Inevitable Progress—Relying on the Immune System, Not Chance

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SUMMARY

Locoregional recurrence of head and neck cancer after curative therapy portends a poor prognosis even when resectable. Immunotherapy has opened the door to novel strategic approaches in the curative treatment paradigm. Potentially improving outcomes for patients with recurrent, resectable disease through combination immune modulators highlights a new frontier.

See related article by Hanna et al., p. 468

In this issue of *Clinical Cancer Research*, Hanna and colleagues evaluate the efficacy of dual checkpoint inhibition as neoadjuvant and adjuvant therapy for patients with recurrent squamous cell carcinoma of the head and neck (SCCHN) who are candidates for salvage surgery with curative intent (1). The authors' work highlights an area of opportunity where an unmet need exists across multiple solid tumors. Locoregional cancer recurrence after curative therapy portends a poor prognosis even when resectable. The paradigm in SCCHN is to operate when possible and then observe for recurrence (i.e., active surveillance). These patients essentially wait for their cancer to return without any recourse or option. There is no established benefit for adjuvant chemotherapy alone, and adjuvant reirradiation with or without chemotherapy carries significant toxicity without improved survival. Thus, introducing immunotherapy into the treatment paradigm to potentially improve outcomes represents an attractive strategy that could ultimately extend beyond SCCHN. Such a strategy, however, requires thoughtful consideration related to the timing and selection of therapy, and identification of relevant biomarkers of response.

This phase II, open-label, nonrandomized trial included one cycle of nivolumab plus lirilumab prior to salvage surgery followed by six adjuvant cycles. Primary endpoint was 1-year disease-free survival (DFS). Among 28 evaluable patients with heavily pretreated, locoregionally recurrent disease, pathologic response rate was 43% after one cycle of neoadjuvant nivolumab and lirilumab. One-year DFS for the entire cohort was 55%. Among pathologic responders, 2-year DFS and overall survival (OS) were 64% and 80%, respectively. Completion of all six adjuvant cycles was associated with an improved DFS. Patients with a pathologic response had improved DFS although this was not statistically significant. Positive surgical margins portended worse outcomes. Neither PD-L1 expression nor tumor mutational burden correlated with outcome, and similar mutational landscapes were observed amongst the group. In a subset of patients ($n = 6$) with paired tumor and peripheral blood samples before and after immunotherapy exposure, the tumor microenvironment demonstrated increased CD39 and CD69 expression on T cells, natural killer T cells, and B cells.

Timing of immunotherapy may influence outcome (2). For patients undergoing salvage surgery, immunotherapy may be administered in the neoadjuvant setting, the adjuvant setting, or both. A neoadjuvant approach has the advantage of using existing tumor as an *in situ* source of tumor-specific antigens to enhance systemic immunity by rejuvenating and priming cytotoxic T cells (2). Preclinical models in a variety of cancers have highlighted the potential benefits of neoadjuvant immunotherapy. Mouse models of spontaneous metastatic breast cancer demonstrated that neoadjuvant, rather than adjuvant therapy, improved survival by suppressing metastatic lesions (2). Neoadjuvant immunotherapy plus surgery was also more effective than surgery alone in generating tumor-specific $CD8^+$ T cells (2). Preclinical mouse models have shown that the specific interval between neoadjuvant exposure and surgery was also relevant, suggesting the need for adequate time to establish a potent systemic response (2). In a syngeneic mouse model of HPV-unrelated oral cavity carcinoma, neoadjuvant anti–programmed cell death protein 1 (PD-1) therapy led to conversion of functional immune dominance and induced effector T cell immunity that resulted in robust antitumor responses (2). Clinical trials involving neoadjuvant immunotherapy for previously untreated SCCHN have demonstrated this type of approach is safe, feasible, and can induce pathologic response (3). Additional potential benefits may include cancer downstaging and reduced rate of high-risk pathologic features, with the latter independently demonstrating worse outcomes even in the recurrent setting (1, 3).

As the current study and other clinical trials often include a neoadjuvant and adjuvant component, it is unclear to what extent each setting may be uniquely beneficial and if both are necessary. The findings in the current study suggested improved outcomes if patients experienced a pathologic response to one cycle of neoadjuvant therapy, or if they were able to complete the full 6-month interval of adjuvant therapy. Interestingly, Leddon and colleagues recently reported the findings of a phase II multicenter study evaluating the benefit of 6 months of adjuvant nivolumab in 39 patients with locally recurrent SCCHN undergoing curative salvage surgery (4). This study did not include a neoadjuvant approach yet resulted in 2-year DFS and OS rates (60% and 74%) that were comparable with those observed in the study by Hanna and colleagues. The preliminary results from Leddon and colleagues may suggest that enhancing preoperative systemic immunity does not have any bearing on overall outcome if patients received adjuvant therapy. An ongoing trial by Cohen and colleagues (NCT02769520) including one to two cycles of neoadjuvant pembrolizumab prior to salvage surgery followed by 12 months of adjuvant pembrolizumab for patients with recurrent SCCHN recently

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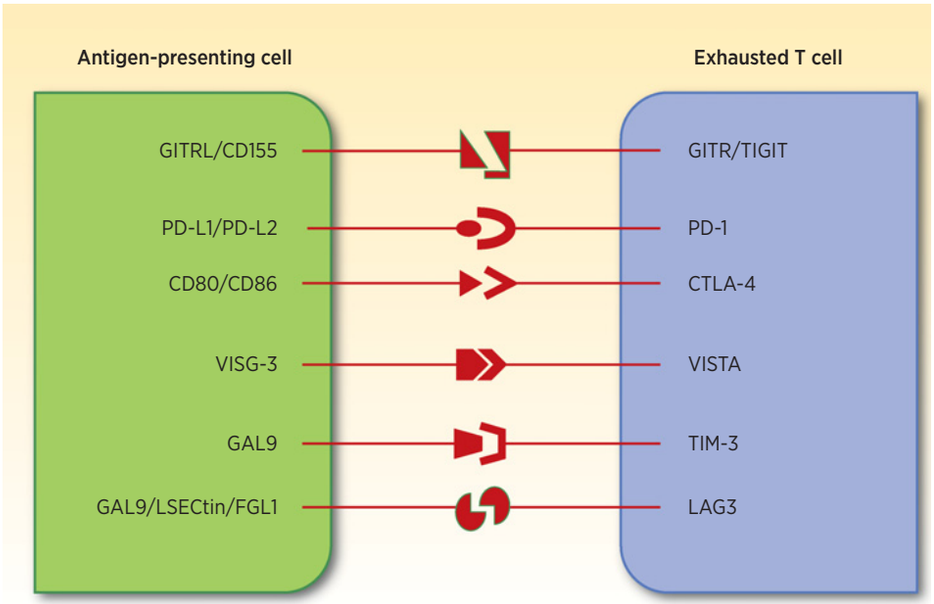

Figure 1.
Coinhibitory pathways in SCCHN.

completed accrual. These data may confer further insights regarding the impact of an extended adjuvant period on outcome. Ultimately, trials designed to rigorously and independently evaluate neoadjuvant versus adjuvant immunotherapy in the therapeutic package should be considered. Future trials should also assess the appropriate duration of the neoadjuvant and adjuvant intervals as patient burden and health care expenditures related to cost and toxicity are not negligible.

In terms of therapeutic selection, the next generation of trials incorporating immunotherapy in the surgical salvage treatment paradigm should explore novel combinations involving an anti–PD-1 backbone. This rationale is predicated on the knowledge that most SCCHN tumors display primary resistance to anti–PD-1 monotherapy. Various resistance mechanisms have been postulated, including low tumor immunogenicity, limited intratumoral immune infiltration, coexpression of coinhibitory molecules, and induction of immunosuppressive pathways within the tumor microenvironment (5). Coexpression of multiple inhibitory molecules, such as LAG-3, TIM-3, TIGIT, and VISTA may represent potential therapeutic targets (**Fig. 1**). Preclinical SCCHN models and tumoral assessments of patients on anti–PD-1 therapy have demonstrated that higher expression of TIM-3 or LAG-3 correlates with reduced likelihood of response to anti–PD-1 and worse prognoses (5). Trials in recurrent/metastatic SCCHN that combined anti–LAG-3 with anti–PD-1 have shown promising efficacy and could represent a potential novel combination in the salvage setting as well. For example, anti–LAG-3 plus anti–PD-1 could be considered in select cases of recurrent SCCHN eligible for surgical salvage if tumor biopsies and/or circulating T cells obtained preoperatively demonstrated LAG-3 coexpression, which is predictive of anti–PD-1 resistance.

The key to selecting novel therapeutic combinations lies in the identification of relevant biomarkers of response. PD-1 has proven to be an imperfect biomarker in SCCHN. Similarly, results have varied regarding the predictive value of the mutational profile, tumor mutational burden, T-cell inflamed phenotype, viral status (human papillomavirus), and tumor and circulating immune cell signatures. SCCHN is well suited for testing various immune biomarkers as tissue is often readily accessible and can be paired with the surgical specimen and serial blood samples to identify dynamic changes occurring before and after immunotherapy exposure. As prior treatments such as radiation may modulate the tumor microenvironment, correlative analyses will be particularly important in the salvage population as identification of robust biomarker signatures are sorely needed to better refine therapeutic strategies.

Immunotherapy has clearly opened novel strategic approaches to curative therapy. Hanna and colleagues illustrate the possibility of improving outcomes in patients with recurrent, resectable disease by using combination immune modulators. Given the pathologic responses observed, one wonders whether the field advances to the point of no longer requiring resection. There are many questions unanswered and we are at the beginning of the journey. Undoubtedly the path will be exciting but with many challenges.

Authors' Disclosures

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