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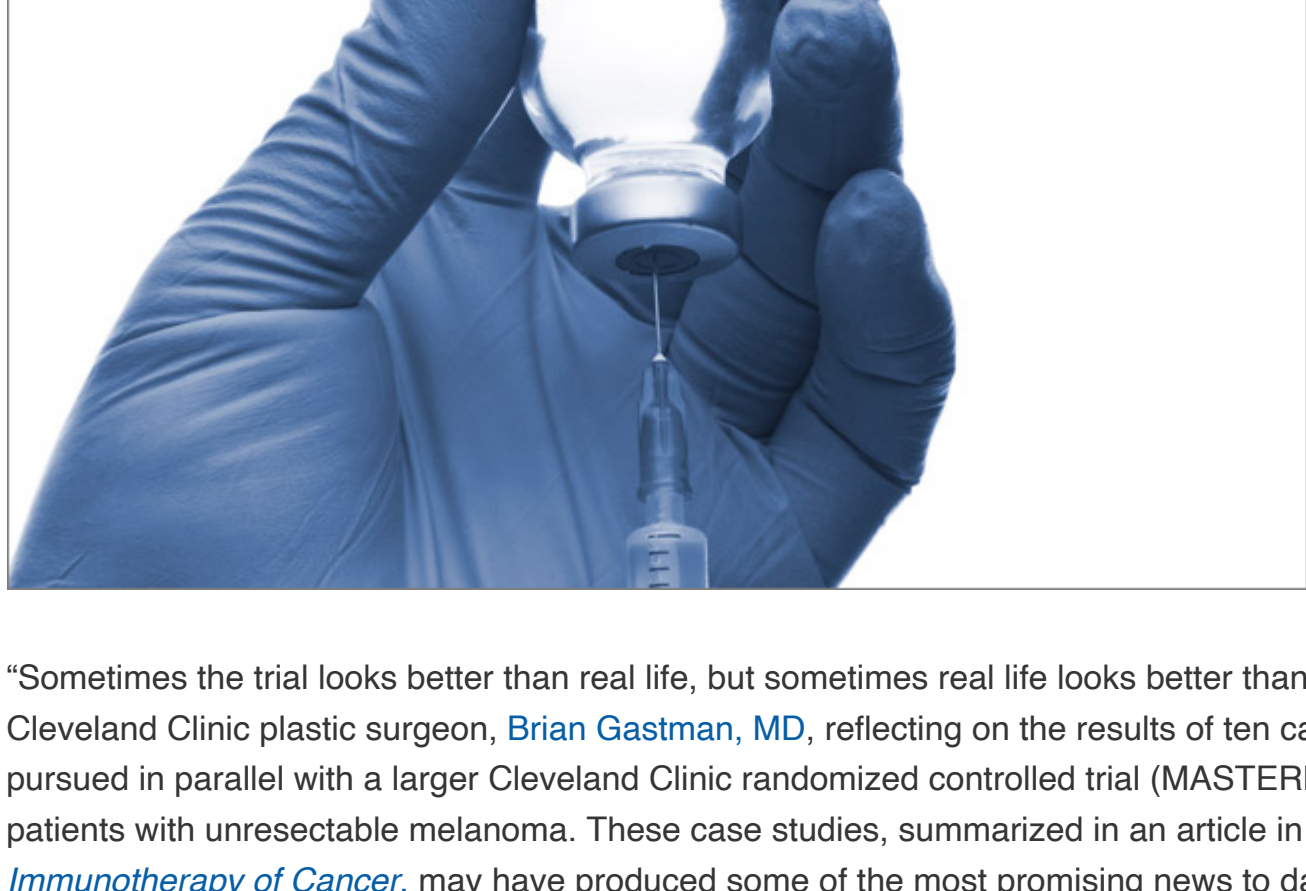
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Case Series: Patients with Unresectable Melanoma Respond to New Combination Treatment

Outcomes hold promise for future RCT results

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"Sometimes the trial looks better than real life, but sometimes real life looks better than the trial," says Cleveland Clinic plastic surgeon, [Brian Gastman, MD](#), reflecting on the results of ten case studies he pursued in parallel with a larger Cleveland Clinic randomized controlled trial (MASTERKEY-265) on patients with unresectable melanoma. These case studies, summarized in an article in *Journal for Immunotherapy of Cancer*, may have produced some of the most promising news to date for patients with late-stage disease.

Targeted and remote lesions responded

Dr. Gastman, who routinely performs oncology surgery on patients with melanoma, teamed with colleagues in pharmacy and oncology to review results of combination therapy for patients with unresectable stage IIIC-IVM1b melanoma. On varying schedules and in different combinations, the patients had received injections of talimogene laherparepvec (T-VEC) oncolytic virus and either anti-PD-1 checkpoint inhibitors (pembrolizumab or nivolumab) alone or with anti-CTLA-4 (ipilimumab) agents as well.

The outcomes were surprisingly positive. At follow-up (median eight weeks), nine of the ten patients had experienced a partial response (tumor reduction), and six experienced a complete response to the treatment. Most unexpectedly, two of the six patients with complete response had uninjectable pulmonary lesions in addition to their injectable lesions, providing evidence that this therapy stimulated the immune system to respond to and destroy remote tumors.

How the therapy works

T-VEC is the only FDA-approved intratumoral injection therapy for melanoma. The injected virus is tasked with evoking both an oncolytic and an immune-stimulating response within the lesion. Until now, T-VEC, combined with an anti-CTLA-4 checkpoint inhibitor, such as ipilimumab, was the best studied combination for inducing an anti-tumor immune response. However, ipilimumab has a high toxicity profile and greatly increases autoimmunity risk. Dr. Gastman and his team's findings suggest that substituting an anti-PD-1 agent as the backbone checkpoint inhibitor may avoid these high toxicity side effects and, Dr. Gastman says, "just may work better."

Patient experience

Patients' adverse events did not exceed grade 3, and all resolved following treatment. The injections were well-tolerated. Dr. Gastman's 13-year plastic surgery background in preparing sites and performing injections enabled him to mitigate discomfort but, he says, the biggest factor was in the patients' mindset. "Some patients had 15 lesions, and yes, it can hurt. But once they see them start to melt away, they're pretty motivated. Once they are mentally above the pain — because they are seeing improvement or they are so hopeful and so wanting to be cured — the pain becomes a tertiary issue."

Post-treatment follow-up and further questions

The median follow-up was seven months, with 80 percent of the patients surviving at the end of the follow-up (one died from disease progression and one from unrelated causes). All of the patients who had a complete response remained cancer-free. "We were limited to a short follow-up time for the study group as a whole, but even now, months out from follow-up, we are in touch with several patients who have not had a recurrence."

Blood tests in some of the patients revealed that the CD4:CD8 ratio was elevated in complete responders but not in partial responders. Percentages of PD1+ CD4T and CD8 T cells, thought to contain tumor-reactive lymphocytes, were much higher after the therapy in the complete responders but not the partial responders. While these findings might be expected, the question of why some people develop this more favorable environment for tumor destruction than others is fuel for further research.

Trials and real life

Researchers appreciate the rarity of case study patients faring better than randomized controlled trial (RCT) patients with the same condition and similar therapy. In an RCT, patients are a more homogenous group, usually healthier on average, and their treatment is tightly controlled, which gives the therapy the best opportunity to work. Yet, this case study population had slightly superior results than found in phase 1b of the MASTERKEY-265 population receiving T-VEC and anti-PD1 agents. "Our findings with patients who were sicker and had various factors we didn't control for were particularly heartening," Dr. Gastman says. "If the treatment works with a highly variable population, this is powerful medicine."

Because the final phase of MASTERKEY-265 results will not be available for years to come, Dr. Gastman suggests that the case study results may lead physicians to prescribe this combination off-label.

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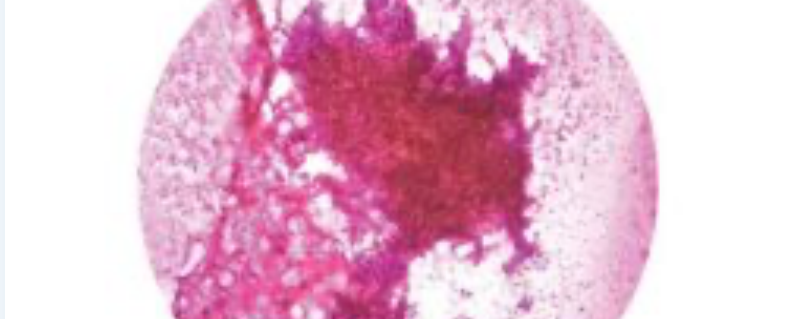
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