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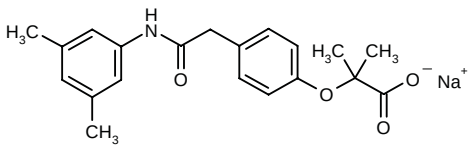
Efaproxiral Sodium

Prop INNM; USAN

Allosteric Hemoglobin Modifier
Radiosensitizer

RSR-13

2-[4-(3,5-Dimethylphenylcarbamoylmethyl)phenoxy]-2-methylpropionic acid sodium salt



$C_{20}H_{22}NO_4.Na$

Mol wt: 363.3868

CAS: 170787-99-2

CAS: 131179-95-8 (as free acid)

EN: 170977

Abstract

Efaproxiral (RSR-13) is a synthetic allosteric modifier of hemoglobin. Pharmacological studies have demonstrated the ability of this compound to effect a rightward shift in the oxygen dissociation curve, thereby increasing the delivery of oxygen to the tissues. Studies in rodent and feline models have also demonstrated the efficacy of efaproxiral in cerebral and cardiac ischemia. The effect of efaproxiral on tumor response to radiotherapy has been investigated in rodent models and has been the focus of pharmacokinetic and clinical studies. Rodent studies demonstrated radiation dose-modifying factors up to 2.6. Pharmacodynamic studies have shown that a mean maximum increase in P_{50} is achieved with doses of 75-100 mg/kg efaproxiral, an effect proportional with the concentration of efaproxiral in red blood cells. Phase II studies have been completed in patients with glioblastoma multiforme, brain metastases and non-small cell lung cancer. These studies and a phase III study in patients with brain metastases have demonstrated the efficacy of efaproxiral administered with standard radiotherapy regimes in improving survival outcomes in these populations compared with radiotherapy alone.

Synthesis

Reaction of 4-hydroxyphenylacetic acid (I) with refluxing $SOCl_2$, followed by treatment of the resulting polymeric phenol ester with 3,5-dimethylaniline (II) in refluxing xylene, provides amide (III), which is finally condensed with acetone and chloroform by means of powdered NaOH (1, 2). Scheme 1.

Introduction

There are a number of clinical conditions characterized by an insufficient oxygenation, or hypoxia, of the tissues. These include tumor growth, ischemic coronary artery disease, cerebral ischemia and the management of patients during surgery and in intensive care. The tissue hypoxia may be due to inadequate blood flow, inadequate hemoglobin function or increased tissue oxygen demand. Hemoglobin (Hb) is an allosteric protein present in red blood cells that binds and transports oxygen. As an allosteric protein, Hb exists in an equilibrium between an oxy state and a deoxy state. Compounds known as allosteric modifiers are able to shift this equilibrium. Efaproxiral sodium (RSR-13) is a synthetic allosteric modifier of Hb. It noncovalently binds in the central water cavity of the hemoglobin tetramer, reducing the Hb oxygen affinity, and thereby enhancing the diffusion of oxygen to the tissues (3, 4).

Pharmacological Actions

The effect of efaproxiral on the oxygen dissociation curve was investigated in rats. Conscious rats were treated with efaproxiral 84 mg/kg i.v. followed by 84 mg/kg/h for 2 hours. The partial pressure of oxygen (pO_2) at which

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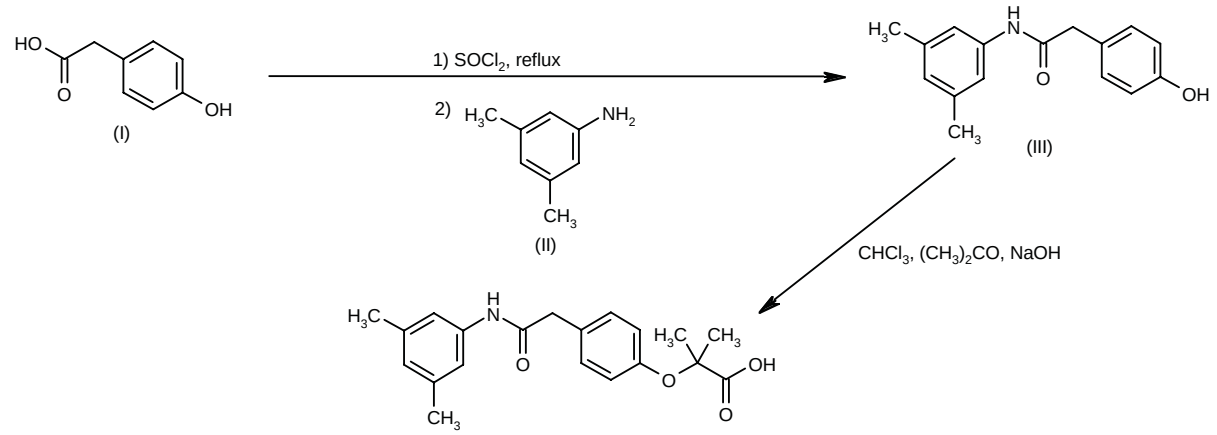
Scheme 1: Synthesis of Efaproxiral



Hb was 50% saturated (P_{50}) increased from 36.0 mmHg to 61.4 mmHg, representing a shift to the right of the oxygen dissociation curve, compared with a decrease in P_{50} in control rats from 36.7 mmHg to 33.2 mmHg. The Hill coefficient decreased from 2.62 to 1.73 (5).

These *in vivo* effects of efaproxiral on Hb saturation and tissue pO_2 were also observed in anesthetized C3Hf/Sed mice. Following i.p. administration of efaproxiral (300 mg/kg), P_{50} increased by a mean of 53% and tissue pO_2 increased by a mean of 66% (6).

The effect of i.v. infusion with efaproxiral on tissue pO_2 and arteriolar diameter and flow was investigated in Sprague-Dawley rats. Studies were performed on the cremaster muscle of anesthetized rats administered efaproxiral 200 mg/kg over 15 min. P_{50} increased from 36 mmHg to 52 mmHg and tissue pO_2 increased to a maximum 146% above its control value. Calculated arteriolar flow decreased from 9 nl/s to a minimum of 1.4 nl/s, with a corresponding decrease in diameter from 27 μm to a minimum of 13 μm. These values were significantly lower than those in the control group, where similar changes were not observed. The results were consistent with the hypothesis that a decrease in the oxygen affinity of Hb increases oxygen delivery to muscle, thereby increasing vascular resistance via local oxygen-dependent autoregulatory mechanisms (7). Earlier studies in a feline model had also shown that efaproxiral significantly reduced the vasodilatation in cerebral arterioles induced by arterial hypoxia and hypotension (8).

An increase in systemic and vascular resistance was also demonstrated in rats treated with efaproxiral 200 mg/kg over 15 min, using an electromagnetic flow probe on the ascending aorta, or an iliac, mesenteric or renal Doppler flow probe. There was a significant increase in arterial P_{50}. Three hours after the infusion, cardiac output decreased significantly (from 358 ml/kg/min to 243 ml/kg/min), with a corresponding significant increase in total peripheral resistance from 0.31 mmHg/ml/kg/min to 0.43 mmHg/ml/kg/min. These results supported data in the previous study (7), confirming that a decreased oxygen affinity leads to an increase in total peripheral resistance and regional vascular resistance (9).

The effect of efaproxiral on tumor response to radiotherapy has been investigated in a number of studies in rodent models. The response to radiotherapy is dependent upon the presence of well-oxygenated, radiosensitive cell populations. However, solid tumors contain regions where large numbers of cells may be transiently or chronically hypoxic and are less sensitive to the effects of radiation. Coadministration of an agent which could improve the delivery of oxygen to tumors should result in an increased oxygenation of previously hypoxic tissue and potential improvement in tumor response to therapy (10).

Efaproxiral increased the response of EMT-6 mammary tumors to irradiation in mice. Tumors were induced in BALB/c mice by inoculating mouse mammary tumor cells (subline EMT-6) in the flank. Analysis of tumor cell survival curves demonstrated that efaproxiral plus oxygen reduced the hypoxic fraction from 24% found in air-breathing and oxygen-breathing mice to 9%. The results were consistent with an improvement in tumor oxygenation and showed that approximately 62% of the hypoxic tumor cells were radiosensitized by the treatment. There was no evidence that efaproxiral had a direct effect on the radiosensitivity of the cells *in vitro* or *in vivo*. There were also no enhanced radiation reactions observed in normal tissues (10).

In a radiation sensitization study, hypoxic EMT-6 mouse mammary tumor cells were exposed to efaproxiral (100 μM) prior to, during and for 1.5 h after radiation delivery. Efaproxiral increased the slope of the radiation survival curve of the cells, resulting in a radiation dose-modifying factor of 2.6. In cell cultures, efaproxiral also sensitized EMT-6 cells to the effects of certain cytotoxic agents. *In vivo*, efaproxiral (100 mg/kg/day i.p.) induced tumor growth delay and reduced the number of lung metastases when administered as an adjunct to

fractionated radiotherapy to mice bearing Lewis lung carcinoma (11).

The effect of efaproxiral on tumor oxygenation and response to therapy was studied in rats bearing mammary adenocarcinoma 13762. Rats were injected with efaproxiral (100, 150 or 200 mg/kg i.v.) and the hypoxic fraction of the tumor, defined as the percent of pO_2 readings < 5 mmHg, was calculated during and after the administration. A decrease in the hypoxic fraction was observed that was dependent on efaproxiral dose, and was maximal 30 min after administration of efaproxiral 150 mg/kg (hypoxic fraction 15% compared with 49% in the controls). There was a corresponding increase in pO_2, and breathing carbogen (95% O_2, 5% CO_2) resulted in markedly increased tumor oxygenation. Lewis lung carcinoma and MB-49 bladder carcinoma grown in mice were also studied in tumor growth delay studies. Administration of efaproxiral to mice bearing Lewis lung carcinoma resulted in radiation dose-modifying factors up to 1.66 following the maximum efaproxiral dose of 200 mg/kg i.p. Efaproxiral also decreased the number of lung metastases and the percent of large lung metastases, and resulted in increased responses of the primary tumor to chemotherapy (12).

An increased radiation response has also been observed in FSaII fibrosarcoma isotransplants in C3H mice. FSaII cell survival was measured following administration of efaproxiral 300 mg/kg i.p. 20 min prior to radiation. Tumor growth was significantly delayed in mice treated with efaproxiral compared to those which received radiation alone. Tumor cell survival was also significantly reduced in mice exposed to efaproxiral and carbogen, compared to mice exposed to efaproxiral and air, carbogen only or air only. These results confirmed the finding that efaproxiral had the potential to increase oxygen delivery to tumors, thus reducing their hypoxic fraction (13).

Studies to characterize the relationship between the radiation response of tumors and P_{50}, with the influence of inspired pO_2 were performed using *ex vivo* clonogenic survival analyses in FSaII tumor and SCCVII squamous cell carcinoma models in C3H mice. Efaproxiral 100 mg/kg i.p. and air breathing resulted in significant radiosensitization, whilst there was a marked decrease in radiosensitivity at a dose of 300 mg/kg. However, the latter dose combined with carbogen breathing resulted in the most significant enhancement of activity, indicating that a reduced Hb oxygen affinity led to an insufficient oxygen loading in air-breathing mice. The hypoxic fractions of SCCVII tumors were reduced to 58-67% of control values in mice irradiated over 4 days (14).

The effect of efaproxiral on the tissue oxygenation of NCI-H460 human lung carcinoma xenografts in athymic nude mice has also been studied using the technique of blood oxygen level-dependent magnetic resonance imaging (BOLD MRI). Magnetic resonance images were obtained for up to 60 minutes after injections of 0-300 mg/kg efaproxiral. There was a dose-dependent increase in the MRI signal ratio, consistent with an increase in tumor oxygenation. Maximum increases were observed 30 min after administration of the drug and the optimal response was seen with a dose of 200 mg/kg efaproxiral. Tumor growth delay studies also showed that efaproxiral enhanced the effect of a single dose of radiation by a factor of 2.8 (15).

The effect of efaproxiral on cerebral ischemia has been studied in rodent and feline models. Incomplete or near-complete forebrain ischemia was induced in Wistar rats by bilateral carotid occlusion. Efaproxiral 150 mg/kg i.v. was administered either before occlusion or at onset of reperfusion in the incomplete ischemia model, and at onset of reperfusion in the near-complete model. The outcome was assessed by the percent of dead hippocampal CA1 neurons, determined 5 days postischemia. There was a significant reduction in CA1 damage (58% dead neurons versus 81% in controls) following efaproxiral administration at the onset of reperfusion in the incomplete ischemia model. However, no effect was demonstrated when efaproxiral was administered either preocclusion or to rats with near-complete ischemia (16).

In a feline model, efaproxiral has been shown to reduce infarct size after acute focal ischemia. Cats were studied in a randomized, blinded study of efaproxiral compared with saline. Efaproxiral was administered prior to permanent middle cerebral artery occlusion followed by continuous infusion for 5 h. Cats treated with efaproxiral had a mean infarct volume in the left hemisphere of 21% compared to 33% in control animals. The difference between the groups was statistically significant. An inverse relationship between the dose of efaproxiral and infarct size was also observed (17).

Transient focal cerebral ischemia was induced in Wistar rats by middle cerebral artery occlusion (MCAO). Efaproxiral 150 mg/kg was infused either before or 30 min after the onset of 75 min of MCAO. Efaproxiral alone did not significantly improve outcome in either anesthetized or conscious rats. Rats given dizocilpine (MK-801), an NMDA antagonist (0.5 mg/kg i.v.), had a 90% reduction in mean infarct size. Further experiments with coadministration of dizocilpine with efaproxiral showed these rats had both a significantly smaller cortical and total cerebral infarct volume than rats administered dizocilpine alone. These studies showed that efaproxiral alone did not improve the outcome from cerebral ischemia, but did significantly improve the outcome when administered concomitantly with the neuroprotective agent dizocilpine (18).

In additional studies with Wistar rats, dizocilpine (0.25 mg/kg i.v.) was administered alone or in combination with efaproxiral (150 mg/kg i.v.) at the onset of reperfusion following 75 min of temporary MCAO in conscious rats. The combination of drugs significantly reduced subcortical and cortical infarct size, assessed 7 days later. Mean subcortical infarct sizes were 52 mm^3 following dizocilpine alone versus 37 mm^3 for the combination. Corresponding mean cortical infarct sizes were 35 and 8 mm^3, respectively. The combination of drugs also significantly improved neurological scores compared with dizocilpine alone. The study demonstrated the continued

benefit of efaproxiral in improving oxygen delivery, and the ability of cerebral tissues to respond, after the initial ischemic insult (19).

The cardioprotective effects of efaproxiral in cardiac ischemia have also been investigated. Isolated rat hearts were examined using [31]P nuclear magnetic resonance spectroscopy during constant-flow (control) and low-flow conditions. Efaproxiral improved the mechanical function of hearts subjected to 30 min of reduced flow, when they were reperfused with normokalemic blood perfusate. Efaproxiral also conserved the adenosine triphosphate (ATP) content of potassium-arrested hearts, compared with a decrease in control hearts exposed to low-flow ischemia, after 30 min. There was no difference in phosphocreatinine (PCr) between the 2 groups, nor any effect of efaproxiral on ATP content after 55 min of low-flow conditions. The results indicated a protective effect of efaproxiral during the early ischemic period induced by low-flow conditions (20).

The effect of efaproxiral on ATP levels, pH and ventricular function were also studied in open-chest dogs by [31]P NMR spectroscopy during a reversible reduction of left anterior descending (LAD) coronary artery blood flow. Dogs were randomized to receive efaproxiral 100 mg/kg i.v. or vehicle. The decline in myocardial creatine phosphate (PCr) caused by low-flow ischemia was significantly less in efaproxiral-treated dogs than in the control group. The PCr/ATP ratio and mean intracellular pH were also significantly higher in efaproxiral-treated dogs during the ischemic interval. There were no significant changes in regional myocardial blood flow, heart rate or systolic blood pressure. Efaproxiral also improved the contractile function of the ischemic region measured by pressure segment–length relations. These findings were consistent with the changes observed in the metabolic parameters (21).

In a further study, dogs were randomized to receive either efaproxiral 100 or 150 mg/kg by bolus followed by infusion, or vehicle. Anesthetized dogs underwent 5-min periods of LAD coronary artery occlusion, separated by corresponding periods of reperfusion. There was a final period of 180 min of reperfusion. Contractile function, as measured by percent segment shortening in the ischemic zone, was significantly greater during the 5-min reperfusion periods in the high-dose group compared with either the low-dose or vehicle-only groups. In dogs which received the higher dose of efaproxiral, there was also an enhanced recovery of contractile function at the end of the final 180-min period (47% vs. 10% of baseline in the low-dose group). At this time, there was a positive correlation between the degree of recovery of contractile function and P_{50}. The results suggest that the lower dose of efaproxiral did not sufficiently improve the flow of oxygen to the myocardium to enhance the recovery of contractile function. The dose-related increase in P_{50} was only 8 mmHg in the low-dose group, compared with an increase of 13 mmHg in the high-dose group (22).

The cardioprotective effects of efaproxiral have also been studied in a canine model of cardiopulmonary bypass that closely simulates the conditions of clinical hypothermic-cardiac surgery. Dogs were subjected to global myocardial normothermic ischemia followed by hypothermic cardioplegic protection (with or without efaproxiral 1.75 mmol/l) and normothermic reperfusion. Cardioplegia supplemented with efaproxiral significantly improved cardiac mechanical function, indices of oxidative metabolism, water content and tissue morphology (23).

The potential benefit of efaproxiral in ischemic brain injury has been demonstrated in the rat acute subdural hematoma model (24). However, studies in an *in vivo* model of acute renal failure in the rat have shown that administration of efaproxiral could exacerbate acute renal dysfunction (25).

Pharmacokinetics and Metabolism

The pharmacokinetics and pharmacological effects of escalating i.v. doses of efaproxiral have been investigated in healthy volunteers. In a placebo-controlled, double-blind, partial crossover study, 19 subjects were given single doses of 10-100 mg/kg of efaproxiral as infusions over 30-90 min. The pharmacokinetics were nonlinear. Total clearance decreased from 56 ml/min to 28 ml/min for the 25 and 100 mg/kg doses, respectively. Arterial oxygen saturation and P_{50} showed dose-related responses. There was a maximum increase in P_{50} of 11.9 mmHg for efaproxiral 100 mg/kg administered over 90 min. The corresponding change in arterial oxygen saturation was a decrease of 9.3%. The duration of the effects was also dose-related, with the maximum dose resulting in continuation of effect for approximately 10 h. No dose-limiting effects were observed in the subjects, nor any indication of systemic intolerance (26-28).

Single i.v. doses of 50, 75 or 100 mg/kg efaproxiral were given to 16 patients with stable effort angina in a placebo-controlled, double-blind phase Ib study. The results indicated nonlinear systemic pharmacokinetics and saturable plasma protein binding. The shift and change in slope of the oxygen equilibrium curve of whole blood increased dose-dependently and were linearly related to red blood cell concentrations of efaproxiral (29).

In 17 patients undergoing elective surgery and receiving general anesthesia, single doses of efaproxiral 10-100 mg/kg were administered by i.v. infusion. Clearance values were highly correlated with preoperative creatinine clearance and the volume of distribution depended on body weight. Fluid replacement and general anesthesia were contributing factors in the population variability observed in the modelled pharmacokinetic parameters (30).

A prospective, randomized, double-blind, placebo-controlled, dose-escalation study was performed in 26 patients undergoing general surgery. Single doses of 10-100 mg/kg efaproxiral were administered by i.v. infusion in an ascending-dose scheme, to determine the dose of efaproxiral that would cause an increase in P_{50} of 10 mmHg. Efaproxiral was administered after induction of

anesthesia, at the start of the surgical procedure. The increases in P_{50} were dose-dependent, and doses of 75 and 100 mg/kg efaproxiral resulted in mean maximum increases of 7.3 and 11.8 mmHg, respectively. There was a population variability across dose groups of approximately 40% in total plasma clearance and volume of distribution. Efaproxiral was well tolerated and there were no clinically significant changes in hemodynamic parameters. Changes in laboratory parameters were unremarkable, with the exception of clinically relevant increases in creatinine in 3 of 17 patients who received efaproxiral. These changes were transient and returned to clinically normal values within 1 week (31).

An open phase Ib study was performed in 17 oncology patients receiving palliative radiation therapy. Doses of 75 or 100 mg/kg of efaproxiral by i.v. infusion were escalated from 1 to 5 times per week over 2 weeks. Total clearance was 35.5 ml/min and volume of distribution 16.6 ml/kg. The terminal half-life in plasma was 6.8 h. The drug accumulation was negligible from the first to the last day in most patients (32).

Clinical Studies

The tolerance of repeated i.v. doses of efaproxiral was assessed in a multicenter, open phase I study in oncology patients receiving palliative radiotherapy. The first cohort received 75 mg/kg efaproxiral once a week for 2 doses. The maximum administration was 100 mg/kg/day for 10 days. Efaproxiral was administered immediately before radiotherapy. A total of 20 patients were enrolled in the study. The maximum pharmacodynamic effect was achieved at the end of the infusion, and was proportional to the concentration of efaproxiral in red blood cells. The mean maximum increase in P_{50} after a dose of 100 mg/kg efaproxiral was 8.1 mmHg, with a half-life of approximately 5 h. Repeated doses of efaproxiral were generally well tolerated (33).

Efaproxiral was also administered to 19 patients with newly diagnosed glioblastoma multiforme in a phase I study. Patients received efaproxiral 100 mg/kg by i.v. infusion every other day or daily, prior to cranial radiotherapy administered over a 6-week period. The pharmacodynamic findings were consistent with previous studies, with a mean shift in P_{50} of 9.24 mmHg, representing a 34% increase from baseline. There was no significant difference in mean peak shift between the dosing regimens. Efaproxiral was well tolerated and no significant drug accumulation occurred with either regimen. In 1 patient who received efaproxiral every other day, intratumoral cyst pO_2 measurements were made because of the presence of a Rickham reservoir. On day 21 of radiation, cyst pO_2 was 57 mmHg prior to therapy, 75 mmHg after 4 l of oxygen by nasal cannula, and 93-96 mmHg at the end of the efaproxiral infusion and 60 min later. After a further 60 min continuing with supplemental oxygen, cyst pO_2 was 79 mmHg. These results indicated that efaproxiral can enhance intratumoral oxygen delivery above that caused by supplemental oxygen alone (34, 35).

In the previously described phase I study (34), patients received efaproxiral, every other day or daily, prior to cranial radiotherapy (60 Gy/30 fractions). Efaproxiral was given over 1 h by central venous access. Radiotherapy was administered within 30 min. Patients were given supplemental oxygen (4 l/min) by nasal cannula, starting 5 min before efaproxiral administration and continuing at least until the end of radiation treatment. There was no enhancement of the acute toxicity of radiotherapy with efaproxiral. Grade 3 dose-limiting toxicity (at least possibly related to efaproxiral treatment) did not occur in the every-other-day dosing group, but occurred in 2/10 patients who received daily doses of efaproxiral. Grade 2 or greater toxicity was observed in 3/9 and 6/10 patients, respectively. The most frequently reported grade 2 event was chronic nausea. All patients in the every-other-day dosing group completed the planned treatment schedule. In the daily dosing group, 6 patients completed the treatment. The median survival from histological diagnosis was 13.7 months, which did not indicate any unexpected incidence of early deaths associated with efaproxiral administration (34).

The clinical outcomes of a subgroup of patients treated in another phase I study (33) have also been assessed. Five of 20 patients had palpable or radiographically measurable extracranial solid tumors measuring 5-9 cm in greatest dimension. Patients received up to 100 mg/kg/day of efaproxiral for 10 days during 2-3 weeks of radiotherapy. A complete response was observed in 4 patients and a partial response in the other patient. Symptoms improved in all patients, including resolution of a fistulous tract in a patient with recurrent ovarian carcinoma (36).

A multicenter phase II study was conducted in 50 patients with newly diagnosed glioblastoma multiforme to determine patient survival and safety of efaproxiral. The study was conducted by the New Approaches to Brain Tumor Therapy (NABTT) Central Nervous System Consortium. Patients received efaproxiral 100 mg/kg daily prior to cranial radiotherapy (60 Gy in 30 fractions) given over 6 weeks. Efaproxiral was administered over 30 min. Patients had a median survival of 12.3 months. One-year and 18-month survival rates were 54 and 24%, respectively. In a comparative population of 122 patients treated in other NABTT trials of agents shown to lack efficacy or to be suboptimally dosed, the median survival was 9.6 months. However, the patients in this database received treatment that may have had a negative effect on survival, thus biasing the comparison. Eight (16%) patients experienced dose-limiting toxicity and a total of 24% patients experienced grade 3 or greater toxicity at least possibly related to efaproxiral. The toxicities were generally transient and self-limiting. Five patients had grade 2 or greater renal dysfunction, which resolved in all cases after interruption of efaproxiral therapy. The hazard ratio, adjusted for key parameters, comparing the death rate per patient-year for efaproxiral to the comparison

population was 0.72. This greater than 25% reduction in hazard ratio indicated a survival benefit for efaproxiral compared to cranial radiotherapy alone, and warranted the initiation of a phase III trial according to NABTT recommendations (37).

A further phase II study assessed the efficacy and safety of efaproxiral in patients with brain metastases. Fifty-seven patients were enrolled in this multicenter, open study and received efaproxiral at a dose of 100 mg/kg over 30 min (with dose adjustments to 75 or 50 mg/kg), prior to cranial radiotherapy (30 Gy/10 fractions). Survival rates were compared with data from the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis Brain Metastases Database (BMD). There was a significant improvement in median survival time for patients who received efaproxiral, both in the overall comparison with the control group and in an exact-matched case analysis. In the latter analysis, median survival time in the efaproxiral group was 7.3 months compared with 3.4 months in the control group. Six-month and 1-year survival rates were 58 and 24% versus 21 and 8% for the efaproxiral and RTOG BMD patients, respectively. These data correlated with a 54% reduction in the risk of death for patients who received efaproxiral. Imaging-based response data showed that 7 (12%) patients achieved a complete response and 13 (23%) a partial response. The corresponding median survival times were 13.7 and 8.8 months, respectively (38).

A multicenter, open phase II study has been conducted to assess the response rate, toxicity and survival of patients with locally advanced inoperable non-small cell lung cancer treated with efaproxiral and thoracic radiation therapy. Forty-seven patients received efaproxiral 75 mg/kg (with adjustments to 50 or 100 mg/kg, as required) over 30 min, prior to daily radiation (64 Gy/32 fractions). Radiation therapy was delivered after 2 cycles of induction paclitaxel and carboplatin. In 44 patients with response results, the overall response rate was 89% (39/44 patients); complete and partial response rates were 9 and 80%, respectively. For all patients, the estimated 1-year overall survival rate was 65% (39).

The survival results from this phase II study in non-small cell lung cancer have been compared to those of a randomized phase III RTOG study in the same patient population. A retrospective, case-matched analysis showed that the median survival of patients treated in the efaproxiral study was 20.6 months, compared with 14.6 and 17.0 months for patients in the sequential chemoradiotherapy arm and concurrent chemoradiotherapy arms, respectively, of the phase III study (40).

A randomized, open, pivotal phase III trial in patients with brain metastases completed enrollment in July, 2002. A total of 538 patients were recruited at more than 80 centers in 11 countries. Patients received standard cranial radiotherapy (30 Gy/10 fractions) alone versus standard cranial radiotherapy with preirradiation efaproxiral (75-100 mg/kg over 30 min). The primary endpoint of the study was a 35% improvement in survival of patients treated with efaproxiral. Preliminary results showed that patients who received efaproxiral and radiotherapy experienced a 17.6% improvement in median survival compared to those who received cranial radiotherapy alone (control); however, there was no statistically significant difference between the groups. Greater improvements in median survival with efaproxiral therapy were observed in subgroups of the population, including patients with brain metastases only from breast cancer and non-small cell lung cancer (32.4%). In the subgroup of 115 patients with metastatic breast cancer, median survival was doubled in eligible patients who received efaproxiral (8.7 months vs. 4.6 months for patients who received radiation therapy alone). A complete or partial response was achieved in 72% patients who received efaproxiral compared with 53% in the control group. Six- and 12-month survival estimates were 62 and 34%, respectively, in the efaproxiral group versus 42 and 17%, respectively, in the control group (38, 41, 42).

Efaproxiral has been extensively studied in a number of clinical conditions. Seventeen studies have been conducted, including 9 oncology studies, recruiting over 700 adult cancer patients. The studies include a phase I/II trial in patients with locally advanced cervical cancer and a phase Ib/II NABTT trial in patients receiving carmustine chemotherapy for the treatment of recurrent malignant glioma. Phase II studies have shown that efaproxiral improves survival and is reasonably well tolerated (43, 44).

The second of 3 data components of the NDA for efaproxiral have been submitted to the U.S. FDA. The drug has fast track status and the final clinical section of the NDA for the treatment of patients with metastatic breast cancer is scheduled to be submitted by the end of 2003 (45).

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Virginia Commonwealth University, Richmond, VA (US); codeveloped with Allos Therapeutics, Inc. (US).

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