Association of Steroids Use with Survival in Patients Treated with Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis

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Abstract: Immune checkpoint inhibitors (ICIs) can elicit toxicities by inhibiting negative regulators of adaptive immunity. Sometimes, management of toxicities may require systemic glucocorticoids. We performed a systematic review and meta-analysis of published studies to evaluate the correlation between steroids use, overall survival (OS), and progression-free survival (PFS) in cancer patients treated with ICIs. Publications that compared steroids with non-steroid users in cancer patients treated with ICIs from inception to June 2019 were identified by searching the EMBASE, PubMed, SCOPUS, Web of Science, and Cochrane Library databases. The pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using a random-effects model. Patients (studies, n = 16; patients, n = 4045) taking steroids were at increased risk of death and progression compared to those not taking steroids (HR = 1.54, 95% CI: 1.24–1.91; p = 0.01 and HR = 1.34, 95% CI: 1.02–1.76; p = 0.03, respectively). The main negative effect on OS was associated with patients taking steroids for supportive care (HR = 2.5, 95% CI 1.41–4.43; p < 0.01) or brain metastases (HR = 1.51, 95% CI 1.22–1.87; p < 0.01). In contrast, steroids used to mitigate adverse events did not negatively affect OS. In conclusion, caution is needed when steroids are used for symptom control. In these patients, a negative impact of steroid use was observed for both OS and PFS.

Keywords: immunotherapy; immune-related adverse events; prognosis; steroids; meta-analysis

1. Introduction

Immune checkpoint inhibitors (ICIs) have improved patient outcomes in different tumors. The anti-Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) antibody ipilimumab and the anti-Programmed...
Death 1 (PD-1) drugs nivolumab and pembrolizumab have radically changed the therapeutic scenario in melanoma. The anti-Programmed Death Ligand 1 (PDL-1) durvalumab is the gold standard in unresectable locally advanced PDL-1 positive (tumor proportion score > 1%) Non-Small Cell Lung Cancer (NSCLC) as maintenance treatment after definitive chemoradiotherapy. In advanced NSCLC without EGFR or ALK aberrations, immunotherapy alone is the standard treatment in second line and, in PDL-1 strong positive (tumor proportion score > 50%) tumors, in first line [1]. The combination of chemotherapy plus immunotherapy is a new option in first line in advanced NSCLC, regardless of PDL-1 expression [2–4].

Corticosteroids have immunosuppressive properties through pleiotropic activities on T cell activation, differentiation, and migration [5], suppressing IL-2 mediated activation of effector T cells [6] and increasing regulatory T-cells [7]. Steroids can modify microbiome [8] and stimulate M2 macrophage polarization [9]. Because of their immunosuppressive properties, corticosteroids are both the principal treatment of immune-related adverse events due to ICIs [10] and an exclusion criterion for ICIs clinical trials; a threshold of ≥10 mg of prednisone equivalent daily is the usual cutoff [11,12]. Doses ≥ 10 mg of prednisone daily are related to increasing infection rates in patients chronically treated with steroids [13], and are therefore considered immunosuppressive. However, corticosteroids are often used at higher doses as palliative treatment for cancer-related symptoms such as dyspnea, fatigue, and symptomatic brain metastases [14–16].

The role of steroids administration during treatment with ICIs is still debatable. Their use, also at high doses, to manage immune-related adverse events did not affect ICIs efficacy in patients with melanoma [17] and NSCLC [18]. However, the early daily administration of ≥10 mg of prednisone equivalent at the time of ICIs initiation was related to poor outcomes in patients with NSCLC in some retrospective analysis [19–21]. Furthermore, a recent paper confirmed the worse outcomes in NSCLC patients treated with ICIs if doses ≥ 10 mg of prednisone equivalent were administered within 24 h of ICIs initiation. However, the detrimental corticosteroids effect was evident only in patients who were on steroids therapy because of cancer-related palliative indications; doses ≥ 10 mg of prednisone for cancer-unrelated indications, such as treatment of autoimmune disease, chronic obstructive pulmonary disease flare, and prophylaxis for hypersensitivity reactions, were not associated with worse outcomes in comparison with less than 10 mg of prednisone or no steroids administration [22].

A prospective randomized controlled clinical trial of steroids dose reduction or interruption is difficult to conduct. To better define their role during treatments with ICIs alone, we performed a systematic review and meta-analysis.

2. Materials and Methods

The search process followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. The outcomes of the present meta-analysis were reported according to the Meta-analysis of Observational Studies in Epidemiology criteria [23].

2.1. Search Strategy and Inclusion Criteria

A systematic search of electronic databases was conducted to identify studies that analyzed outcome in advanced cancer patients treated with ICIs and steroids. Published articles that compared steroids with non-steroid users in cancer patients treated with ICIs from inception to June 2019 were identified by searching the EMBASE, PubMed, SCOPUS, Web of Science, and Cochrane Library databases. Hand searches were also performed to identify other potentially eligible studies. The following keywords were used as search terms: (steroid or glucocorticoid or corticosteroid) and survival and (pd-1 or pd-l1 or ctla-4 or “immune checkpoint inhibitors”).

Three independent authors (F.P., G.T., and D.S.) performed the searches and assessed study eligibility. Prospective or retrospective studies, published in English language, comparing overall survival (OS) and progression-free survival (PFS) between ICIs + steroids use (intervention group) and ICIs use alone (comparator group) in cancer patients were selected. Exclusion criteria applied during
the selection process were as follows: (1) conference abstracts; (2) reviews, editorials, comments, and letters; (3) case reports; (4) studies not reporting the survival outcome of steroid user patients; (5) lack of information regarding a comparator group; and (6) insufficient data to extract hazard ratios (HRs) and 95% confidence intervals (CIs). The name of the institution or database included in the final set of eligible studies was reviewed. When multiple studies were based on the same dataset, the one with the longest-duration study period and the largest number of patients was selected. The study selection process was assessed independently by a third investigator (FG).

2.2. Data Extraction

The data were extracted independently by three authors (FP, GT, and AG). When discrepancies occurred, the authors discussed to reach a consensus. Author, year of publication, type of studies, diseases included, median follow up, dose and steroid regimens, number of steroid users, and reason for steroids intake were extracted from publications. Risk of bias assessment was conducted independently by three authors (FP, AG, and MG). For randomized studies, the Cochrane Collaboration’s tool for assessing the risk of bias in randomized trials was used. Since almost all of the included studies were non-randomized observational studies, the Risk of Bias Assessment tool for Nonrandomized Studies was used to assess the following six domains: the selection of participants; confounding variables; intervention measurement; blinding of the outcome assessment; incomplete outcome data; and selective outcome reporting [24,25]. Regarding potential discrepancies among the three authors, a consensus was obtained after further review and discussion with a senior author (FG). Quality of paper was evaluated through the Nottingham–Ottawa-Scale (NOS) for observational studies [26]. The total scores ranged from 0 (worst) to 9 (best) for cohort studies, with a score of at least seven indicative of high quality.

2.3. Statistical Analysis

The primary outcome of interest was OS and the secondary endpoint was PFS. The HRs and 95% CIs from each study were either extracted directly from original papers or calculated using Kaplan–Meier curves based on the method of Tierney et al. HRs were calculated using a random-effects model with the inverse variance method. Cochrane Q tests and the I² index were used to evaluate heterogeneity. Funnel plots with Egger’s regression tests were used to examine publication bias. Additional stratified OS analyses were performed to compare results from mono- and multi-center studies, retrospective and prospective studies, reason for steroid use (e.g., supportive care vs. brain metastases vs. adverse events [AEs]), number of patients (>100 vs. <100)), type of disease (NSCLC vs. melanoma vs. others), type of agent (anti-PD-(L)1 vs. anti-CTLA-4 vs. combinations, if data were available), type of analysis (uni- vs. multi-variate), and quality of paper (NOS ≥ 7 vs. < 7) were performed. RevMan software (ver. 5.3; Cochrane Collaboration, Copenhagen, Denmark) was used for all pooled analyses.

3. Results

In total, 346 potentially relevant citations were reviewed (Figure 1). Ultimately, 16 studies published from 2009 to 2019 that reported OS and/or PFS data were included in the final analysis [17,19–22,27–37]. The total number of patients included was 4045 ranging from 45 to 1025 patients per study (median, 151). The major characteristics are shown in Table 1. All but one (Weber 2009) were retrospective studies. Seven studies included patients with melanoma; the remaining n = 9 studies included NSCLCs (n = 7) or various histotypes (n = 2). Stages were mixed (III–IV) with n = 11 studies including only metastatic disease. According to the different study, patients received ICIs (nivolumab, pembrolizumab, atezolizumab, durvalumab, and ipilimumab) alone or in combination. In most studies (n = 9), steroids were administered for supportive care reasons; in six studies, steroids were used following immune-related adverse events (IrAEs). The quality of paper expressed by the NOS
scale ranged from 4 to 8, with almost all studies (94%) of sufficient to high quality (mean NOS scale scores: 6.69).

Figure 1. Flow diagram of included studies.
Table 1. Characteristics of included studies.

| Author/Year       | N of Pts (Total for Study) | Type of Study/Median FU (Months) | Disease                | Stage %         | ICIs Used          | Steroids Used/ N of Pts | Duration/Dose mg (p Equivalent) | Reason for Steroid Use | HR (95% CI) for OS | HR (95% CI) for PFS | Type of Analysis | Quality (NOS)/Risk of Bias |
|-------------------|-----------------------------|---------------------------------|------------------------|-----------------|--------------------|------------------------|-------------------------------|-----------------------|-------------------|---------------------|-------------------|------------------------|
| Acharya/2017 [33] | 72 Retrospective/8.9        | Melanoma IV (100)               | NIVO, PEMBRO, IPI, anti-BRAF-MEK | DEX (90%)/21    | BMs (100%)        | NR/25–50 mg (DEX)    | 2.32 (1.1–4.80) *          | -                     | MVA 6/low         |
| Arbour/2018 [19]  | 640 Retrospective/NR        | NSCLC IV (100)                  | PEMBRO, NIVO, ATEZO or DURVA (100%) | NR/90          | BMs (17%), BSC (83%) | 1.66 (1.28–2.16) *       | -                     | MVA 7/low          |
| Chasset/2015 [32] | 45 Retrospective/21.9       | Melanoma III–IV                 | IPI                    | PZN, methyl-P/12 NR/10 | BMs (16%), BSC (84%) | 5.82 (2.45–13.8) *        | -                     | UVA 7/low          |
| Dumenil/2018 [34] | 67 Retrospective/NR         | NSCLC III–IV                    | NIVO                   | 1st cycle of ICI/10–40 mg die in 5 patients | BMs (100%)         | 1.31 (0.51–3.38)        | -                     | UVA 7/low          |
| Faje/2018 [35]    | 98 Retrospective/NR         | Melanoma IV (100)               | IPI                    | NR (high vs low dose)/69 | IrAEs (100%)    | 4.16 (1.61–14.28) *      | -                     | MVA 6/low          |
| Fuca'/2019 [21]   | 151 Retrospective/28.6      | NSCLC IV (100)                  | anti-PD-1/PD-L1/anti-PD-L1 + anti-CTLA-4 | NR/35          | BMs (100%)        | 2.38 (1.48–3.83) *       | -                     | MVA 8/low          |
| Hendriks/2019 [37]| 1025 Retrospective/15.8     | NSCLC Advanced                  | anti-PD-1/PD-L1        | NR/141         | BSC (54%), NR (35%), IrAEs (11%) | 1.46 (1.16–1.84) *       | -                     | MVA 8/low          |
| Horvat/2015 [17]  | 298 Retrospective/NR        | Melanoma III–IV                 | IPI                    | NR/103         | IrAEs (100%)      | 0.99 (0.71–1.39)         | -                     | UVA 6/moderate     |
| Johnson/2015 [28] | 90 Retrospective/≥24        | Melanoma III–IV                 | IPI                    | NR/12          | IrAEs (100%)      | 1.06 (0.39–2.83)         | -                     | UVA 8/low          |
| Ricciuti/2019 [22]| 650 Retrospective/NR        | NSCLC IV (100)                  | anti-PD-1/PD-L1 + anti-CTLA-4 | PZN/93         | BMs (35%), BSC (43%), other (50%) | 1.60 (1.07–2.39) *       | -                     | MVA 7/low          |
| Scott/2018 [20]   | 210 Retrospective/NR        | NSCLC IV (100)                  | NIVO                   | PZN/66         | BMs (27%), BSC (39%), IrAEs (17%) | 2.3 (1.27–4.16) *        | -                     | MVA 6/moderate     |
| Shafiq/2018 [36]  | 157 Retrospective/6.7       | Various IV (100)                | PEMBRO, NIVO or ATEZO  | PZN/21         | -                  | 0.83 (0.16–4.918) *      | -                     | MVA 6/moderate     |
| Sukari/2019 [31]  | 168 Retrospective/26        | Various IV (100)                | PEMBRO, NIVO          | NR/77          | IrAEs (100%)      | 0.81 (0.51–1.30)         | -                     | MVA 8/low          |
| Taniguchi/2017 [27]| 201 Retrospective/NR        | NSCLC IV (100)                  | NIVO                   | NR/23          | -                  | 2.37 (1.44–3.74) *       | -                     | MVA 6/moderate     |
| Weber/2009 [30]   | 115 Randomized phase 2/14  | Melanoma III–IV                 | IPI                    | BUD/58         | IrAEs (100%)      | 1.06 (0.66–1.7)          | -                     | UVA 4 (Jadad)/low  |
| Zaragoza/2016 [29]| 58 Randomized phase 2/14   | Melanoma IV (98.3)              | IPI                    | NR/15          | -                  | 1.28 (0.54–3.06)         | -                     | MVA 8/low          |

*, statistically significant; ICIs, immune checkpoint inhibitors; PZN, prednisone; DEX, dexamethasone; methyl-P, methylprednisolone; BUD, budesonide; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; NSCLC, non-small cell lung cancer; PEMBRO, pembrolizumab; NIVO, nivolumab; ATEZO, atezolizumab; DURVA, durvalumab; IPI, ipilimumab; TTF, time to treatment failure; TTNTD, time to next treatment or death; *, both for cancer-related and unrelated reasons; NOS, Nottingham–Ottawa Scale; NR, not reported; IPI, ipilimumab; °, comparison of high vs low dose steroids; BM, brain metastases; BSC, best supportive care.
3.1. Meta-Analysis of OS

OS data were available in \( n = 14 \) studies. Because the heterogeneity test showed a high level of heterogeneity (\( I^2 = 64\% \), \( p < 0.001 \)) between the studies, a random-effects model was used for the analysis. Overall prognosis of patients receiving steroids for any reason during treatment with ICIs was significantly worse (HR = 1.54, 95% CI: 1.24–1.91; \( p = 0.0001 \); Figure 2).

| Study or Subgroup  | log(Hazard Ratio) | SE   | Weight | Hazard Ratio IV, Random, 95% CI | Hazard Ratio IV, Random, 95% CI |
|--------------------|-------------------|------|--------|---------------------------------|---------------------------------|
| Acharya 2017       | 0.8416            | 0.2090 | 5.1%   | 2.32 [1.19, 4.56]               |                                  |
| Arbour 2018        | 0.5066            | 0.1526 | 10.5%  | 1.55 [1.29, 1.85]               |                                  |
| Chassot 2018       | 1.7163            | 0.4414 | 4.2%   | 5.82 [2.45, 13.82]              |                                  |
| Dummer 2018        | 0.2773            | 0.4813 | 3.7%   | 1.31 [0.51, 3.30]               |                                  |
| Falke 2018         | 1.4565            | 0.4840 | 3.7%   | 4.16 [1.61, 10.75]              |                                  |
| Floyd 2018         | 0.6271            | 0.2424 | 7.6%   | 2.38 [0.49, 12.03]              |                                  |
| Hanania 2019       | 0.3784            | 0.1174 | 19.9%  | 1.46 [0.61, 3.44]               |                                  |
| Harvald 2016       | -0.0101           | 0.1036 | 9.6%   | 0.99 [0.77, 1.28]               |                                  |
| Johnson 2019       | 0.5065            | 0.5102 | 3.4%   | 1.59 [0.59, 4.50]               |                                  |
| Richaud 2019 (CSS group) | -0.0943     | 0.3371 | 5.6%   | 0.91 [0.47, 1.76]               |                                  |
| Richaud 2019 (RSC group) | 0.47   | 0.3553 | 8.7%   | 1.60 [0.87, 2.99]               |                                  |
| Song 2018          | 0.6326            | 0.2303 | 8.5%   | 2.20 [1.27, 4.17]               |                                  |
| Sukal 2016         | -0.2107           | 0.3366 | 8.6%   | 0.81 [0.45, 1.47]               |                                  |
| Yeebot 2008        | 0.0583            | 0.3417 | 7.8%   | 1.06 [0.65, 1.70]               |                                  |
| Zangare 2016       | 0.2469            | 0.4403 | 4.2%   | 1.28 [0.54, 3.03]               |                                  |
| **Total (95% CI)** |                   |       | 100.0% | 1.54 [1.24, 1.91]               |                                  |

Figure 2. Overall survival comparing use or not of steroids concomitant to immune checkpoint in patients with cancer.

3.2. Meta-Analysis of PFS

PFS data were available in \( n = 9 \) studies with high heterogeneity (\( I^2 = 75\% \), \( p < 0.001 \)), thus a random-effects model was used for the analysis. Concomitant use of steroids in patients treated with ICIs was associated with a 34% higher risk of progression or death (HR = 1.34; 95% CI: 1.02–1.76; \( p = 0.03 \)) (Figure 3).

| Study or Subgroup  | log(Hazard Ratio) | SE   | Weight | Hazard Ratio IV, Random, 95% CI | Hazard Ratio IV, Random, 95% CI |
|--------------------|-------------------|------|--------|---------------------------------|---------------------------------|
| Arbour 2019       | 0.27              | 0.1227 | 13.0%  | 1.31 [0.53, 3.30]               |                                  |
| Dummer 2018       | 1.1609            | 0.4095 | 6.1%   | 3.27 [1.39, 7.69]               |                                  |
| Faja 2018         | 1.1664            | 0.4177 | 6.4%   | 3.22 [1.42, 7.39]               |                                  |
| Floyd 2018        | 0.0931            | 0.2920 | 9.4%   | 1.09 [0.89, 2.37]               |                                  |
| Harvald 2016      | 0.37              | 0.1033 | 14.5%  | 1.31 [0.87, 2.23]               |                                  |
| Hommel 2015       | -0.1744           | 0.1832 | 12.6%  | 0.84 [0.61, 1.16]               |                                  |
| Richaud 2019 (CSS group) | -0.476         | 0.2316 | 9.5%   | 0.62 [0.33, 1.10]               |                                  |
| Richaud 2019 (RSC group) | 0.3255      | 0.1022 | 12.3%  | 1.40 [0.90, 2.19]               |                                  |
| Sholdt 2018       | -0.0537           | 0.4455 | 6.0%   | 0.93 [0.60, 1.43]               |                                  |
| Taniguchi 2017    | 0.9629            | 0.2542 | 10.3%  | 2.37 [0.44, 1.39]               |                                  |
| **Total (95% CI)** |                   |       | 100.0% | 1.34 [1.02, 1.76]               |                                  |

Figure 3. Progression-free survival comparing use or not of steroids concomitant to immune checkpoint in patients with cancer.

3.3. Subgroup Analysis

A further subgroup analysis was performed according to the following variables: number of patients (\( \geq 100 \) or \( <100 \)), type of study (multi- vs. mono-centric), study quality (NOS score \( \geq 7 \) vs. NOS score \( <7 \)), type of agent, and type of disease (NSCLC vs. melanoma) and found no significant differences that would confirm a worse prognosis associated with steroid use. However, when the reason for using steroids was split by supportive care vs. brain metastases, the supportive care subgroup was associated with a worse prognosis (HR = 2.51, 95% CI 1.41–4.43; \( p < 0.01 \)). Conversely, in patients taking steroids for IrAEs, the outcome was not compromised (Table 2).
Table 2. Subgroup analysis for overall survival.

| Subgroup Analysis                          | N of Studies/pts | HR (95% CI)   | \( p \)  | \( I^2 \) | Type of Analysis          |
|--------------------------------------------|------------------|---------------|---------|---------|---------------------------|
| Multi- vs. mono-centric studies            |                  |               |         |         |                           |
| - Multi-center                             | 7/2866           | 1.47 (1.25–1.72) | <0.01  | 0%      | Random effect model       |
| - Single institution                       | 9/1179           | 1.71 (1.18–2.46) | <0.01  | 75%     | Random effect model       |
| Type of agent                              |                  |               |         |         |                           |
| - Anti-PD-L1                               | 8/2540           | 1.50 (1.15–1.95) | <0.01  | 54%     | Random effect model       |
| - Anti-CTLA-4                              | 6/704            | 1.68 (0.97–2.92) | 0.06   | 76%     | Random effect model       |
| Reason for steroid use                     |                  |               |         |         |                           |
| - BSC                                      | 3/836            | 2.5 (1.41–4.43)  | <0.01  | 76%     | Random effect model       |
| - BMs                                      | 3/1164           | 1.51 (1.22–1.87) | <0.01  | 49%     | Random effect model       |
| - AEs                                      | 9/926            | 1.08 (0.79–1.49) | 0.62   | 48%     | Random effect model       |
| Number of patients                         |                  |               |         |         |                           |
| - >100                                     | 10/3615          | 1.31 (1.05–1.64) | 0.02   | 64%     | Random effect model       |
| - <100                                     | 6/430            | 2.21 (1.44–3.41) | <0.01  | 47%     | Random effect model       |
| Type of analysis                           |                  |               |         |         |                           |
| - UVA                                      | 4/548            | 1.49 (0.78–2.84) | 0.23   | 79%     | Random effect model       |
| - MVA                                      | 12/3497          | 1.59 (1.28–1.97) | <0.01  | 52%     | Random effect model       |
| Quality of study                           |                  |               |         |         |                           |
| - NOS score ≥7                             | 8/2827           | 1.52 (1.16–1.99) | <0.01  | 66%     | Random effect model       |
| - NOS score <7                             | 8/1218           | 1.84 (1.07–3.17) | 0.03   | 71%     | Random effect model       |
| Type of study                              |                  |               |         |         |                           |
| - Retrospective                            | 15/3930          | 1.59 (1.26–2)   | <0.01  | 65%     | Random effect model       |
| - Prospective (1 study)                    | 1/115            | 1.06 (0.66–1.7)  | 0.81   | NA      | Random effect model       |
| Type of disease                            |                  |               |         |         |                           |
| - NSCLC                                    | 7/2944           | 1.62 (1.36–1.93) | <0.01  | 23%     | Random effect model       |
| - melanoma                                 | 7/776            | 1.75 (1.07–2.88) | 0.03   | 74%     | Random effect model       |

BM, brain metastases; BSC, best supportive care; NSCL, non-small cell lung cancer; UVA, univariate analysis; MVA, multivariate analysis; NOS, Nottingham-Ottawa Scale; AEs, adverse events; PD-L1, programmed death ligand 1.

3.4. Publication Bias

There was no publication bias in the overall pooled results (\( p = 0.18 \) and \( p = 0.20 \) for OS pooled analysis through Begg’s and Egger’s test, respectively) (Figure 4).

![Figure 4. Funnel plots showing log hazard ratios and standard errors for overall survival.](image-url)
4. Discussion

ICIs can elicit toxicities by inhibiting negative regulators of adaptive immunity. Usually, events of mild intensity do not require specific treatments but supportive care only. When more severe events develop, moderate to high-dose systemic glucocorticoids (generally prednisone 1 mg/kg or equivalent or intravenous formulations) are needed. Metastatic cancer patients may also need steroids for symptoms control such as dyspnea, pain, brain edema, and fatigue or for concomitant autoimmune diseases. Registered trials of ICIs used to exclude patients with pre-existing steroids use at equivalent doses greater than 10 mg of prednisone. Therefore, its potential detrimental effect on efficacy is currently unknown.

We performed a systematic review and meta-analysis of all published studies where outcome of corticosteroid user patients treated with immunotherapy was compared with those not assuming or using steroids at lower doses (inferior to 10 mg equivalent of prednisone).

We found that patients taking steroids for any reason were at increased risk of death and progression compared to those not using steroids (HR = 1.54, \(p < 0.01\) and HR = 1.34, \(p = 0.03\), respectively). In subgroup analysis, the greatest negative effect on prognosis was evident in patients taking steroids for supportive care (e.g., disease-related symptoms), where the risk of death was more than doubled, and for brain metastases, where the risk of death was similar to the whole population and increased by 50%. Conversely, the effect of steroids administered to mitigate AEs did not seem to negatively affect OS; this finding was similar in NSCLC and melanoma. Similar results were presented by Ricciuti et al., where steroids’ detrimental effect appeared to be linked to the poor-prognosis subgroup of patients who received corticosteroids for palliative indications [22]. This may be associated with a larger number of patients with poor performance status or brain metastases where steroids are provided for cancer-related palliation. A potential association with better prognosis in patients reporting immune-related adverse events has been described [38,39], thus balancing the negative effect of steroid use. Specifically, in a pooled analysis of 28 studies where the OS of patients experiencing IrAEs was compared with that of patients without AEs, the risk of death was reduced by 50% in the IrAE group (Petrelli, personal communication).

The negative effect of steroids on survival in patients receiving ICIs appears intuitive. In preclinical models, dexamethasone whether given alone or in combination with anti-PD-1 therapy resulted in significant reductions of circulating CD4+T cells. Absolute numbers of circulating CD8+T cells also displayed similar significant trends with dexamethasone treatment. In the same experimental model, mice that received anti-PD-1 therapy alone experienced significantly longer tumor doubling times, thus delaying tumor growth compared to control group. Conversely, dexamethasone alone and anti-PD-1 + dexamethasone combination treatment group displayed a similar effect on tumor volume [40]. Another explanation of the way steroids impairs function of activated T lymphocytes is with the enhancing expression of PD-1 on T-cells [41]. More in general glucocorticoids induce apoptosis in hematological cells, thus supporting their use as therapeutic agents for leukemias, lymphomas, and myeloma [42]. Patients taking steroids at start of immunotherapy can so hamper the immune cascade, preventing the activation of an effective antitumor immune response.

Our paper has some intrinsic limitations but may provide an important clinical message to oncologists. First, this is a meta-analysis of mainly retrospective studies, where imbalance in prognostic factors may have led to negative association of steroids with outcome. Second, in many trials, type, dose, and duration of steroids used are unknown, and thus a correlation with timing and intensity of exposure was not possible. Third, papers include patients treated with anti-PD-(L)1 agents or ipilimumab for various cancers and a subgroup analysis was not possible. Fourth, the average effect was likely driven by negative prognostic factors and palliation indication for steroids in many cancer patients. Brain metastases or higher burden of thoracic or bone disease conditioning respiratory symptoms or pain seems to represent the primary indications for steroids in these studies. In addition, more advanced age, anorexia/weight loss, and poor performance status may have weighted as bad prognostic factors in steroid’s cohort and may have influenced the final analysis of OS. Finally, median follow up
was relatively short or not reported in many publications, thus results could have been different if prolonged observation of events were performed by the authors. However, this meta-analysis is the first systematic collection and pooling of all data regarding the association of steroids use and prognosis during treatment with ICIs. Despite the overall results being derived from small single-center studies, it reassures the use of steroids during treatment with ICIs and highlights that low systemic dose of steroids used to manage AEs may not affect survival. On the contrary, symptomatic patients requiring steroids at the start of ICIs may require a different treatment approach (e.g., chemotherapy) or a rapid tapering of steroids before commencing immunotherapy.

5. Conclusions

In summary, even though high-grade immune-related toxicities necessitate corticosteroid therapy for improvement, use of steroids in these cases seems not to reduce OS in cancer patients treated with ICIs and may be safely administered without compromising outcome [10,43]. Conversely, more caution is needed for metastatic patients where steroids are used for reasons different from AEs (e.g., disease-related symptoms or brain metastases) and a detrimental effect on survival is likely. In these cases, discussing different treatment options (e.g., chemotherapy or radiotherapy) may avoid futile treatment while delaying treatment with ICIs until the symptom conditions are ameliorated and controlled without systemic steroids.

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