“The Best-Laid Plans . . . Often go Awry . . .”

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This phrase “The Best-Laid Plans . . . Often go Awry . . .” is adapted from a line in the poetry of Robert Burns—“To a Mouse.” Here, it seems apropos as we consider the work by Arrieta et al.1 Alas, our ability in the last decade to improvise better therapies for patients with inoperable stage III non-small cell lung cancer, has been limited. Here, the investigators attempt to combine a potent radiation sensitizer, gemcitabine, with a definitive course of thoracic radiation. In doing so, the authors observed an encouraging overall response rate of 68% and a provocative median survival of 21 months. Although this study is limited to 19 patients, the results would suggest this combination may have activity. Unfortunately, the authors report that 32% of patients experienced a grade 3 to 5 pulmonary toxicity. Although we can debate what is an acceptable level of toxicity—in a cohort of patients with a very limited possibility of cure, what we must accept is the very narrow therapeutic ratio when combining gemcitabine and a course of definitive thoracic radiation. As reflected in Figure 1, with the addition of a radiation sensitizer, we hope to increase the tumor-control rate using the same or lower dose of radiation (shifting the green curve to the left). This has to be balanced with monitoring the risk of a normal tissue injury (not shifting the blue curve to the left). A number of clinical trials, including the work from Arrieta et al., would suggest that the radiation sensitization is not selective and both curves are being shifted to the left. For gemcitabine in particular, achieving an acceptable therapeutic ratio has been more than challenging.

In the first reported study of concurrent gemcitabine and thoracic radiation, the trial was terminated early after the first eight patients were accrued.2 Although Scalliet et al. observed an 88% response rate, this study also determined a 75% grade 3 to 4 pneumonitis rate with 38% patients succumbing to treatment related toxicities. One concern was that full-dose (1000 mg/m²) gemcitabine weekly was administered with the 60 Gy of thoracic radiation. Several experiences used moderated doses of gemcitabine and still the concern for toxicity remains. With preclinical data indicating that gemcitabine possessed radiation sensitizing properties at much lower doses, Blackstock et al.3 completed a phase Ia/Ib study of twice-weekly gemcitabine given at a dose of 10 to 50 mg/m² with 66 to 74 Gy thoracic radiation. Again, an impressive 88% response rate was observed in the 39 patients accrued, but grade 3–4 pneumonitis was seen 24% of the patients treated. The first Cancer and Leukemia Group B (CALGB 9431) study evaluating thoracic radiation and concurrent gemcitabine, used a dosing scheduled that delivered 350 mg/m² given on days 1 and 8 every 21 days—not weekly.4 The grade III/IV pneumonitis rate was an acceptable 14%. This moderate pulmonary toxicity may have to do with the gemcitabine being dosed only 3 to 4 times during the thoracic radiation. However, the 74% response rate and 18.3 month median survival while encouraging were not interesting enough for further study. In a subsequent CALGB trial (30105), in which the radiation volumes were prospectively mandated, 37% of patients receiving concurrent twice-weekly gemcitabine and thoracic radiation experienced a grade 3 to 5 pulmonary event.5 This arm of the randomized phase II study was terminated early because of unexpected toxicity. It should be noted that the V₂₀ (percent of normal lung receiving greater than 20 Gy) for 2 patients experiencing...
and this discussion should remind us that some chemotherapeutic agents are less forgiving than others as they relate to normal tissue toxicity. Furthermore, current studies combining biologics, such as the epidermal growth factor receptor inhibitors, to standard chemoradiation strategies should be carefully evaluated, in terms of a potential reversal of the radiation sensitization properties of the conventional chemotherapeutics or for potential unanticipated toxicities.

Moving forward, all clinical trials combining radiation with radiation sensitizing agents, should mandate detailed radiation planning parameters and reporting. This represents our only opportunity for developing the “best laid plans.”

REFERENCES


