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Editorial

Recall Those Thrilling Days of Yesteryear . . .

ANDREW T. TURRISI III

Sinai Grace Radiation Oncology Center, Detroit Medical Center, Detroit, Michigan, USA

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The blaring theme of the William Tell Overture, with trumpet fanfare, and its "off-to-the-races" tempo harkens one of my favorite TV shows: The Lone Ranger. In fact, the stirring theme song was known to me only as "The Lone Ranger," knowing nothing about Gioacchino Rossini or opera. The Lone Ranger, a masked man played by Clayton Moore, somewhat of a paradox and a mystery because only bandits wore masks hiding their identity. He only used silver bullets, and had a trusted friend named Tonto (played by Jay Silverheels), an Indian who referred to him as "Kemosabe." What an unlikely pairing. As The Lone Ranger galloped to rear his steed at the same dessert rock each week, the announcer would intone something about: "Recall those thrilling days of yesteryear . . ." and we were enthralled by another episode of a single righteous man doing deeds that righted wrongs and there was never a hint of impropriety or dirty backhanded tactics. Corny, huh? Surely it would not make it today.

Howard (Skip) Burris brings back some other thrills about the subject of combined modality use and the curious phenomenon of "radiation recall." Talk about odd pairings, chemotherapy was the "chemo-sabe" to the lone ranger of radiotherapy, but unlike Jay Silverheels and Clayton Moore, this couple has not always gotten along, retreating to opposite camps rather than celebrating their small steps of success. Skip Burris brings to light a new drug, ixabepilone, from a new class, epothilones, which stabilize microtubules. It is approved for use in the second line of refractory breast cancer. It purports a new interaction with radiotherapy characterized as "radiation recall." It is a case report and review of the literature [1]. Skip's review relies heavily on the Camidge and Price treatise from 9 years ago [2], and adds the case reports and other agents causing "recall" reported in the interim years. Timing may greatly influence these phenomena. "Recall versus radiosensitization" is a key concept from the Camidge and Price essay that Burris picks up and adopts. In "sensitization," the drugs and chemotherapy are used together so that the chemotherapy tees up the cells for the damage by the radiotherapy. The classic use of fluorouracil and cisplatin fit the bill here. On the other hand, Camidge and Price distinguished "recall versus impaired healing," and caution that "all radiation reactions in the skin [need to] have completely recovered before a reaction can be said to produce radiation recall dermatitis" [2]. If radiotherapy has so injured tissue, bringing chemotherapy in too soon can exacerbate the toxicity and make a subliminal toxicity overt. Dr. Burris, in this case report, didn't seem to accept this concept. The case report describes such an exacerbation of the damage produced *by the radiotherapy* more than radiation recall. But radiation recall is hard to explain in the first place. Both the Burris and Camidge and Price papers try to bring reason to what is mysterious and enigmatic. Although they each take pains to describe the dermatologic phenomena, both admit that there are visceral aspects (pneumonitis/lung scar, enteritis/bowel obstruction?) that

Correspondence: Andrew T. Turrisi III, M.D., Sinai Grace Radiation Oncology, Detroit Medical Center, Detroit, Michigan 48201, USA. Telephone: 313-966-3116; Fax: 313-966-4301; e-mail: aturrisi@dmc.org Received September 9, 2010; accepted for publication October 11, 2010; first published online in ***The Oncologist*** *Express* on November 2, 2010; available online without subscription through the open access option. 1083-7159/2010/$30.00/0 doi: 10.1634/theoncologist.2010-0311

are likely and harder to characterize. Can anyone make sense of why there is a seemingly idiosyncratic reaction on the first exposure, but nothing when the same drug is bravely used again after an interval? It is the gap between either radiotherapy and chemotherapy or chemotherapy that makes the question of timing uncertain and unpredictable. So we rely on clinical prudence and anecdotes. There are more stories about this than episodes of The Lone Ranger on radio and TV combined.

The timing of modalities has been an interest since I started my academic career. The analysis by Rafi Catane that influenced the twice-daily radiotherapy with concurrent cisplatin etoposide small cell regimen [3] had a strong influence. That report suggested that concurrent therapy produced better survival, but concurrent therapy for too long increased toxicity and treatment-related death. Yes, accelerated radiotherapy fraction schemes are likely to produce more acute toxicity, with or without drugs known to produce radiation recall, like doxorubicin or the taxanes. The choice of agents also is essential: agents having toxicity to an organ in the radiotherapy field are likely a bad choice for concurrent or sequential therapy, for example, doxorubicin and the heart. The National Cancer Institute/Radiation Oncology Branch chemotherapy was cyclophosphamide, doxorubicin, and vincristine, and we all know we can't do that today, but they did it and had some very provocative findings despite the toxicity. Today, the answers to some are to not use either altered fractionation or drugs concurrently, but there are now two trials testing whether more will be better than the condensed 3-week schedule all using the old, but very friendly to use with radiotherapy, cisplatin and etoposide. These are all issues of timing and compatibility rather than recall. Combined modalities increase toxicity, concurrent therapy more than sequential therapy.

Radiotherapy factors have largely been influenced by modern treatment planning techniques. This is not the place to go into any detail about the complexities of radiotherapy treatment planning, but the condensed version is that many beams directed at a defined target reduce the dose to surrounding normal tissues as compared with one, two, or few beams, and also reduce the dose per fraction. As the volumes of the targets increase, more normal tissues get radiotherapy, and acute and delayed effects increase proportionately.

In Dr. Burris' case report, the radiotherapy model was to treat 10 of 12 thoracic vertebrae (a large field) with a protracted treatment regimen that caused excessive toxicity, both to the skin and to the esophagus. It was not healed/repaired when the ixabepilone was delivered. This unmasked the radiotherapy toxicity—like Tonto pulling The Lone Ranger's mask off, treachery not cooperation. Perhaps the patient selection, performance status, negative nitrogen balance, and other physical factors may have contributed. However, suggesting that ixabepilone is the culprit is false . . . the delayed skin recovery might be worse, but this really isn't recall. There is ample evidence for single fraction therapy producing relief and no more than equal toxicity [4, 5]. In many quarters, the longer fractions are justified under the mistaken notion that they are "less toxic." Sadly, in some places, the profit motive plays a role in whether, consciously or unconsciously, to use many rather than few fractions. The Lone Ranger knows that a single fraction of 8 Gy is a silver bullet at least eight times out of 10, and in failures an additional single fraction rescues most.

Chemotherapy and radiotherapy can work together like the Lone Ranger and Tonto . . . we need to be "chemo savvy" as well as "radio savvy" rather than "tonto" (Spanish for stupid). We should not confuse sensitizing or inhibition or delayed repair with the somewhat mysterious and idiosyncratic r*adiation recall*. New ways of delivering radiotherapy make identification of the radiotherapy ports much less obvious. The dose on entry of each beam is remarkably lower, and inversely related to the number of beams. It is unusual to see skin reactions in multiple port beam arrangements. We may spend more time in target identification (treatment planning) and beam arrangements, giving dosimetrists more work. Moreover, one of the perverse realities is that radiotherapy departments may be paid less to do it the right way, then making believe it is safer and stretching the treatment out for more reimbursement.

Although it makes sense that ixabepilone may delay healing from radiotherapy toxicity, it causes alopecia in about half of the patients treated, and cutaneous reactions in $<5\%$; the described reaction is not radiation recall based on the facts of this case. The fault seems to lie more with the radiotherapy techniques and starting treatment before the radiotherapy reactions subsided. The timing of the modalities was maladroit, more than the enigmatic radiation recall.

REFERENCES

1 Burris H. Radiation recall with anticancer agents. ***The Oncologist*** 2010;15: 1227–1237.

2 Camidge R, Price A. Characterizing the phenomenon of radiation recall dermatitis. Radiother Oncol 2001;59:237–245.

3 Catane R, Lichter A, Lee YJ et al. Small cell lung cancer: Analysis of treatment factors contributing to prolonged survival. Cancer 1981;48:1936–1943.

4 Foro Arnalot P, Fontanals AV, Galceran JC et al. Randomized clinical trial with two palliative radiotherapy regimens in painful bony metastases: 30 Gy in 10 fractions compared with 8 Gy in a single fraction. Radiother Oncol 2008;89:150–155.

5 Hartsell WF, Scott CB, Bruner WD et al. A randomized trial of short- versus long-course radiotherapy for palliation of painful bony metastases. J Natl Cancer Inst 2005;97:798–804.