Low-Dose Steroids Don't Impair ICI Survival

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> The use of corticosteroids in patients receiving immune checkpoint inhibitors (ICIs) has been a clinical dilemma, with concerns that immunosuppression might attenuate ICI efficacy.1 Recent evidence indicates that low-dose corticosteroid administration, particularly for managing immune-related adverse events (irAEs), does not compromise overall survival in patients undergoing ICI therapy.

KEY TAKEAWAYS

- The Pivot: Low-dose corticosteroids, often necessary for managing irAEs, do not appear to diminish the survival benefit of ICIs.
- The Data: Meta-analyses and observational studies consistently show no significant negative impact on overall survival (OS) or progression-free survival (PFS) with concurrent low-dose steroid use.
- The Action: Clinicians should not hesitate to use low-dose corticosteroids when clinically indicated for irAEs, as this does not appear to negate ICI benefits.

Immune checkpoint inhibitors have transformed cancer treatment, but their efficacy can be complicated by immune-related adverse events. Corticosteroids are the primary treatment for these irAEs, yet their immunosuppressive properties have raised concerns about potential interference with ICI mechanisms of action. This has led to a cautious approach among oncologists regarding concurrent steroid use, particularly at higher doses or for prolonged periods. The critical question has been whether the necessary management of irAEs with corticosteroids might inadvertently reduce the anti-tumour efficacy of ICIs, thereby impacting patient survival.

The clinical landscape of ICI therapy frequently necessitates corticosteroid intervention. irAEs can affect virtually any organ system, ranging from mild dermatologic reactions to severe, life-threatening events like myocarditis or colitis. The incidence of irAEs varies depending on the ICI agent, combination therapy, and patient characteristics, but can be as high as 60-70% for any grade and 15-20% for grade 3-4 events. Given this high prevalence, a significant proportion of patients receiving ICIs will require corticosteroid treatment at some point during their therapy. This widespread need underscores the importance of understanding the interaction between corticosteroids and ICI efficacy to optimize patient management and outcomes.

Impact of Corticosteroids on ICI Outcomes

Multiple retrospective analyses and meta-analyses have investigated the relationship between corticosteroid use and ICI outcomes. These studies have largely focused on patients receiving ICIs for various advanced malignancies, including melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma. The definition of 'low-dose' corticosteroids typically refers to prednisone equivalent doses of less than 10 mg/day, often used for managing mild to moderate irAEs or for pre-medication in some settings. Higher doses, generally defined as greater than 10 mg/day, are usually reserved

for severe irAEs.

A consistent finding across several large datasets is that concurrent low-dose corticosteroid use does not significantly impair overall survival (OS) or progression-free survival (PFS) in patients treated with ICIs. For instance, a pooled analysis of patients across different tumour types demonstrated that those receiving low-dose corticosteroids (e.g., prednisone equivalent) at the initiation of ICI therapy or during treatment for irAEs exhibited comparable OS and PFS rates to those who did not receive corticosteroids. Hazard ratios for OS in these low-dose groups have frequently been reported as approximately 1.0, with p-values consistently above 0.05, indicating no statistically significant detriment to survival. Similarly, objective response rates (ORR) have not shown a significant reduction in patients on low-dose steroids.

Conversely, the data regarding high-dose corticosteroid use (e.g., prednisone equivalent >10 mg/day) presents a different picture. Several studies have indicated that higher doses, particularly when administered for prolonged periods or at the initiation of ICI therapy, may be associated with poorer outcomes. This effect is often more pronounced when high-dose steroids are used to manage severe irAEs that necessitate treatment interruption or discontinuation of ICIs. However, it is important to differentiate between corticosteroids used for irAE management and those used for other indications, such as brain metastases or chronic obstructive pulmonary disease exacerbations, where the underlying condition itself might confound survival analyses.

The mechanism by which low-dose steroids avoid compromising ICI efficacy is not fully elucidated but may relate to their selective immunosuppressive effects or the transient nature of their administration for irAEs. It is hypothesised that the benefits of controlling severe inflammation and preventing irreversible organ damage from irAEs may outweigh any potential negative impact on anti-tumour immunity at lower steroid doses. Furthermore, the immune system's complex response to ICIs might be resilient to mild, short-term immunosuppression. Corticosteroids exert their effects by binding to intracellular glucocorticoid receptors, leading to altered gene expression that suppresses pro-inflammatory pathways. At lower doses, this suppression might be sufficient to mitigate irAEs without broadly inhibiting the T-cell activation critical for ICI anti-tumour activity.

Limitations of the current evidence include the retrospective nature of many studies, which introduces potential for confounding by indication. Patients requiring corticosteroids for irAEs may inherently have a different clinical profile or disease burden. For example, patients developing severe irAEs might have a more robust immune response, which could paradoxically correlate with better ICI efficacy in some contexts, making the interpretation of steroid impact complex. Heterogeneity in corticosteroid dosing, duration, and indications across studies also complicates direct comparisons. Prospective studies specifically designed to evaluate the impact of corticosteroid dosing on ICI outcomes are challenging to conduct but would provide more definitive evidence. Nevertheless, the consistent signal from numerous observational studies and meta-analyses provides a strong basis for clinical decision-making.

For broader insights into oncology principles and informed clinical decision-making regarding cancer management, we recommend consulting the Oxford Handbook of Oncology.

> **CLINICAL IMPLICATIONS**
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> The accumulating evidence regarding low-dose corticosteroids and ICI efficacy offers welcome clarity for oncologists. For too long, the fear of blunting the immune response has led to a reluctance to adequately treat

immune-related adverse events, potentially compromising patient safety and quality of life. This data should reassure clinicians that managing irAEs with appropriate low-dose steroid regimens is not a trade-off against survival benefit.

This distinction between low and high-dose steroids is critical. It underscores the importance of precise dosing and duration, advocating for the lowest effective dose for the shortest possible time. Guidelines from bodies like ASCO and ESMO already reflect this nuanced approach, but the consistent data reinforces the rationale. It also highlights the need for continued vigilance in monitoring patients for irAEs, allowing for prompt intervention with low-dose steroids before escalation to higher doses becomes necessary, which may indeed carry a survival penalty.

From an industry perspective, this clarity may influence future trial designs, potentially allowing for more standardised irAE management protocols without fear of confounding primary efficacy endpoints. For patients, it means better management of often debilitating side effects, potentially leading to improved adherence to ICI therapy and a better overall treatment experience, without compromising their chances of long-term survival. The focus remains on judicious use, but the evidence now firmly supports low-dose corticosteroids as a necessary and safe adjunct to ICI therapy when clinically indicated.

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