

# Efaproxiral: Should We Hold Our Breath?

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Suh et al<sup>1</sup> breathe a bit of new life into two long-standing endeavors with their report in this issue of a phase III study of whole-brain radiotherapy (WBRT) and efaproxiral (RSR13), a hemoglobin modifier meant to increase tissue oxygenation. For decades, radiation oncologists have sought to enhance tumor control and patient survival by addressing the problem of hypoxia and, separately, to improve results of WBRT by sensitization, dose escalation, or altered fractionation. In this large randomized trial, efaproxiral added to WBRT and oxygen breathing increased median survival time from 4.4 to 5.4 months ( $P = .16$ ) and the overall response rate from 38% to 46% ( $P = .10$ ). Larger gains were seen in the combined non-small-cell lung cancer (NSCLC) and breast cancer subset, for whom the median survival time improved from 4.4 to 6.0 months ( $P = .07$ ) and overall response rate improved from 41% to 54% ( $P = .01$ ).<sup>1</sup>

## HYPOXIA AND RADIORESISTANCE

Since at least the early 1950s, hypoxic cells have been suspected as a cause of radioresistance. Hypoxic cells are two to three times more resistant to conventional radiation than normally oxygenated cells, although this effect occurs only at very low levels of oxygen.<sup>2</sup> A partial pressure of 3 mmHg (an oxygen concentration of 0.5%) yields radiosensitivity midway between anaerobic and fully aerobic conditions, and there is essentially no difference in radiosensitivity for oxygen concentrations ranging from 2% to 100%.<sup>2</sup> Poor oxygenation also affects angiogenesis, apoptosis, and other processes that may influence treatment outcome. It is difficult to determine the hypoxic fraction in patients' tumors before or after maneuvers to increase oxygen levels, and the most relevant measure of hypoxia is not known clearly. The problem of anemia and hypoxia in cancer patients was reviewed recently by Varlotto and Stevenson,<sup>3</sup> including a brief summary of strategies that have been used to address the problem of hypoxic cells: hyperbaric oxygen; carbogen breathing; hypoxic cell sensitizers such as misonidazole, etanidazole, and nimorazole; and the hypoxic cell cytotoxin tirapazamine. Some of these treatments appear to hold promise, but none has become firmly established.

Efaproxiral is another drug that is meant to improve oxygenation of hypoxic tumor cells. It is a synthetic modifier of hemoglobin that reduces its oxygen-binding affinity, causing hemoglobin to release oxygen more readily into tissues; this action is unaffected by the blood-brain barrier. On the basis of preclinical data, it is expected that efaproxiral increases mean partial pressure of oxygen ( $P_{O_2}$ ) in both normal and tumor tissue by about 5 to 15 mmHg.<sup>4</sup> This increase in  $P_{O_2}$  presumably will not affect the radiosensitivity of normal tissue, but it is hoped that it will reduce the fraction of severely hypoxic cells to

overcome their radioresistance. For the protocol reported by Suh et al,<sup>1</sup> efaproxiral was administered intravenously via a central access device at 75 or 100 mg/kg during 30 minutes, ending within 30 minutes of daily WBRT. Both treatment arms received standard WBRT to 30 Gy in 10 fractions during 2 weeks along with oxygen at 4 L/min per nasal cannula for 35 minutes before, during, and for at least 15 minutes after WBRT. Efaproxiral was fairly well tolerated; the most common adverse effect was grade 3 hypoxemia occurring in 11% of patients in the experimental arm compared with 1% in the control arm. If additional study shows that efaproxiral significantly improves local control or patient survival, this level of toxicity would be acceptable.

## WBRT

Other investigators during the last several decades have attempted without success to improve the results of WBRT for brain metastases using higher doses, altered fractionations, and radiosensitizers.<sup>5</sup> Before the availability of radiosurgery, WBRT was the treatment for all but a small minority of patients with a single metastasis who underwent surgical resection, usually followed by adjuvant WBRT. It was recognized that survival was only 3 to 5 months after WBRT for brain metastases and that one third to one half of all patients still died of neurologic causes. As stereotactic radiosurgery has become more widespread, a great deal of controversy has been generated and much more attention has been focused on the problem of brain metastases. A broader spectrum of options is being considered, ranging from supportive care alone in poor-prognosis patients to multiple sessions of radiosurgery alone for multiple metastases, omitting WBRT at both extremes. Nonetheless, essentially all participants in the controversy would concede that WBRT continues to play an important role in the treatment of brain metastases (and dural and cranial leptomeningeal metastases), and they would agree that a means of improving results of WBRT would be welcome.

Suh et al<sup>1</sup> offer efaproxiral as a way to boost the antitumor efficacy of standard-fractionation WBRT. The primary end point in the efaproxiral/WBRT study was survival time, which is difficult to improve given the fact that patients with brain metastases commonly die as a result of systemic disease progression. One would expect that the mechanism by which efaproxiral would augment survival would be through increasing response or duration of control of brain metastases. From better local control, improved survival, quality of life, neurocognitive function, and duration of functional independence could follow, although any gains would be diluted by

adverse effects of systemic disease progression as well as adverse effects of treatment. Thus, it is not surprising or disappointing that the stand-alone survival results of this efaproxiral study are not that impressive. The median survival times of 5.4 months for the efaproxiral arm and 4.4 months for the control arm are not very different from other trials of WBRT<sup>5</sup>; the 6.0-month median survival time for 397 NSCLC and breast patients sounds more promising, and we are told that most of the difference was seen in breast cancer patients ( $n = 107$ ; hazard ratio = 0.51;  $P = .003$ ).<sup>1</sup> A trial specifically in breast cancer patients is underway.

Efaproxiral improved response of brain metastases to WBRT modestly.<sup>1</sup> Complete response (CR), partial response, and overall response rates are summarized in Table 1 along with data reported previously in the literature, though it should be noted that response rates evaluated by patient appear lower than response rates evaluated by lesion. Suh et al<sup>1</sup> found that efaproxiral increased the CR rate by patient from 6% to 11%. The overall response rate by patient increased from 38% to 46% for all histologies and from 41% to 54% for the NSCLC and breast cancer patients ( $P = .01$ ).<sup>1</sup> These response rates are similar to those reported previously using WBRT to 30 Gy in 10 fractions<sup>6,7</sup> and they appear to be lower than the response rates observed after radiosurgery, with or without WBRT,<sup>8</sup> but it is encouraging that there was a difference between the control and efaproxiral arms.

Nieder et al have performed excellent analyses of the influence of tumor characteristics, radiation dose, and fractionation on response and control of brain metastases after WBRT.<sup>6,9</sup> They have pointed out that response may be a less sensitive measure of treatment efficacy for brain metastases than actuarial local freedom from progression (FFP).<sup>9</sup> The high focal dose made possible by radiosurgery significantly improves actuarial FFP probability without necessarily affecting the response rate, perhaps by reducing proliferative potential of tumor cells. Some lesions remain visible for years after radiosurgery without progressing. Suh et al<sup>1</sup> do not directly provide FFP results for the efaproxiral/WBRT study; the progression-free survival curves shown in their Figure 1B are dominated by deaths, and the 1-year radiographic and clinical progression data presented in their Table 5 provide less insight than actuarial curves and fail to show any efaproxiral benefit. I would like to have seen

how efaproxiral affected actuarial local FFP, freedom from new brain metastases, and overall CNS control with censoring at last imaging follow-up, given that these end points more closely reflect the mechanisms by which I would expect efaproxiral to improve outcome in patients with brain metastases.

Relevant to the strategy of combining WBRT with oxygen breathing and efaproxiral, other investigators have studied response or FFP of brain metastases as a function of tumor imaging characteristics that may relate to degree of hypoxia. After WBRT to 30 Gy in 10 fractions, Nieder et al<sup>6</sup> found that CR and overall response rates were 39% and 63%, respectively, for 142 lesions without radiographic evidence of necrosis, 15% and 53% for 99 lesions with less than 50% necrosis, and 11% and 57% for 95 lesions with  $\geq 50\%$  necrosis. Among newly diagnosed or recurrent brain metastases treated with radiosurgery  $\pm$  WBRT, Goodman et al<sup>8</sup> reported 1-year FFP probabilities of 90% for 306 homogeneously enhancing lesions, 76% for 168 heterogeneously enhancing lesions, and 57% for 44 ring-enhancing lesions. Pattern of enhancement was significantly associated with FFP on multivariate analysis adjusting for radiosurgery dose and treatment era, and stratifying by primary site and type of radiosurgery (alone, as a boost, or for recurrence after prior WBRT;  $P = .019$ ).<sup>8</sup> It would be interesting to compare response rates and actuarial FFP for the control and efaproxiral arms of the current study according to percent necrosis or pattern of enhancement, as a surrogate for degree of hypoxia.

Despite the fact that I would like to have seen actuarial FFP data and also could not help but speculate that many of the patients included in this study may have been eligible for radiosurgery based on number and size of brain metastases, I want to congratulate the authors for completing this large prospective, randomized trial showing that efaproxiral may improve results of WBRT, at least for breast cancer patients. It is unfortunate that improvements were not seen in other tumor types, but I look forward to seeing results of the breast cancer study. Breast cancer patients tend to live longer and to have more treatment-responsive disease, allowing greater opportunity for clinical and imaging follow-up. It will also be interesting to see results of efaproxiral in combination with radiation for other tumors for which there is good evidence that hypoxia exists and confers a poorer outcome, such as head

**Table 1.** Response and Control of Brain Metastases

Reference	Treatment	Tumor Type	No.	CR (%)	PR (%)	CR + PR (%)	1-Year Local FFP
Suh et al <sup>1</sup>	WBRT/O <sub>2</sub> arm	All	250 patients	6	33	38	—
	WBRT/O <sub>2</sub> /efaproxiral arm	All	265 patients	11	35	46	—
	WBRT/O <sub>2</sub> arm	NSCLC/breast	194 patients	—	—	41	—
	WBRT/O <sub>2</sub> /efaproxiral arm	NSCLC/breast	203 patients	—	—	54	—
Nieder et al <sup>6</sup>	WBRT, 30 Gy/10 fx	All except small cell	242 lesions	Approximately 19	Approximately 32	Approximately 51	—
Antoniou et al <sup>7</sup>	WBRT, 30 Gy/10 fx	NSCLC	155 patients	11	27	38	—
Nieder et al <sup>6</sup>	WBRT, 30 Gy/10 fx	Breast	46 lesions	35	30	65	—
Nieder et al <sup>9</sup>	WBRT, 25 Gy/5 or 30 Gy in 10–12 fx	All	257 patients	—	—	—	56% by patient
Goodman et al <sup>8</sup>	RS $\pm$ WBRT	All	518 lesions	25	28	54	82% by lesion
	Subset data	NSCLC	168 lesions	29	30	58	78% by lesion
	Subset data	Breast	80 lesions	39	26	65	92% by lesion

Abbreviations: CR, complete response; PR, partial response; FFP, freedom from progression; WBRT, whole-brain radiotherapy; NSCLC, non-small-cell lung cancer; fx, fractions; RS, radiosurgery.

and neck cancer, advanced cervical cancer, and glioblastomas, although I am not overly optimistic.

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**Author's Disclosures of Potential Conflicts of Interest**

The author indicated no potential conflicts of interest.

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