THE ABSCOPAL EFFECT

RTS 9

Introduction

Radiation therapy has impacted cancer treatment by controlling and eradicating all types of cancers. Radiation is effective by maximizing tumor cell death, which then causes a release of immunogenic factors. These immunogenic factors can play a very important role in stimulating an immune system cascade that subsequently causes the abscopal effect to occur.[1] This is important because the abscopal effect describes a process of destroying not only the primary malignancy, but also the secondary metastatic lesions elsewhere in the body (shown in Image 2). This has been an interesting medical phenomenon because treatment is strictly given at the primary lesion site, yet the secondary malignancies will respond as if they were also treated.

How The Magic Happens

The abscopal effect starts when the immunogenic factors trigger the release of endogenous damage-associated molecular patterns (DAMPs). These DAMPs help prime the body's immune system by then triggering dendritic cells (DCs) which results in an amplified antigen presentation to T cells (shown in Image 1). More specifically, this tumor cell surface antigen is known as calreticulin. When this antigen is processed by DCs there is an increase in the cytotoxic T lymphocyte stimulation, which boosts the body's immune system to attack and eradicate these cancer cells.[2]

Therapies That Do The Trick

Due to the infrequency of this phenomenon, there is ongoing research about what exactly induces this effect. Researchers have studied a combination of implementing radiation therapy along with immunotherapy drugs, one such as ipilimumab. This drug is a monoclonal antibody which is a check-point inhibitor that will also enhance the formation of cytotoxic T cells.[3] Even with some success, there is still much to investigate about specific dosing, fractionation, and histologic responses of different malignancies.

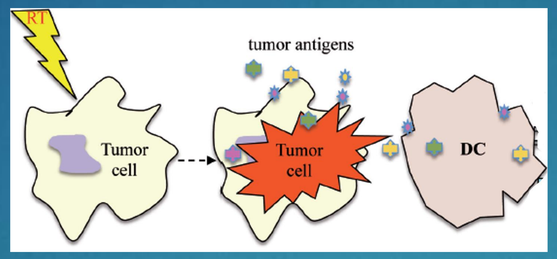

Image 1. Radiation induces tumor cell death which releases immunogenic factors to stimulate dendritic cells.[4]

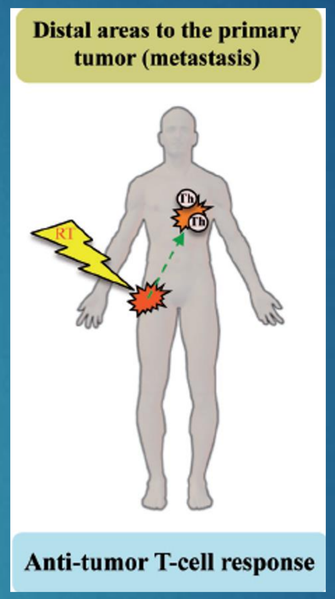

Image 2. Diagram showing radiation treatment to primary malignancy with abscopal effect to secondary metastasis in chest.[4]

Therapies That Work Best

In conventional radiation therapy, an inevitable side effect is immunosuppression. With too much depletion and damage to the T lymphocytes, this prohibits the body's immune system from carrying out this cascade effect to attack the metastatic disease on its own. This has lead researchers to conduct extensive studies to investigate which specific fractionation and dosage, combined with the immunotherapy is best for provoking the body to stimulate this abscopal effect (see Chart 1). Studies have evaluated single-fraction doses, hypofractionated doses over 1 – 2 weeks, conventional doses that take place over up to 7 weeks, as well as the different cycles for ipilimumab regimens. Studies have shown that the daily fractionation of conventional therapy is not effective. Single-fraction doses have been shown to work better in combination with immunotherapy; however, the hypofractionated scheme has produced the best tumor control and anti-tumor immune responses.[2, 5]

Fractionation Schemes
Single fraction – 12 Gy; 17 Gy; 20 Gy
Hypofractionation – 8 Gy x 3; 5 Gy x 4
Conventional – 1.8 Gy x 25-40 (Not effective)
Ipilimumab Cycles – 4 week

Chart 1. Different fractionation schemes used in studies.[2, 5]

Malignancies That Are Affected

Unfortunately, not all cancers have demonstrated a response to this abscopal effect during treatment. Identifying effective biomarkers prior to treatment can aid in predicting abscopal responses in patients who have received combination therapy regimens of immunotherapy and radiation therapy. Due to the initial incidental findings of this abscopal effect, many of the current clinical studies have been focused on breast cancer, prostate cancer, melanoma, colorectal cancer, and even renal cancer.[5]

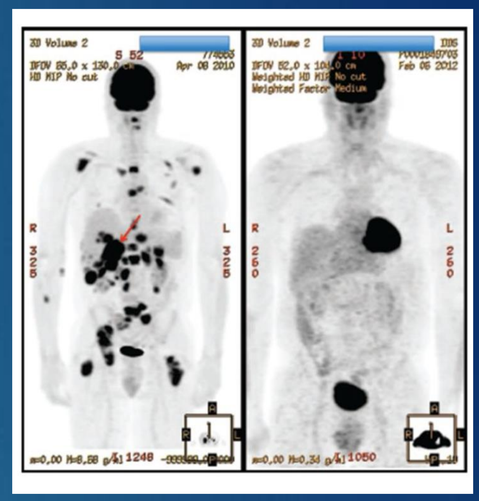

Image 3. PET/CT demonstrating initial tumor site (red arrow) with widespread metastases prior to treatment (left). Follow-up scan shows remarkable abscopal effect with dramatic improvement of metastases.[6]

Conclusion

The abscopal effect is a phenomenon that could have a major impact on future cancer treatments. While there is still a great amount of research to definitively pinpoint the most effective combination of treatments, the results are encouraging. Though limited, this effect will continue to advocate for advances in treatments related to improved control of metastatic disease. Radiation therapy combined with immunotherapy drugs, such as ipilimumab, have demonstrated the greatest responses thus far.

References

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