Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2013 April 1; 85(5): 1312–1318. doi:10.1016/j.ijrobp.2012.11.042.

A Phase 3 Trial of Whole Brain Radiation Therapy and Stereotactic Radiosurgery Alone Versus WBRT and SRS With Temozolomide or Erlotinib for Non-Small Cell Lung Cancer and 1 to 3 Brain Metastases: Radiation Therapy Oncology Group 0320.

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Abstract

Background—A phase 3 Radiation Therapy Oncology Group (RTOG) study subset analysis demonstrated improved overall survival (OS) with the addition of stereotactic radiosurgery (SRS) to whole brain radiation therapy (WBRT) in non-small cell lung cancer (NSCLC) patients with 1 to 3 brain metastases. Because temozolomide (TMZ) and erlotinib (ETN) cross the bloodbrain barrier and have documented activity in NSCLC, a phase 3 study was designed to test whether these drugs would improve the OS associated with WBRT + SRS.

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Presented at the Annual Meeting of the American Association for Cancer Research, Chicago, Illinois, April 1, 2012.

Conflict of interest: The authors report no other conflict of interest.

Methods and Materials—NSCLC patients with 1 to 3 brain metastases were randomized to receive WBRT (2.5 Gy×15 to 37.5 Gy) and SRS alone, versus WBRT + SRS + TMZ (75 mg/m²/day× 21 days) or ETN (150 mg/day). ETN (150 mg/day) or TMZ (150–200 mg/m²/day ×5 days/month) could be continued for as long as 6 months after WBRT þ SRS. The primary endpoint was OS.

Results—After 126 patients were enrolled, the study closed because of accrual limitations. The median survival times (MST) for WBRT + SRS, WBRT + SRS + TMZ, and WBRT + SRS + ETN were qualitatively different (13.4, 6.3, and 6.1 months, respectively), although the differences were not statistically significant. Time to central nervous system progression and performance status at 6 months were better in the WBRT þ SRS arm. Grade 3 to 5 toxicity was 11%, 41%, and 49% in arms 1, 2, and 3, respectively (P<.001).

Conclusion—The addition of TMZ or ETN to WBRT + SRS in NSCLC patients with 1 to 3 brain metastases did not improve survival and possibly had a deleterious effect. Because the analysis is underpowered, these data suggest but do not prove that increased toxicity was the cause of inferior survival in the drug arms.

Introduction

The annual incidence of lung cancer in the United States is 226,160 patients (14% of all cancer patients), and 160,340 (28% of cancer mortality) will die of the disease, making it the leading cause of cancer mortality in the United States (1). An estimated 16% to 34% of patients with non-small cell lung cancer (NSCLC) experience brain metastases every year, and the lifetime risk may exceed 50% (2, 3). Outcomes vary significantly by diagnosis, and the prognostic factors predicting survival also vary by diagnosis, as reflected by the Graded Prognostic Assessment (4).

Historically, the treatment options for patients with brain metastases include surgery, whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), or some combination. Chemotherapy has not been a standard treatment for these patients. Radiation Therapy Oncology Group (RTOG) 9508, a phase 3 trial of WBRT versus WBRT plus SRS in patients with 1 to 3 brain metastases (5), showed a survival advantage for WBRT plus SRS over WBRT alone for patients with 1 brain metastasis, and it also showed, on post-hoc analysis, improved survival, local control, performance status, and steroid independence for NSCLC patients with 1 to 3 metastases. That finding was the rationale for selecting WBRT plus SRS as the standard therapy for this trial.

Numerous trials have investigated chemotherapy in patients with brain metastases, with no categorically proven survival benefit. The rationale for the 2 experimental arms of this trial stems from the known modest activity of both temozolomide (TMZ) and erlotinib (ETN) in NSCLC, their potential synergistic action with radiation therapy, and their known ability to cross the blood-brain barrier. Three trials have suggested that TMZ might be active in NSCLC brain metastases, and the addition of TMZ to WBRT may improve response rates (6–8). In addition, other studies from the Eastern Cooperative Oncology Group (H.I. Robins et al, ECOG Technical Report 1172e, October 9, 2008, personal communication) and Schering-Plough (9) have investigated the role of WBRT plus TMZ. These results are summarized in Table 1.

Erlotinib is an epidermal growth factor receptor tyrosine kinase inhibitor. The rationale for the ETN arm stemmed from the 2 large phase 3 trials in NSCLC that combined ETN (vs placebo) with chemotherapy: cisplatin and gemcitabine (10) and carboplatin and paclitaxel (11), with improvement in progression-free survival and overall survival (OS) (especially in the epidermal growth factor receptor-positive subgroup), leading to approval by the US

Food and Drug Administration for the treatment of metastatic NSCLC after first relapse. The purpose of this trial was to investigate whether the addition of either TMZ or ETN would improve outcomes, specifically survival, when added to WBRT plus SRS in NSCLC patients with 1 to 3 brain metastases.

Methods and Materials

Patient population

Eligibility requirement for the trial were as follows: age >18 years; histologically confirmed NSCLC; 1 to 3 brain metastases confirmed by magnetic resonance imaging (MRI); maximum size of any brain metastasis ≤ 4.0 cm; Zubrod status 0 to 1 (Karnofsky performance status 70–100); neurologic function status 0, 1, or 2; stable extracranial metastases (defined as no progression in the month before enrollment); adequate bone marrow reserve (defined as hemoglobin ≥ 8 g/dL, absolute neutrophil count ≥ 1000/mm³, platelets ≥ 100,000/mm³); liver function test results <2 times the institutional upper limit of normal; bilirubin within normal limits; no liver metastases; negative pregnancy test; no evidence of leptomeningeal disease; no brainstem metastases; no prior cranial irradiation. Patients who had with brain metastases at the time of initial diagnosis were considered eligible and did not need to demonstrate 1 month of stable scans. Prior resection of a brain metastasis was allowed if the patient had a separate brain metastasis that would be treated with SRS.

Trial design and treatment

The protocol was approved by the National Cancer Institute, the RTOG, and the institutional review boards of each institution. Patients were randomized to arm 1 (WBRT plus SRS), arm 2 (WBRT plus SRS plus TMZ), or arm 3 (WBRT plus SRS plus ETN) in a permuted block design using the method described by Zelen (12). Stratification factors were RTOG recursive partitioning analysis class I (< age 65 and no extracranial metastases) versus class II (< age 65), number of brain metastases (1 vs 2 or 3), and extent of extra-cranial metastases (none vs present).

The WBRT began within 1 week of randomization. A dose of 2.5 Gy was delivered with 4 to 10 megavoltage machines, 5 days per week, for 15 fractions for a total of 37.5 Gy. The SRS was delivered to each of the brain metastases within 14 days of completion of WBRT. Each participating institution was credentialed by the RTOG for SRS before enrolling patients. The SRS dose was size dependent: lesions <2 cm, 2.1 to 3.0 cm, and 3.1 to 4.0 cm received 24, 18, and 15 Gy, respectively. Doses to the optic nerves, chiasm, and brainstem were limited to 8 Gy and the motor strip to 15 Gy. Arm 1 patients received WBRT plus SRS.

In Arm 2, TMZ 75 mg/m²/day was prescribed for 21 days beginning on day 1 of WBRT. After completion of WBRT and SRS, the TMZ could be discontinued at the investigators' discretion or continued at 150 mg/m²/day for 5 days/month for as long as 6 months.

In arm 3, ETN 150 mg/day was prescribed beginning on day 1 of WBRT. After WBRT and SRS, the ETN could be discontinued at the investigators' discretion or continued for as long as 6 months. Patients randomized to receive ETN who were receiving an enzyme-inducing anticonvulsant were switched to a non-enzyme-inducing anticonvulsant. Other systemic chemotherapy was allowed after the completion of WBRT at the discretion of the investigator. In the original version of the protocol, nonprotocol chemotherapy could be delivered at the time of tumor progression or after 6 months. After the protocol was amended, nonprotocol chemotherapy could be delivered after the radiation therapy (3–5 weeks after enrollment). The protocol was amended on May 8, 2007, to allow the study

drugs to be discontinued or continued after the WBRT at the investigator's discretion in an effort to enhance accrual.

Objectives

The primary objective was to determine whether either TMZ or ETN combined with WBRT and SRS improved OS from the date of randomization when compared with WBRT and SRS alone. The secondary objectives included analysis of the time to central nervous system (CNS) progression, performance status at 6 months, steroid dependence, and cause of death (neurologic vs other).

Evaluations

Baseline examinations included history, physical examination, performance status evaluation, brain MRI, complete blood count/differential, platelets, liver function tests, serum pregnancy test for women, steroid dose, and Functional Assessment of Cancer Treatment- General (FACT-G). Complete blood count/differential/platelets and liver function tests (LFTs) were scheduled monthly during protocol therapy. Every 3 months, brain MRI, Functional Assessment of Cancer Treatment- General (FACT-G), performance status evaluation, and steroid dose recording (0–4 mg, >4–8 mg, >8–12 mg, and >12 mg) were performed. Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. CNS progression was defined as any increase in perpendicular bidimensional tumor area for any of the 1 to 3 tracked brain metastases, or the appearance of any new brain metastasis on a follow-up MRI. For lesions smaller than 1 cm in maximum diameter, a minimum increase of 50% in perpendicular bidimensional treatment area was required to score as progression. Zubrod score, which runs from 0 to 5, with 0 denoting perfect health and 5 death, was used to assess the performance.

Statistical considerations

The primary endpoint was OS. Assuming an exponential survival with a median survival time of 5.9 months for the standard arm (based on RTOG 95-08), the hypothesis was that there would be a reduction of at least 34% in hazard rate for death for either of the experimental arms, corresponding to a median survival time of 8.9 months. A 1-sided log-rank test at significance level of 0.025 would have 85% power to detect this survival difference between the standard arm and either of the experimental arms with a sample size of 120 randomized patients in each arm. No direct comparisons between the 2 experimental arms were planned or performed. After adjustment for a 5% rate of ineligibly and inevaluability, the study target sample size was 381 patients.

The statistical analysis was based on the modified intent-to-treat principle (including all of the eligible and randomized patients, regardless of treatment). OS was defined as the interval from randomization to death of any cause. OS was estimated by use of the Kaplan-Meier method, and differences between treatment groups were tested with the 1-sided log rank test. The Cox proportional hazards model was used to estimate the treatment hazard ratios (HRs) associated with OS while adjusting for stratification factors. Time to CNS progression was defined as the interval from the date of randomization to documentation of progression. CNS progression rates were estimated through a cumulative incidence approach, with death treated as a competing event. The difference in time to CNS progression was compared between arms by use of the method developed by Gray (13). Also, χ^2 tests were also used to compare frequency distributions of patient pretreatment characteristics, differences in binomial proportions of grade 3p toxicities, cause of death, and change in performance status and in steroid use at 6 months between treatments. For all endpoints except the OS

comparison between treatments (protocol-specified overall 1-sided type I error of 0.025), $P < .05$ (2-sided) was defined as the significance threshold.

Results

Patients

The planned accrual was 381 participants. Between October 2004 and August 2009, 126 patients with NSCLC and 1 to 3 brain metastases were enrolled from 28 institutions in the United States and Canada. The median follow-up time was 33.6 months for the 20 (16%) patients still alive. The study was closed because of slower than anticipated accrual, with an enrollment of 33% of the target. One patient was excluded after pathology review showed small cell lung cancer, leaving 125 evaluable patients. The patient characteristics were well balanced for prognostic variables across all 3 arms (Table 2), including the recursive partitioning analysis. The study was not stratified by GPA (7), but post-hoc analysis showed that the 3 arms were well balanced by GPA.

Treatment

Figure 1 shows the Consolidated Standards Of Reporting Trials (CONSORT) diagram of patient disposition for each arm. After disease progression, the number of patients receiving chemotherapy other than TMZ or ETN in arms 1, 2, and 3 were 15 of 20 (75%), 12 of 21 (57.1%), and 9 of 15 (60%), respectively.

Treatment outcomes

Neither the addition of TMZ nor of ETN to WBRT/SRS resulted in an improvement in OS or time to CNS progression compared with WBRT/SRS alone. The MSTs of WBRT/SRS, WBRT/SRS/TMZ, and WBRT/SRS/ETN were 13.4 (95% CI: 6.5–20.8), 6.3 (95% CI: 3.4–10.1), and 6.1 (95% CI: 3.6–12.1) months (HR [WBRT/SRS/TMZ vs WBRT/SRS] 1.43, 95% CI: 0.89–2.31, $P = .93$ [1-sided]); HR [WBRT/SRS/ETN vs WBRT/SRS] 1.47, 95% CI: 0.92–2.36, $P = .95$ (1-sided)), respectively (Fig. 2). After adjustment for the 3 stratification factors with Cox proportional hazard modeling, the OS HRs were 1.46 (95% CI 0.91–2.36; $P = .94$ [1-sided]) and 1.46 (95% CI 0.91–2.34; $P = .94$ [1-sided]), respectively. The times to CNS progression for the WBRT/SRS, WBRT/SRS/TMZ, and WBRT/SRS/ETN arms were not statistically significant ($P = .30$ for WBRT/SRS vs WBRT/SRS/TMZ and $P = .48$ for WBRT/SRS vs WBRT/SRS/ETN, respectively). The estimated 6-month CNS progression rates by arm were 16%, 29%, and 20%, respectively. The median CNS progression-free survivals by arm were 8.1, 4.6, and 4.8 months, respectively. WBRT/SRS produced less deterioration in performance status at 6 months than did either drug arm. The deterioration rates of performance status at 6 months for WBRT/SRS, WBRT/SRS/TMZ, and WBRT/SRS/ETN were 53%, 86%, and 86% ($P = .002$ for WBRT/SRS vs WBRT/SRS/TMZ and $P < .001$ for WBRT/SRS vs WBRT/SRS/ETN), respectively (Table 3).

There was no significant improvement in steroid dependence at 6 months for any of the experimental arms over the standard, and investigator-reported causes of death between treatments were similar in incidence and type. Approximately half of all patients had decreased steroid dependence. The rates of death resulting from neurologic causes for WBRT/SRS, WBRT/SRS/TMZ, and WBRT/SRS/ETN were 17%, 15%, and 19% ($P = .78$ for WBRT/SRS vs WBRT/SRS/TMZ and 0.80 for WBRT/SRS vs WBRT/SRS/ETN), respectively (Table 3).

Toxicity

The rates of serious (grade 3–5) toxicity related to therapy for WBRT/SRS, WBRT/SRS/TMZ, and WBRT/SRS/ETN were 11%, 41%, and 49% ($P<.001$), respectively (Table 4). Brain necrosis was reported in 1 patient (arm 3, grade 4).

Discussion

RTOG 0320 demonstrates a qualitatively large difference in survival between the WBRT/SRS arm (MST 13.4 months) and the 2 experimental drug arms, WBRT/SRS/TMZ (MST 6.3 months) and WBRT/SRS/ETN (MST 6.1 months), although the difference did not reach statistical significance. The most likely reason this difference did not reach statistical significance is that we enrolled only one third of the planned total number of patients.

The possible explanations for the qualitatively large difference in survival include 1 or more of the following: (1) increased toxicity was seen in the drug arms; (2) better outcomes were seen in arm 1 than have been seen in prior studies of WBRT plus SRS could be due to the relatively small sample size of this study; (3) patients in the drug arms received less standard doublet chemotherapy than did those in arm 1; (4) NSCLC patients presenting with brain metastases may do worse than NSCLC patients who do not have brain metastases at presentation but subsequently experience them; and (5) TMZ and ETN are not as effective as standard doublet chemotherapy for control of systemic disease, which is responsible for 80% of deaths in such patients. Another important observation is that intracranial disease control, reflected in the time to CNS progression, is not enhanced by either drug.

This study was not designed to compare arms 2 and 3, but because the survival in arms 2 and 3 were so similar, and so different from that in arm 1, we performed a post-hoc analysis, pooling arms 2 and 3 and then comparing their survival with that in to arm 1. In this post-hoc analysis, the difference in survival (13.4 months for arm 1 and 6.1 months for pooled arms 2 and 3) approached, but did not reach, statistical significance (PZ.07 and HR 1.45). This finding provides speculative support for the possibility that if the study had reached the targeted accrual, a statistically significant difference might have been demonstrated.

Comparison with other trials

Three other trials provide context for interpreting these findings (Table 1) (5, 9, H. I. Robins et al, unpublished data). Analysis of the subset of patients with NSCLC (nZ211 of 333) in RTOG 9508 (phase 3 trial of WBRT vs WBRT/SRS in patients with 1 to 3 brain metastases) showed MSTs of 3.9 and 5.9 months, respectively. ECOG-E1F03 was a 1-arm phase 2 non-randomized trial, which closed because of poor accrual (nZ26). The MST for WBRT/TMZ was 7.0 months (H. I. Robins et al, unpublished data). A trial sponsored by Schering-Plough was initially planned as a phase 3 trial but was converted to a phase 2 trial and closed prematurely, again because of poor accrual. The MSTs for WBRT/TMZ and WBRT alone were 4.4 and 5.7 months, respectively (9). In comparison with these trials, the MST of the WBRT plus SRS in the current trial seems unusually long and may be an outlier caused by chance, the small sample size, or other unidentified prognostic factors.

In summary, our trial, in addition to the others just summarized, provides no evidence to suggest that the addition of either TMZ or ETN is beneficial for patients with NSCLC and brain metastases. It is feasible that because this trial did not stratify treatment on the basis of predictive biomarkers (14, 15), TMZ or ETN may have caused more adverse effects for some patients, such as ETN for patients with K-ras mutation.

Barriers to accrual

The slow accrual of this study and others in this patient population also highlights the presence of many barriers to accrual in patients with metastatic cancer. Possible explanations for the slow accrual include 1 or more of the following: (1) All of these trials that suffered from accrual issues were initiated in an era when SRS alone (and actively omitting WBRT) had become a popular option; and (2) some investigators may have been reluctant or may have even deemed it unethical to enroll patients because standard doublet chemotherapy would be delayed (until progression or for 6 months in the original version of the protocol and by 3 weeks in the amended version). These factors also provide insight to investigators and funding agencies when they contemplate future trial design in this patient population.

Conclusions

This study and data from other series show that adding either TMZ or ETN to WBRT and SRS provides no benefit to patients with NSCLC and 1 to 3 brain metastases, in terms of OS, performance status improvement, neurologic death, or intracranial disease progression, and in fact significantly increases grade 3 to 5 toxicities. The performance status at 6 months was better in the WBRT/SRS arm than in either drug arm. There was no difference in steroid dependence or cause of death between arms. One further speculation is that in the drug arms, the increased toxicities might have compromised the ability to deliver subsequent “definitive” combination chemotherapy for metastatic NSCLC, and this could have caused deterioration in survival. Further research is needed to better individualize treatment and hopefully improve outcomes for this patient population. Until then, TMZ and ETN should not be used routinely in patients with NSCLC and 1 to 3 brain metastases, in combination with WBRT and SRS.

Acknowledgments

This trial was conducted by the Radiation Therapy Oncology Group (RTOG) and was supported by RTOG grant U10 CA21661 and CCOP grant U10 CA37422 from the National Cancer Institute (NCI). This article's contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

Dr. Robins is a consultant for Genentech; Dr. Khuntia is a on the Board of Directors of Medical Physics Publishing, is a consultant for Varian Medical Systems, Accuray and Radion Global, owns stock in Radion Global and has received honoraria from Accuray and Varian Medical Systems; Dr. Suh is a consultant for Abbott Oncology and has received other remuneration from Varian Medical Systems; Dr. Mehta is on the Board of Directors for Pharmacyclis, is a consultant to Abbott Oncology, Bristol-Myers-Squibb, Elekta, Merck, Novartis, Novocure and Tomotherapy, owns stock in Pharmacyclis and Accuray, and has received honoraria from Merck.

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Fig. 1. RTOG 0320 CONSORT diagram of patient disposition. ETN Z erlotinib; SRS Z stereotactic radiosurgery; TMZ Z temozolomide; WBRS = whole brain radiation therapy.

Fig. 2.
Overall survival by treatment arm.

Table 1

Comparison with other series: Median survival (mo) in clinical trials of patients with non-small cell lung cancer and brain metastases.

Treatment	RTOG 0320	RTOG 9508 (5)	ECOG Technical Report 1172e, Robins et al, 10-9-2008	Schering-Plough (9)
WBRT		3.9		5.7
WBRT + SRS	13.4	5.9		
WBRT + SRS + TMZ	6.3			
WBRT + SRS + Erlotinib	6.1			
WBRT + TMZ			7.0	4.4
Phase	3	3	2	2
Design	Random	Random	Nonrandom	Nonrandom
Sample size (n)	126	211 of 333 *	26	95
Accrual reached	no	yes	No	No
Dates	2005–09	1996–2001	2005–07	2004–07
Maintenance drug Rx	Optional	none	Yes	Yes

Abbreviations: ECOG Z Eastern Cooperative Oncology Group; RTOG Z Radiation Therapy Oncology Group; SRS Z stereotactic radiosurgery; TMZ Z temozolomide; WBRT Z whole brain radiation therapy.

*
211 of the 333 patients in RTOG 9508 had NSCLC.

Table 2

Pretreatment patient characteristics.

Characteristic	Arm 1	Arm 2	Arm 3
n	44	40	41
Median age	64	63	61
RPA class			
I	32%	30%	37%
II	68%	70%	63%
GPA			
0–1.0	14%	13%	7%
1.5–2.0	27%	35%	51%
2.5–3.0	50%	47%	32%
3.5–4.0	9%	5%	10%
No. of brain metastases			
1	45%	45%	37%
2	30%	33%	44%
3	25%	22%	19%
Extracranial disease			
None	52%	52%	56%
Present	48%	48%	44%

Abbreviations: GPA = graded prognostic assessment; RPA = recursive partitioning analysis. No significant difference in the above pretreatment characteristic or other factors including sex, race, Zubrod status, neurologic function status, steroid dependence, histology or graded prognostic assessment.

Table 3

Median survival, time to central nervous system progression, performance status, steroid dependence, and cause of death.

Characteristic	Arm 1	Arm 2	Arm 3
Median survival	13.4	6.3	6.1
95% Confidence Interval	6.5–20.8	3.4–10.1	3.6–2.1
P value (1-sided)	-	.93	.95
Time to CNS progression			
6 mo CNS progression rate	16%	29%	20%
P value	-	.30	.48
Time to new metastases			
6 mo rate	9%	21%	15%
P value	-	.40	.74
Time to targeted metastases progression			
6 mo rate	9%	10%	10%
P value	-	.57	.32
Performance status at 6 mo [*]			
Deterioration rate	52.5%	85.7%	85.7%
P value	-	.002	<.001
Steroid use at 6 mo [†]			
Rate of stable/increase	54%	44%	41%
P value	-	.51	.56
Cause of death			
Due to CNS	17%	15%	19%
P value	-	.78	.80

Abbreviation: CNS = central nervous system.

^{*} For the Zubrod performance scale, patients with baseline scores who had died by 6 mo were included in the analysis with a score of 5 at 6 mo. Zubrod score with at least 1 point increase compared with baseline was defined as performance deterioration.

[†] For the steroid use, change from baseline at 6 mo was evaluated to have decreased, remained stable, or increased. Only patients alive at 6 mo, and with both baseline and 6-mo steroid dose, were included in this analysis.

Table 4

Type and grade of treatment-related toxicity.

Type	Grade	Arm 1	Arm 2	Arm 3
Patients		44	39	41
Overall	1–2	36%	38%	39%
	3–5	11%	41%	49%
	3–5	41%	82%	66%
Nonhemorrhagic	1–2	39%	41%	42%
	3–5	9%	36%	46%
Grade	3	5 (11%)	13 (33%)	17 (42%)
	4	0	2 (5%)	2 (5%)
	5	0	1 (3%)	1 (2%)

Arm 1: grade 3: anemia, fatigue, muscle weakness, confusion, headache; grade 4: none; grade 5: none.

Arm 2: grade 3: cytopenia, fatigue, dehydration, gastrointestinal bleeding, infection, hyperglycemia, seizures; grade 4: cytopenia, hypokalemia, fatigue; grade 5: thrombocytopenia.

Arm 3: grade 3: cytopenia, fatigue, dehydration, acne, anorexia, vasculitis, diarrhea, pneumonia, hyperkalemia, muscle weakness, confusion, ataxia; grade 4: myocardial ischemia, brain necrosis; grade 5: hemorrhagic stroke.