapazamine plus cisplatin/etoposide and concurrent thoracic radiotherapy in limited-stage small cell lung cancer (S0004): A Southwest Oncology Group study. *Clin Cancer Res* 10:5418-5424, 2004
18. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organisation for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 92:205-216, 2000
19. Kaplan ES, Meier P: Non-parametric estimations from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958
20. McCracken JD, Janaki LM, Crowley JJ: Concurrent chemotherapy/radiotherapy for limited small cell lung carcinoma. *J Clin Oncol* 8:892-898, 1990
21. Edelman MJ, Gandara DR: Small cell lung cancer: Current status of new chemotherapeutic agents. *Crit Rev Oncol Hematol* 27:211-220, 1998
22. Edelman MJ, Chansky K, Gaspar LE, et al: Phase II trial of cisplatin/etoposide and concurrent radiotherapy followed by paclitaxel/carboplatin consolidation for limited small-cell lung cancer: Southwest Oncology Group 9713. *J Clin Oncol* 22:127-132, 2004
23. Cobb LM, Nolan J, O'Neill P: Microscopic distribution of misonidazole in mouse tissues. *Br J Cancer* 59:12-16, 1989
24. Parliament MB, Wiebe LI, Franko AJ: Nitroimidazole adducts as markers for tissue hypoxia: Mechanistic studies in aerobic normal tissues and tumour cells. *Br J Cancer* 66:1103-1108, 1992
25. Hay MP, Pchalek K, Pruijn FB, et al: Hypoxia-selective 3-alkyl 1,2,4-benzotriazine 1,4-dioxides: The influence of hydrogen bond donors on extravascular transport and antitumor activity. *J Med Chem* 50:6654-6664, 2007
26. Hicks KO, Pruijn FB, Secomb TW, et al: Use of three-dimensional tissue cultures to model extravascular transport and predict in vivo activity of hypoxia-targeted anticancer drugs. *J Natl Cancer Inst* 98:1118-1128, 2006
27. Wilson WR, Hicks KO, Pullen SM, et al: By-stander effects of bioreductive drugs: Potential for exploiting pathological tumor hypoxia with dinitrobenzamide mustards. *Radiat Res* 167:625-636, 2007
28. Patterson AV, Ferry DM, Edmunds SJ, et al: Mechanism of action and preclinical antitumor activity of the novel hypoxia-activated DNA crosslinking agent PR-104. *Clin Cancer Res* 13:3922-3932, 2007
29. Overgaard J: Hypoxic radiosensitization: Adored and ignored. *J Clin Oncol* 25:4066-4074, 2007
30. Winter SC, Buffa FM, Silva P, et al: Relation of a hypoxia metagene derived from head and neck cancer to prognosis of multiple cancers. *Cancer Res* 67:3441-3449, 2007
31. Chi JT, Wang Z, Nuyten DS, et al: Gene expression programs in response to hypoxia: Cell type specificity and prognostic significance in human cancers. *PLoS Med* 3:e47, 2006
32. Le QT, Kong C, Lavori PW, et al: Expression and prognostic significance of a panel of tissue hypoxia markers in head-and-neck squamous cell carcinomas. *Int J Radiat Oncol Biol Phys* 69:167-175, 2007
33. Fasanaro P, D'Alessandra Y, Di Stefano V, et al: MicroRNA-210 modulates endothelial cell response to hypoxia and inhibits the receptor tyrosine kinase ligand Ephrin-A3. *J Biol Chem* 283:15878-15883, 2008
34. Camps C, Buffa FM, Colella S, et al: Hsa-miR-210 is induced by hypoxia and is an independent prognostic factor in breast cancer. *Clin Cancer Res* 14:1340-1348, 2008
35. Lawrie CH, Gal S, Dunlop HM, et al: Detection of elevated levels of tumour-associated microRNAs in serum of patients with diffuse large B-cell lymphoma. *Br J Haematol* 141:672-675, 2008
36. Rischin D, Peters L, O'Sullivan B, et al: Phase III study of tirapazamine, cisplatin and radiation versus cisplatin and radiation for advanced squamous cell carcinoma of the head and neck. *J Clin Oncol* 26:318s, 2008 (LBA6008)
37. Rischin D, Peters L, Fisher R, et al: Tirapazamine, cisplatin, and radiation versus fluorouracil, cisplatin, and radiation in patients with locally advanced head and neck cancer: A randomized phase II trial of the Trans-Tasman Radiation Oncology Group (TROG 98.02). *J Clin Oncol* 23:79-87, 2005
38. Johnson DH, Bass D, Einhorn LH, et al: Combination chemotherapy with or without thoracic radiotherapy in limited-stage small-cell lung cancer: A randomized trial of the Southeastern Cancer Study Group. *J Clin Oncol* 11:1223-1229, 1993
39. Choi NC, Herndon JE 2nd, Rosenman J, et al: Phase I study to determine the maximum-tolerated dose of radiation in standard daily and hyperfractionated-accelerated twice-daily radiation schedules with concurrent chemotherapy for limited-stage small-cell lung cancer. *J Clin Oncol* 16:3528-3536, 1998
40. Bogart JA, Herndon JE 2nd, Lyss AP, et al: 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: Analysis of Cancer and Leukemia Group B study 39808. *Int J Radiat Oncol Biol Phys* 59:460-468, 2004
41. Doherty N, Hancock SL, Kayes S, et al: Muscle cramping in phase I clinical trials of Tirapazamine (SR4233) with and without radiation. *Int J Radiat Oncol Biol Phys* 29:379-382, 1994
42. Shulman LN, Buswell L, Riese N, et al: Phase I trial of the hypoxic cell cytotoxin tirapazamine with concurrent radiation therapy in the treatment of refractory solid tumors. *Int J Radiat Oncol Biol Phys* 44:349-353, 1999
43. Bogart JA: Rationale for phase III trials of thoracic radiation therapy doses in limited-stage small-cell lung cancer. *Clin Lung Cancer* 9:202-205, 2008