

In a recent review in *The Lancet Oncology*, Chargari and colleagues¹ conclude that "as long as there is no proof-of-principle study that demonstrates any benefit to adding endocrine therapy concurrently with breast or chest radiotherapy, hormonal therapy should be delayed until after completion of adjuvant radiation therapy in breast cancer patients". However, preclinical studies of human breast-cancer xenografts in nude mice show an optimum reduction in breast-tumour size with simultaneous administration of the selective oestrogen receptor modulator, acolbifene (EM-800), with radiotherapy.^{2,3}

In 1999, we examined the effect of the pure oestrogen antagonist acolbifene in mice with human breast-tumour xenografts, given alone or in combination with radiotherapy using various schedules of administration.⁴ Treatment with radiotherapy alone led to an 11% decrease in mean tumour size, and treatment with acolbifene alone resulted in a decrease in size of 73%. Simultaneous treatment with acolbifene and radiation led to a 98% reduction in tumour size, and 86% of the tumours disappeared completely with continuous combined treatment. Most importantly, no tumours reappeared when oestrogenic stimulation was applied after stopping treatment.⁴ The study data indicate that treatment of the mammary gland with a pure antioestrogen (acolbifene) combined with radiotherapy yields a faster response, a greater reduction in tumour size, and a higher percentage of complete responses or tumour disappearance (cure) than either treatment alone.⁴

In a separate study,⁵ we investigated possible time-dependent interactions between acolbifene and radiation therapy to find the optimum timing of a combined treatment regimen. We assessed the effect of several sequences of treatment on the

growth of oestrogen-sensitive human breast-cancer xenografts in nude mice.⁵ Treatment with acolbifene was initiated 3 weeks before, at the same time as, or immediately after radiotherapy. After 156 days of treatment, acolbifene given alone caused a decrease in average tumour area of 75% and radiotherapy alone caused a transient decrease in size of 30% at 21 days, irrespective of treatment sequence. Combined treatment with acolbifene and radiotherapy led to an 88% reduction in tumour size—50% within 2 weeks—which was sustained for 156 days or until the end of study.

Results from our preclinical studies could differ from others because we used a highly potent and pure antioestrogen instead of a mixed antioestrogen-oestrogen compound, such as tamoxifen.⁶ Our results, obtained with a well-characterised model of human breast cancer (ZR-75-1 xenograft), suggest that the best possibility of cure in patients with breast cancer is with a combination of a pure antioestrogen with radiation therapy, started simultaneously and as early as possible. Randomised clinical trials of radiotherapy combined with a pure antioestrogen or a potent aromatase inhibitor should show the benefits of simultaneous oestrogen blockade and radiation therapy in patients with breast cancer.

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