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Review Article

Corticosteroid therapy in older adults with cancer: Expert recommendations from a task force of the International Society of Geriatric Oncology

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ABSTRACT

Corticosteroids are used frequently in oncology and many patients require short- or long-term corticosteroid therapy. General clinical guidelines and recommendations exist on the use of corticosteroids; however, evidence is lacking for recommendations on their appropriate use in older adult with cancer.

Treatment of chemotherapy-induced nausea and vomiting (CINV) has dramatically improved over the last decade with 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists and neurokinin-1 (NK−1) receptor antagonists or a combination of both. However, corticosteroids continue to play an important role in the management of acute and delayed CINV prevention. While highly efficacious, the toxicity profile of corticosteroids must be considered, particularly in heterogeneous older patients with multiple comorbidities and polypharmacy.

Guidance on corticosteroid-reducing/sparing strategies in this specific population is needed. This consensus, supported by the International Society of Geriatric Oncology, aims to provide evidence-based recommendations for the use of corticosteroid therapy in older adults with cancer.

1. Introduction

Cancer is a disease of aging and as many as 60 % of people living with cancer are 65 years of age or older [1,2]. The use of corticosteroids is frequent in oncology and many patients require short- or long-term use of corticosteroid therapy as part of the therapeutic management of their cancer, as prophylaxis for chemotherapy-induced nausea and vomiting (CINV), as anti-allergy prophylaxis, as a treatment to manage adverse effects of immunotherapies, and/or as part of the management of comorbidities (i.e., inflammatory diseases).

General clinical guidelines and recommendations exist on the use of corticosteroid therapies for specific diagnoses and most of them encourage corticosteroid-reducing/sparing strategies [3]. Evidence is lacking for recommendations on the appropriate use of corticosteroid therapy in older patients with cancer.

Treatment of CINV has dramatically improved over the last decade with 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists and neurokinin-1 (NK-1) receptor antagonists or a combination of both, as well as the addition of other anti-emetic drugs such as the atypical antipsychotic agent olanzapine. Nonetheless, corticosteroids continue to play an important role in the management of acute and delayed CINV prevention [4–7]. While highly efficacious, the toxicity profile of these

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Box 1
In practice.

Corticosteroids in the older adults with cancer

In-practice: Task-force recommendations

Chemotherapy-induced nausea & vomiting (CINV) prevention

- A 4-drug regimen including a combination of palonosetron plus netupitant with single dose dexamethasone on day 1 as well as olanzapine may be a reasonable corticosteroid-sparing option in older patients receiving AC and non-AC highly emetogenic regimens [32].
- Alternatively, non-high-emetic-risk chemotherapy should be considered whenever reasonably possible.
- A single dose of a 5-HT_3 receptor antagonist can be considered for prevention of acute CINV in older patients treated with low-emetic-risk antineoplastic agents.
- Consider use of alternative cytotoxic agents that may not require any corticosteroidco-medication.

Corticosteroid therapy for the treatment of side effects of oncological therapies (adverse events)

- ESMO guidelines for the management of infusion reactions to systemic anticancer therapy apply also for older adults.
- Immune-related adverse events and toxicity should be managed according to the international guidelines such as the ESMO or ASCO guidelines. They typically involve the use of immunosuppressive or immune-modulating drugs including high-dose corticosteroids.

Patients with prostate cancer

- We recommend the use of corticosteroids in the treatment of mCRPC according to international clinical guidelines.

Patients with lymphoma/multiple myeloma

- The dose of dexamethasone should be limited to 40 mg weekly at most (or 20 mg in those over age 75 or with other aging-associated vulnerabilities).
- In first-line therapy with lenalidomide and dexamethasone, the dexamethasone may be discontinued after 9 cycles of initial therapy.

Patients with brain metastases

- Lowest possible dose of corticosteroids should be used.
- In case of steroid dependence, we suggest considering bevacizumab, in the absence of contraindications such as major bleeding events, recent major surgery, or arterial thromboembolic events, for the treatment of brain edema related to brain metastases, where available.
- Regarding the bevacizumab dose, no final recommendation can be given but 10 mg/kg body weight once every two weeks may be a meaningful choice.

Patients with primary brain tumors

- High doses of steroids are routinely used in different clinical situations in glioma.
- No clear recommendations on dose adaptations for older patients, except for rapid discontinuation with gradual tapering.

Considerations around comorbid diseases

Glycaemic control and diabetes

- In many older patients it is important to avoid hypoglycemia to reduce the risk of falls, cognitive impairment, or frailty.
- In more robust and younger patients with cancer, achieving an HbA1c <7 % may however be an appropriate goal, especially if the prognosis is favorable.
- If diet and exercise have not achieved target HbA1c in 6 months
  - o **STEP 1:** Recommended management is metformin, beginning 500 mg once or twice a day with titration up to 5 to 7 days to 2000 mg.
  - o **STEP 2:** When HbA1c target is not achieved after 3 months of monotherapy, is to add one of the following: basal insulin with intermediate or long-acting insulin at bedtime or sulfonlyurea (glipizide preferred).
  - o When HbA1c target is still not achieved, then **STEP 3** combines **STEP 2** agents. If HbA1c targets are not achieved after 3 months, a third agent should be added.
- In older patients who are already on an oral hypoglycaemic regimen, dose-intensification, or addition of an alternative agent or initiation of insulin may be required if glycaemic control is not achieved.
- In hospitalized, critically ill older patients with cancer or in patients with a very high glycaemic profile (> 10 mmol/L), management of corticosteroid-induced hyperglycaemia may require insulin therapy at a total daily dose of 0.3 UI/kg, half as long-acting (basal) and half as rapid-acting before each meal. Correction dose is 1 unit for every 2.2–2.7 mmol/L in excess of 7.7 mmol/L.
- In patients with pre-diabetes, in addition to lifestyle modifications, pharmacological treatment with metformin up to 850 mg twice a day may be proposed.

Rheumatic disease

- In patients with comorbid **rheumatoid arthritis**, we recommend corticosteroids (e.g., prednisone <15 mg/d or equivalent) with osteoporosis prevention measures, used as bridging treatment until disease-modifying anti-rheumatic drugs are effective.
  - o If patients achieve persistent remission after taperingcorticosteroids, consider tapering biologicals.
  - o Flares can be managed with increased dose of oral or pulse intravenous corticosteroids (e.g., infusion of up to 1000 mg methylprednisolone per week).
  - o Frequent or severe rheumatic flares should prompt consideration of escalation of dose or modification of regimen.
- For **giant cell arteritis**, we recommend initiating prednisone (40–60 mg/d) or its equivalent.
  - o Corticosteroid can be tapered by 10 mg after 2 weeks and another 10 mg prednisone/day after 4 weeks. Dose tapering should be then gradual (by 10 % every 1–2 weeks) over 9–12 months.
  - o Once the daily dose is 10 mg, taper in 1 mg/month decrements.
  - o Methotrexate 7.5 to 15 mg/week with folate (5 to 7.5 mg/day) may reduce the amount of corticosteroids needed and the risk of relapse, but the effect is moderate at best.
  - o High-dose pulse parenteral steroids (e.g., 1000 mg methylprednisolone IV daily for 3 days) for visual loss is controversial. Treatment should be maintained for 1 year to prevent relapse (35 % relapse within 21 month).
- For **polymyalgia rheumatica**, low-dosage (e.g., 12.5–25 mg/day) prednisone or its equivalent can be considered.
  - o The dose can be increased if symptoms are not controlled within 1 week.
  - o If symptoms are not controlled with 20 mg, then consider an alternative diagnosis (e.g., giant cell arteritis, paraneoplastic syndrome).
  - o Dose tapering to oral of 10 mg/day within 4 to 8 weeks should individualised.
  - o If patients relapse, increase to pre-relapse dose and decrease gradually with 4-8 weeks. Once daily dose is 10 mg, taper in 1 mg/4-week decrements. Minimum duration of the treatment is 1 year.

Adrenal insufficiency

- We recommend for **chronic adrenal insufficiency**, hydrocortisone in 2 or 3 divided doses for a total dose of 15 to 25 mg/day.
  - o Alternatives are dexamethasone (0.5–1.0 mg/day) or prednisone (5–7 mg/day). In the case of primary adrenal insufficiency, addition of fludrocortisone to corticosteroids is recommended.
- For stress doses, hydrocortisone (100 mg iv bolus) can be administered, or if the patient has not been previously diagnosed and in cases of severe stress (i.e., severe illness, injury, or surgery), dexamethasone (4 mg iv bolus). In cases of minor stress (e.g., minor illness), double or triple usual oral replacement dosage for 3 days.
- For **minor surgery** (e.g., hernia repair), hydrocortisone 25 mg/day on the day of surgery and return to usual dosage on the following day is recommended.
- For **moderate-stress surgery** (e.g., cholecystectomy, join replacement), 50–75 mg/day on the day of surgery and the first post-operative day is recommended. Usual dosage can be resumed on the second postoperative day.
- In cases of **major surgical procedures** (e.g., cardiac bypass), a total dose of 100-150 mg/day given in divided doses for 2 to 3 days is recommended before returning to usual dosage.

Bone and muscle health

- In older patients with cancer and history of medium or long-term use, or planned corticosteroids therapy, we recommend evaluation of:
- **Basic energy (caloric) requirements; dietary and supplement needs (consider referral to a nutritionist):**
  (i) Calculation (e.g., using the Harris-Benedict energy equation) of the basic energy requirement according to sex, weight, height, age, activity, stress;
  (ii) Fluid requirements (e.g., in older adults without heart or kidney disease 30 mL/kg/day);
  (iii) Need for *vitamin D and calcium supplementation*: all patients should receive calcium 1200 mg/day and vitamin D 800–1000 IU with Vitamin D3 as preferred form of supplementation. (There is insufficient evidence to recommend screening for 25-OH-VitD deficiency.)
  (iii) Need for *multivitamins and other supplements*.
- In the absence of valid (mal)nutrition screening instruments, focus on issues affecting the nutritional status:
  (i) Economic barriers to securing food and social isolation (e.g., eating alone);
  (ii) Availability of sufficient high-quality food;
  (iii) Dental problems that preclude ingesting food;
  (iv) Medical conditions that interfere with ingestion, digestion, or absorption of food; increase nutritional requirements or cause cachexia; or require dietary restriction;
  (v) Functional disability that interfere with shopping, preparing meals, or feeding;
  (vi) Food preferences or cultural beliefs that interfere with adequate food intake;
  (vii) Depressive symptoms which are a common cause for malnutrition.
- Assessments should systematically include gait, balance, and mobility assessment for fall prevention:
  (i) *Functional gait*: observe patient rising from chair, walking (stride length, base of gait, velocity, asymmetry), turning, sitting with the Timed Up and Go Test;
  (ii) *Cognition*: assess for frontal-lobe cognitive function (Clock Drawing Test, Mini-Cog) to identify any impaired function and judgment that could impact the risk of falling;
  (iii) *Mobility*: observe patient's use and fit of assistance device if any (i.e., cane or walker), personal assistances, restraint use, footwear evaluation;
  (iv) Activities of daily living (ADL): complete ADL skills evaluation, including use of adaptive equipment and mobility aids as appropriate;
  (v) Complete environmental assessment, including home safety, and mitigate identified hazards.
  Follow these steps with development of a plan that tailors intervention to address identified risk factors.

Osteoporosis

- We recommend that:
  (i) Older patients with cancer receive therapies that take into account their fracture risk;
  (ii) Patients be assessed according to bone mineral density and clinical risk factors.
  - Patients with established osteoporosis (history of fragility fracture or bone mineral density T-score ≤ -2.5) are at the highest risk for fracture.
  - For patients without established osteoporosis, fracture risk can be assessed using a fracture risk calculator, such as the Fracture Risk Assessment Tool (FRAX).

  (iii) Patients receiving any dose of chronic corticosteroids therapy or initiating corticosteroids with an anticipated duration of $\geq$3 months receive calcium and vitamin D supplementation.
  (iv) Pharmacologic therapy for all patients with established osteoporosis (T-score ≤ -2.5 or fragility fracture) or osteopenia (T-scores between -1.0 and -2.5) who are receiving or are about to initiate corticosteroids (any dose for any duration). For other patients (e.g., with FRAX-calculated absolute risk <3 or 20 %) we also recommend pharmacologic therapy if they are taking $\geq$7.5 mg/day of prednisone or its equivalent for an anticipated duration of $\geq$3 months.
  (v) Bisphosphonates as first line therapy. If creatinine clearance is <35 mL/min/1.73 m2, denosumab is an alternative.
  (iv) Bisphosphonates are recommended if there is a gastro-intestinal contraindication (e.g., oesogastral disorders, feeding tube) or in patients unable to sit up after oral dosing.
  (v) When initiating treatment with bisphosphonates or denosumab, discuss the risk factors for developing osteonecrosis of the jaw. Cancer and cancer treatment, corticosteroids in addition to smoking, diabetes, and pre-existing dental disease are major risk factors. Thus a routine dental visit is necessary. If an invasive dental procedure (e.g., dental implant or extraction) is planned, then bisphosphonates or denosumab treatment should be delayed for a few months until healing of the jaw is complete.
  (vi) Serum vitamin D levels (25-OH-Vitamin D) should be normal (>75 nmol/L or 30 ng/mL) because bisphosphonates and denosumab can precipitate symptomatic hypocalcaemia if vitamin D levels are low (<50 nmol/L or 20 ng/mL).
  (vii) Proton pump inhibitors reduce the effectiveness of *oral (not intravenous) bisphosphonate*, thus they should be stopped the day before bisphosphonate administration and not administered until >60 min after the bisphosphonate has been taken.

Drug-drug interactions

- In older patients with cancer receiving any dose of chronic corticosteroids therapy or initiating corticosteroids s we recommend:
  (i) Assessing the patient's current medications to avoid medication errors such as omissions, duplications, dosing errors, or drug interactions.
  (ii) A medication review to identify any inappropriate medication according to the patient's comorbid conditions, medical needs, and expectations.
  (iii) Optimizing medications with drug-drug and drug-comorbidity interactions front-of-mind.
  (iv) Attention to concomitant prescribing of medications increasing the risk of gastroduodenal bleeding (aspirin, antiplatelet agents, anticoagulant therapy, and serotonin-specific re-uptake inhibitors).
  (v) Prescribing a proton pomp inhibitor in patients using medications with an increased risk of bleeding; or in patients with a prior history of gastric bleeding, ulcer disease, dyspepsia, or gastro-esophageal reflux disease.

Abbreviations: AC (Adriamycine and Cyclophopshamide), 5_HT3 (5-hydroxytryptamine 3 receptor antagonist), ESMO (European Society of Medical Oncology), ASCO (American Society of Clinical Oncology), mCRPC (metastatic Castration-Resistant Prostate Cancer).

drugs must be considered, particularly in the treatment of vulnerable older patients with multiple comorbidities and polypharmacy. Multiple concomitant medications increase the risk of drug-drug interactions [8–10] and adverse drug reactions, such as constipation or fatigue [11,12]. Some 5-HT3 antagonists can cause torsades de pointe due to QTc prolongation, of which older patients are at risk as they are often treated with QTc prolonging drugs (e.g., antidepressants, neuroleptics, antibiotics) [13,6]. The incidence and severity of adverse reactions to corticosteroids are dose- and duration-dependant. A high single dose can potentially cause acute complications and small doses given over a long period of time can lead to significant long-term effects.

Hyperglycaemia, alterations in lipid metabolism, weight gain, fluid retention, and hypertension are adverse effects of corticosteroids. Corticosteroid-induced hypertension often occurs in older patients and is more common in patients with low serum calcium concentrations and/or in those with a family history of essential hypertension [14]. Other potential corticosteroid adverse effects include immunosuppression, delirium, psychomotor agitation, psychiatric disorders, and insomnia. These side effects may worsen the global condition, depending on pre-existing comorbidities [15]. Additional considerations include the potential impact of long-term exposure to corticosteroids on bone and muscle health and the risk of adrenal insufficiency, [15,16] which may be particularly relevant in patients with prostate cancer, autoimmune disorders, or brain edema associated with brain metastases.

Therefore, guidance on corticosteroid-reducing/sparing strategies is needed for older adults with cancer. This consensus, supported by the International Society of Geriatric Oncology (SIOG), aims to provide evidence-based recommendations for the use of corticosteroid therapy in older oncology patients.

2. Expert Panel and Consensus Recommendations

This is a multi-disciplinary, expert-based paper which relies on author-based expertise and review of the evidence to facilitate understanding. We aim to create a practical guide for clinicians and healthcare professionals managing older patients with cancer requiring corticosteroid therapy.

The article is a narrative review rather than a systematic review. Where there is a paucity of literature specific to the management of certain groups of patients and corticosteroids, the expert author panel has provided recommendations based on relevant publications in their respective fields and their clinical experience. These recommendations are based on available guidance on the use of corticosteroid therapy in specific groups of patients with chronic comorbidities and/or geriatric vulnerabilities (e.g., walking and balance disorders, sarcopenia, and

cognitive impairment).

This paper aims to provide recommendations (see Box 1 'In practice') on corticosteroid administration to older patients with cancer, focusing on the following indications:

- Corticosteroids as CINV prevention
- Corticosteroids for the treatment of side effects of oncological therapies (Adverse events [AE's])
  - o Infusion-related AE's
  - o Immunotherapy-related AE's
- Corticosteroids in the treatment of
  - o Prostate cancer
  - o Multiple myeloma / lymphoma
  - o Brain metastases
  - o Primary brain tumors
- Corticosteroids in older patients with cancer and comorbidities
  - o Diabetes mellitus
  - o Rheumatic disease
  - o Other comorbidities
- Side effects of corticosteroid therapy
  - o Myopathy
  - o Osteoporosis
  - o Endocrine and metabolic side effects
  - o Infectious diseases
- Corticosteroids and drug-drug interactions in older patients

2.1. Corticosteroids to Prevent Chemotherapy-Induced Nausea and Vomiting (CINV)

CINV is a particular problem in older adults with cancer. In addition to reducing quality of life, CINV can lead to functional decline, malnutrition, organ dysfunction, dehydration, and renal dysfunction, and can affect patients' adherence to treatment [17–20].

The key to CINV management is prevention [21–23]. The cytotoxic drugs are classified according to their emetogenic potential as high, moderate, low, or minimal [24]. Both high- and moderate-emetic-risk chemotherapy require complex antiemetic regimens containing corticosteroids. It is important to note that both high- and moderate-emetogenic cytotoxic agents induce delayed nausea and vomiting (CINV), which is conventionally defined as occurring from days 2 to 5 after administration of a single-day chemotherapy regimen.

It is also essential to consider individual patient factors when evaluating an older patient with cancer for a particular type of chemotherapy [19–26]. In the context of CINV, pre-existing renal conditions require particular attention [27–28].

Age may be considered as a protective factor for vomiting in the context of CINV [29]. However, it should be noted that a reduction in functional reserve can result in more severe consequences. Consequently, it is recommended that older patients receive antiemetic drugs to the same extent as younger patients [30–31]. Male sex is also a protective factor, irrespective of anti-emetic treatment, primary cancer site, and other patient-related risk factors [26]. In addition, patients with a modest alcohol intake compared to those who never drink and patients without a history of motion sickness or emesis during pregnancy are less likely to experience CINV [12].

In the setting of high-emetic-risk chemotherapy, the cornerstone of anti-emetic prophylaxis is a four-drug regimen consisting of a 5-$HT3_3$ receptor antagonist plus dexamethasone, an NK1 receptor antagonist, and olanzapine [32–4]. Olanzapine, an atypical antipsychotic agent, is now recommended by treatment guidelines in the setting of high-emetic-risk, but olanzapine-related sedation and orthostatic hypotension can be of particular concern (i.e., risk of falls) [12]. A recent randomized phase 3 trial suggested non-inferiority in antiemetic efficacy of low-dose 2.5 mg/day olanzapine compared to the standard dose of 10 mg/day in a population consisting mainly of patients with breast cancer and resulted in reduced occurrence of daytime somnolence among patients receiving highly emetic chemotherapy [33]. Based on these findings, 2.5 mg olanzapine should be considered the standard recommended dose.

Current guidelines recommend prophylaxis with a three-drug regimen for patients receiving moderate-emetic-risk chemotherapy regimens and a single anti-emetic agent in case of low-emetic-risk antineoplastic agents [32]. They may comprise dexamethasone, a 5-HT3 receptor antagonist, or metoclopramide given on the first day of chemotherapy [32].

In cases where patients require short-term prophylaxis with dexamethasone for high-emetic-risk or moderate-emetic-risk chemotherapy, the potential adverse effects of corticosteroids associated with chronic exposure are of lesser concern. Nevertheless, it should be noted that the use of a short-term prophylactic antiemetic corticosteroid can result in a range of adverse reactions, including hyperglycaemia, acute adrenal insufficiency, indigestion, agitation, and sleep disturbances [34–36]. In a pilot study, 60 patients treated with moderate-emetic-risk chemotherapy regimens and receiving dexamethasone for three days to reduce delayed CINV reported moderate to severe problems with insomnia (45 %), indigestion/epigastric discomfort (27 %), agitation (27 %), increased appetite (19 %), weight gain (16 %), and acne (15 %) in the week following chemotherapy administration [34].

A prospective study investigated the impact of prophylactic dexamethasone on adrenal function and found that both older age and worse performance status were associated with adrenal suppression. [35] Another study looked at bone health and found a reduction of bone mineral density and an increase in markers of bone turnover. [37]

These findings suggest that age is a risk factor for adverse events. This is especially concerning for older adults due to the increased burden of co-morbidities and functional disabilities [20]. Repeated prophylactic dexamethasone should thus be used with caution in patients with diabetes and other conditions that could be exacerbated by corticosteroids (e.g., cataracts, osteopenia/osteoporosis, congestive heart failure), especially in patients undergoing multiple cycles of moderate-to high-emetic-risk chemotherapy.

The approved treatment for the prevention of delayed CINV after moderate-emetic-risk chemotherapy is a combination of palonosetron and netupitant with a single-dose of dexamethasone given at day 1. The addition of dexamethasone on days 2–4 is recommended for the prevention on delayed CINV afet high-emetic-risk chemotherapy [38]. The outcome of a corticosteroid-sparing regimen in high-emetic-risk chemotherapy was investigated in a recent randomized trial involving 228 adult patients with cancer (aged 44–79 years, median age 63 to 66 years) [37]. They were randomized to one of three groups, receiving palonosetron plus netupitant in combination with either (i) a single 12 mg dose of dexamethasone, (ii) a 4 mg dexamethasone dose daily on days 2 and 3, or (iii) a 4 mg dexamethasone dose twice daily on days 2 to 4. In this study, no benefit of prolonged administration of corticosteroids on delayed nausea and vomiting over single-dose dexamethasone on day 1 was observed [39]. Of note, the dexamethasone sparing regimen was not associated with functional impairment or reduced food intake, which is relevant for older adults [40]. In the subset of patients >65 years ($n = 107$), results regarding CINV prevention and impact on daily functioning was comparable with the overall population [39].

Therefore, a combination of palonosetron plus netupitant with single dose dexamethasone on day 1 may be a reasonable corticosteroid-sparing option in older patients receiving high emetic chemotherapy. Alternatively, we suggest considering non-high-emetic-risk chemotherapy wherever reasonably possible. A single dose of a 5-HT3 receptor antagonist can be considered for the prevention of acute CINV in older patients treated with low-emetic-risk antineoplastic agents. Use of alternative cytotoxic agents that may not require corticosteroids co-medication at all (e.g., nano-particle albumin-bound-paclitaxel instead of conventional solvent-based taxanes) may allow reduced patient exposure to steroids.

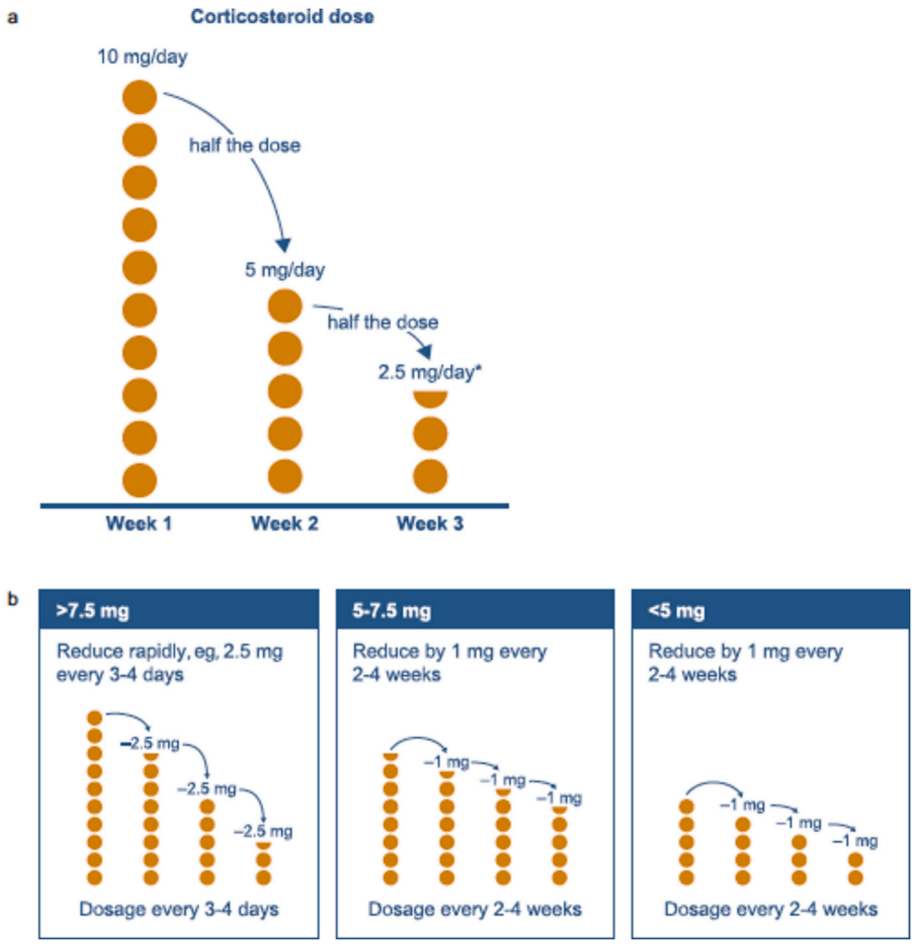

Fig. 1. Recommended schedules for tapering corticosteroid dosing.
Adapted from De Santis et al. 2016, Leppert & Buss 2012.
* Then 2.5 mg/day every 2 days.

2.2. *Corticosteroids in the Treatment of Anticancer Therapy Toxicity*

2.2.1. *Infusion-related side effects*

All cytotoxic and antibody therapies have the potential to cause infusion reaction. Most are hypersensitivity reactions but anaphylactic reactions also exist. Premedications are used according to the risk of developing such reactions. Antihistamines are key medications in this indication and corticosteroids also play an important role in the management of infusion-related reactions. There are no specific guidelines for older patients and therefore the general recommendations, such as the European Society of Medical Oncology (ESMO) guidelines for the management of infusion reactions to systemic anticancer therapy, also apply to older adults [41].

2.2.2. *Immunotherapy-related adverse events*

Immunotherapy with checkpoint inhibitors is increasingly being used in older patients [42]. Although this population shows aging-related immune dysfunction or remodeling (commonly described as immunosenescence), [43] immunotherapy seems to be almost as effective as in younger patients depending on the tumor type [42,44–46]. While the toxicity profile of this type of treatment seems to be similar in patients ≥70 years compared to younger ones, as suggested by the prospective Checkmate 153 trial [46], a more recent study showed that patients aged ≥90 years discontinued immunotherapy due to immune-related adverse events twice as often as patients <90 years [47]. Immune-related adverse events and toxicity should be managed according to the ESMO or American Society of Clinical Oncology (ASCO) guidelines [48,49]. They typically involve the use of immunosuppressive or immune-modulating drugs, including high-dose corticosteroids [48].

Besides checkpoint inhibitor therapy, adoptive cell therapy with chimeric antigen receptor T cell therapy (CAR-T) cells plays an important role in the treatment of hematological malignancies. Infections, cytokine release syndrome, and neurotoxicity are among the most common adverse effects of CAR-T cell therapy. Similarly, it is recommended to follow the international guidelines for the management of their toxicities [50].

It is notable that neither the ESMO nor the ASCO guidelines provide specific recommendations for the treatment of immunotherapy-related toxicities in older patients. Until further evidence is available, the recommended therapy and treatment plan for these patients should align with those used for the general population.

2.3. *Corticosteroids as Part of Oncological Treatment*

2.3.1. *In the treatment of prostate cancer*

For several decades, corticosteroids have been used in combination with chemotherapy for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Corticosteroids are used to treat pain, inflammation, and edema – helping to manage adverse effects, reduce symptoms, and improve quality of life (QoL) [51–53]. Importantly, corticosteroid use can relieve symptom burden, reduce adrenocorticotropic hormone (ACTH)-mediated androgen receptor (AR) expression, and induce prostate specific antigen (PSA) response in patients with

prostate cancer. However, attention should be given to the potential role of corticosteroids in AR cross-activation during therapy with novel anti-androgens such as abiraterone. Since the advent of drugs targeting the AR axis, there has been debate regarding the potential interaction of steroids (including corticosteroids and androgens) with corticosteroids receptors and ARs, and whether use of corticosteroid therapy may actually propagate CRPC and worsen clinical outcomes [51–53].

Selection of the most appropriate corticosteroid dose and regimen requires careful consideration of a patient's profile and comorbidities and an appreciation of potential drug-drug interactions in the setting of prostate cancer and with regards to patient age. Dose tapering recommendations are shown in Fig. 1.

During treatment with CYP17 inhibitors such as abiraterone, the concomitant use of corticosteroids is mandatory to prevent hyperaldosteronism. However as alternative to abiraterone, it may be preferable to prescribe enzalutamide to avoid the corticosteroid supplementation.

For patients treated with second-generation anti-androgens, the lowest effective corticosteroid dose should be used to prevent side effects. For patients treated with taxane chemotherapy, dexamethasone is recommended according to the summary of product characteristics.

2.3.2. *In the treatment of multiple myeloma and lymphoma*

Regimens for treating multiple myeloma nearly universally include corticosteroids due to the direct cytotoxic effect of the drugs on plasma cells [54]. Corticosteroids have single-agent activity in multiple myeloma, but the advent of more effective agents, the substantial toxicities of corticosteroids [55], and the evidence informing modification of steroid dosing in more vulnerable subgroups of older adults with myeloma have resulted in attempts to limit their use.

The first study impacting the standard of care dosing of dexamethasone included patients with multiple myeloma randomized to either lenalidomide in combination with 40 mg dexamethasone on days 1–4, 9–12, and 17–20 of a 28-day cycle (high dose) versus 40 mg dexamethasone on days 1, 8, 15, and 22 of a 28-day cycle (low dose). Though the overall response rate was higher in the high dose dexamethasone arm, one-year overall survival was inferior in this group (87 %) compared to the low dose group (96 %) ($p = 0.0002$) [56]. The discordance of survival compared to response rate was due to the higher toxicity in the high dose arm, including venous thromboembolism and infections. Thus, combination regimens with a maximum of 40 mg of dexamethasone weekly has become the standard of care for patients with multiple myeloma.

In this study, clinicians noted continued corticosteroid toxicity even among patients receiving the lower dose; evidence from clinical trials supports dose reduction even further in more vulnerable subgroups. In the MAIA trial, which compared the regimen of daratumumab, lenalidomide, and dexamethasone with lenalidomide and dexamethasone, patients aged ≥75 received dexamethasone at a reduced dose of 20 mg weekly, while those <75 received 40 mg weekly [57]. The reduced dose of dexamethasone did not appear to reduce the efficacy of the experimental regimen. Another randomized trial enrolled intermediately-fit (i.e., International Myeloma Working Group frailty score of 1) [58] older adults with multiple myeloma and demonstrated that corticosteroids could be discontinued after the initial nine months of induction therapy, resulting in improved event-free survival and similar overall survival compared to the standard regimen, in which dexamethasone was continued indefinitely [59].

In summary, corticosteroids are important components of anti-myeloma regimens, but attention to dosing will improve tolerability and outcomes in older adults. Outside of oncologic emergencies such as spinal cord compression, acute kidney injury, or hypercalcemia requiring large doses of dexamethasone, weekly dosage should be limited to a maximum of 40 mg (20 mg in those over age 75 or with younger as 75 but with aging-associated vulnerabilities, such as comorbidities or dependence in basic or instrumental activities of daily living). In first-line therapy, limiting the duration of treatment to nine cycles of initial therapy is associated with improved event-free survival.

Steroids are also part of the treatment of lymphoma, often administered at an intermittent high dose. Prephase steroid therapy before definitive chemotherapy is recommended, as it may reduce patients' disability and alleviate treatment-related toxicity, especially in older patients with a high disease burden [60].

Age ≥ 80 and coexisting comorbidities often preclude the use of standard chemo-immunotherapy regimens. Reduced-dose regimens are then preferred, such as the protocol with rituximab standard dose with doxorubicine, cyclophosphamide, vincristine, and prednisone, all half-dose (R-mini-CHOP) [61]. The prednisone dose is slightly reduced in the mini-CHOP, with 40 mg/m^2 over five days compared with an absolute dose of 100 mg over five days in the standard CHOP regimen.

2.3.3. *In the treatment of patients with brain metastases*

Brain metastases are a common and devastating complication of malignancies that can reduce QoL and increase cancer-specific morbidity and mortality. [62] [63] Management of brain metastases comprises local treatment options, such as whole-brain radiotherapy, radiosurgery, and/or neurosurgical resection; systemic anti-tumor treatment; and adjunct therapies, including corticosteroids, that aim to decrease brain edema and thereby ameliorate neurological symptoms. In patients with symptomatic and/or progressive brain metastases, prolonged application of high doses of corticosteroids may become necessary.

Use of high-dose corticosteroid therapy over a prolonged period can cause fluid retention, weight gain, and diabetes as well as sleeplessness and psychiatric disorders. It also exposes patients to potential bone health risks and adrenal insufficiency as outlined above. As symptom control, the maintenance of QoL, and functional independence are the foremost aims of palliative cancer therapy, alternatives to corticosteroids for the treatment of brain edema need to be sought.

Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor-A (VEGF-A), has been licensed for the treatment of several malignancies, including metastatic breast cancer [64]. Bevacizumab has been reported to have an acceptable toxicity profile even in older patients, but the specific adverse effects need to be considered when administered in this population [65]. Besides blocking VEGF, bevacizumab also improve the structure of tumor vasculature by reducing the leakiness of tumor vessels. This, in turn, translates into a reduction of metastases-associated brain edema, allowing for lower corticosteroid doses [66–68]. The treatment of radiation necrosis of the central nervous system is another corticosteroids-sparing indication of bevacizumab, if available [69].

2.3.4. *In the treatment of primary brain tumors*

There are a variety of primary brain tumors, the most common being gliomas; other types include meningioma and central nervous system lymphoma. The most common symptoms are headaches, neurological symptoms depending on the tumor location, and seizures, especially in low grade glioma with cortical location. Vasogenic cerebral edema mainly affects the white matter due to fluid extravasation from vessels that are damaged by tumor invasion. As in brain metastases, high doses of steroids are routinely used in different clinical situations in glioma.

At diagnosis, when a patient consults at the emergency room (ER) with neurological symptoms and imaging is suggestive for high grade glioma, steroids can be introduced to relieve symptoms and compression while awaiting debulking surgery. Radiotherapy-induced inflammation can also be effectively treated with lower corticosteroid doses. A usual finding following radiotherapy is pseudoprogression, which accounts for a worsening of the imaging without a true tumor progression [70]; this situation often requires corticosteroid therapy. Finally, at tumor recurrence, high dose corticosteroids, defined as 20 mg dexamethasone-equivalent per day or more, are ideally used only for a short duration, as intravenous bevacizumab is a preferred drug in countries where it is

available and reimbursed. Indeed, the favorable toxicity profile, rapid relieving, and tumor vasculature normalizing effects makes bevacizumab a better drug choice compared to long term corticosteroid treatment, albeit more costly.

Most patients diagnosed with high grade glioma are 65 years old or more [71]. Hence, the use of corticosteroids in this clinical situation is mainly in the context of older patients. There are no clear recommendations on corticosteroids dose adaptations in this population, the only rule being a rapid discontinuation with gradual tapering. When patients do receive corticosteroids for prolonged periods, cortisol insufficiency should be monitored by dosing basal cortisol levels in the morning at the end of the tapering down of the corticosteroids.

2.4. Corticosteroids in Older Patients with Specific Comorbidities

2.4.1. In patients with diabetes

Hyperglycemia may occur in patients with cancer receiving high-dose corticosteroids, and corticosteroid-induced insulin-resistance can have significant clinical implications both in patients with diabetes mellitus and in those without an underlying diagnosis of diabetes. Corticosteroids may exacerbate hyperglycemia in patients with diabetes, unmask undiagnosed diabetes, or cause corticosteroid-induced diabetes.

In patients without diabetes, measuring plasma-fasting glucose, postprandial glucose, and HbA1c can help to predict the risk of corticosteroids-induced diabetes, notably when prediabetes is already present or the patient has some risk factors for diabetes, such as obesity or increased adiposity [72].

For patients without pre-existing diabetes but with corticosteroid-induced hyperglycemia, their blood glucose levels should normalize after discontinuation of corticosteroids, but this does not always happen and close patient monitoring is often required to identify new-onset diabetes [73].

No consensus guidelines exist for the optimal management of hyperglycemia secondary to corticosteroids. The choice of drug(s) to manage hyperglycemia depends on the degree of pre-existing glucose intolerance, the patient's clinical condition, and the degree of hyperglycaemia, and on the type, dose, and frequency of administration of the corticosteroid. Preference should be given to agents that target postprandial hyperglycaemia and have a rapid onset of action, since corticosteroids mainly induce an increase in postprandial blood glucose levels [74].

In patients with a high glycaemic profile during corticosteroid administration, with or without a diabetes history, the management of corticosteroid-induced hyperglycaemia typically requires insulin therapy as other oral and injectable antidiabetics, including newer classes such as GLP-1 receptor agonists and SGLt2 inhibitors, are usually ineffective due to their limited hypoglycaemic effect in these conditions. The corticosteroid type and duration of action must be considered to determine the most appropriate insulin treatment regimen. This will lead to the need for patient education and possibly care giver support for those with cognitive or dexterity issues.

Daily short-acting corticosteroids such as prednisone peak in about 4 to 8 h, [75] so coverage with intermediate acting insulin (NPH) injected in the morning may be sufficient. For long-acting corticosteroids such as dexamethasone or multidose or continuous corticosteroid use, long-acting insulins (such as glargine U100 or U300, detemir, or degludec) may be preferred [76,77]. For higher doses of corticosteroids, adding or increasing doses of prandial and supplemental insulin may be needed in addition to basal insulin [78]. Whatever insulins are started, adjustments based on anticipated changes in corticosteroidsdosing and capillary glucose measurements results are critical.

2.4.2. In patients with rheumatic disease

Older patients with cancer and rheumatic disease are a patient population that requires careful consideration of the risk-benefit ratio of corticosteroid therapies.

Several typical rheumatic diseases in older patients require higher doses or longer courses of corticosteroids, such as polymyalgia rheumatica, giant cell arteritis, and late-onset rheumatoid arthritis. Other conditions, essentially chronic inflammatory musculoskeletal diseases, are diagnosed in younger age groups. These patients are at even higher risk of adverse effects due to long-term corticosteroid use, for example to manage flares, because the cumulative dose throughout their illness may have already led to corticosteroid-related problems.

The European League Against Rheumatism (EULAR) has developed several recommendations regarding the use of corticosteroids therapies, the most generic of which is the “EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose corticosteroids therapy in rheumatic diseases” [1,79]. For some rheumatic conditions of older patients, more specific guidelines are available.

Few alternatives to corticosteroids exist. The common denominator across all current recommendations is to use the lowest possible dose for the shortest period. Short-term, ‘bolus’ style dosing could be preferred, as this can offer long-term protective effects without the long-term risks associated with corticosteroids.

In older patients with cancer and rheumatic disease, careful consideration of the use of proton pump inhibitors and calcium/vitamin D supplements, including antiresorptive treatments with tight monitoring (based on clinical findings and laboratory tests), is strongly advised. The use of corticosteroids with non-steroidal anti-inflammatory drugs (NSAIDs) disproportionally increases the risk for gastrointestinal bleeding events and related complications, particularly in this population. Both selective and non-selective NSAIDs should be prescribed at the lowest dose, frequency, and duration. They must be monitored with caution or completely avoided in patients with moderate to severe renal insufficiency and in those with unexplained anemia, liver insufficiency, and bleeding disorders [80–82].

2.4.3. In patients with other comorbidities

Older patients with cancer are more likely to present with comorbid disorders. While corticosteroids may be appropriate for the management of certain conditions, they may be contraindicated in others. Therefore, consideration needs to be given to those who require corticosteroid regimens as part of their cancer management plan.

Thus the prevention and surveillance and prevention of adverse effects must be particularly rigorous in people aged 75 years or over. Moreover, any single aging-related vulnerability may be revealed or worsened by corticosteroid therapy should be identified at baseline through a comprehensive geriatric assessment. This may include cognitive impairment, walking and balance disorders, or any increased risk of falling, malnutrition, muscle weakness, and polypharmacy. In older patients with cancer and co-existing disorders such as diabetes, inflammatory and rheumatic diseases, dermatological conditions, and/or respiratory diseases, corticosteroid-sparing strategies may be prudent based on existing guidelines for managing the respective condition.

Careful consideration of the most appropriate use of corticosteroids regarding risk/benefit is also required in patients with osteoporosis, peptic ulcer disease, cardiovascular disease, impaired immune competence or recurrent infections, cataract, or glaucoma.

3. Adverse Effects of Corticosteroid Therapy

3.1. Musculoskeletal

3.1.1. Osteoporosis

The chronic use of corticosteroids can cause significant bone loss and increase the risk for fractures [3]. Risk is particularly pronounced in the first few months of use, and fractures occur at a higher bone mineral density (BMD) than is the case in postmenopausal osteoporosis [3]. In older patients who may already be at risk of osteoporosis, this is a key

consideration when cancer treatment containing corticosteroids; corticosteroids -induced osteoporosis is a condition that causes fractures in 30–50 % of adults on long-term treatment [16]. The increased risk of fracture has been reported with doses of prednisone (or its equivalent) as low as 2.5 to 7.5 mg daily [83].

corticosteroids -induced bone loss should be treated aggressively, particularly in those already at high risk for fracture and to prevent fragility fractures (i.e., fractures that result from a fall from a standing height or less, that typically affect the spine, the hip, the wrist, the humerus, the rib, and the pelvis). Although evidence is limited, general principles should be followed in all patients receiving any dose of corticosteroids for three or more months to minimize bone loss [84,3]. The dose and the duration of corticosteroids therapy should be as low as possible and additional measures to prevent falls implemented [85]. Alternative therapy should be used whenever possible and topical therapy (e.g., inhaled corticosteroids or corticosteroids enemas for asthma or bowel disease, respectively) should be used over enteral or parenteral corticosteroids, whenever possible.

The recent 2017 guidelines proposed by the American College of Rheumatology [3] recommend that patients at low to moderate fracture risk according to computer-based FRAX (http://www.sheffield.ac.uk/FRAX) receive calcium and vitamin D supplementation, plus an additional antiresorptive medication (oral bisphosphonate preferred). In adults at moderate and high risk of fracture (10 to 20 % and > 20 %, respectively), recommendations are to continue calcium plus vitamin D but to switch from an oral bisphosphonate to another antifracture medication in adults for whom oral bisphosphonate treatment is not appropriate, or who completed an oral bisphosphonate regiment, but continue to receive corticosteroids treatment. If oral treatment with bisphosphonate is precluded by contraindications, or worsening of bone density or new fractures occur under treatment with these drugs, then the use of another medication may be advised, while continuing calcium plus vitamin D. In patients at higher risk for vitamin D deficiency (i.e., those with osteoporosis, fallers, malnourished, and restrained at home), it is important to complement any 25-hydroxyvitamin D deficiency before starting an antiresorptive therapy and/or calcium/vitamin D supplementation [86]. Moreover, in view of the multiple roles played by vitamin D, vitamin D supplementation should be proposed to patients with cancer of all ages [87,88].

These recommendations should apply to patients in the curative as well as in the palliative setting as the negative effect of corticosteroids can appear surprisingly early even at low doses.

3.1.2. Myopathy

In skeletal muscles, corticosteroids decrease the rate of protein synthesis and increase the rate of protein breakdown by inhibition of insulin-like growth factor-1 and several other mechanisms [89]. Treatment with corticosteroids may also result in myopathy. There are no guidelines issued by any professional society on measures for the treatment or the prevention of steroid-induced muscle loss. Reducing treatment exposure as quickly as possible to reach the lowest possible dose should be implemented and combined with multicomponent resistance exercise training, plus a high protein diet, to help control muscle wasting [90].

3.2. Endocrine and Metabolic Adverse Effects

3.2.1. Hyperkalemia/adrenal insufficiency

Adrenal insufficiency is a serious, potentially life-threatening adverse effect of corticosteroid use. It can result either from the abrupt discontinuation of medium to long-term use of corticosteroids administration for any indication previously detailed and/or occur after brain irradiation. This complication should be managed by or in collaboration with an endocrinologist.

Patients with secondary adrenal insufficiency may require corticosteroids replacement therapy in periods of stress, such as trauma, surgery, or acute illness, until full recovery of adrenal function. In some cases, chronic replacement with physiological doses of corticosteroids therapy is indicated [91]. Neither treatment dose, duration, form of administration, nor random serum cortisol measurements seem to accurately predict the development of adrenal insufficiency after the use of corticosteroids.

3.3. Infectious Diseases

Observational studies have consistently shown a dose-dependent increase in the risk for serious infections and opportunistic infections in patients treated with corticosteroids [92]. The duration of therapy might also be important, but less evidence is available in terms of associated infectious risk. Corticosteroids affect cellular functions of leucocytes and endothelial cells. They inhibit macrophage phagocytic and microbicidal function [93] as well as macrophage production of interleukin-1, interleukin-6, tumor necrosis factor, prostaglandins, and leukotrienes. They also reduce the ability of neutrophils to adhere to vascular endothelium and to exit the circulation, causing neutrophilia. Corticosteroids can also cause marked lymphopenia involving all lymphocyte subpopulations. Those cellular and molecular effects enhance the risk of infection from a daily dose of 5 mg prednisone equivalent, but the exact dosages and duration that substantially change the benefit-risk ratio likely depend on each individual's characteristics and underlying risk factors for infection [92].

3.4. Psychiatric Disorders

The incidence of corticosteroid-related psychiatric effects ranges from 2 % to 60 % and they can be severe and unpredictable. Caution and monitoring are needed throughout treatment, as mood disorders including manic and hypomanic episodes are not rare. Depressive symptoms are most often seen at treatment termination and delirium can occur at any time during corticosteroid use [89].

4. Corticosteroids and Drug-Drug Interactions in Older Patients

Corticosteroids undergo metabolism in the liver and other tissues by cytochrome P450 3A4 (CYP 3A4) and other biotransformations [94]. Typically, pharmacokinetic drug-drug interactions are expected to occur rapidly after the introduction of a CYP inhibitor, whereas CYP induction takes two to three weeks to reach maximal effect. Similarly, after discontinuation of an inhibitor, the corticosteroid dose can be rapidly increased back to standard dosing (approximately after 3–4 inhibitor half-lives), whereas it will take about two to three weeks after withdrawal of an inducer to get back to normal conditions and tapering down the corticosteroid dose is recommended during this interval.

Moderate to strong inhibitors of CYP 3A4 include some antibiotics (e.g., clarithromycin), antifungals (e.g., posaconazole, voriconazole), and cardiovascular drugs (e.g., diltiazem, verapamil, amiodarone), which may significantly increase corticosteroid exposure and require corticosteroid dose adjustment. Aprepitant, fosaprepitant, and netupitant, all CYP 3A4 inhibitors, can increase the exposure to oral dexamethasone and methylprednisolone by approximately two-fold and 34 %, respectively. A dose reduction of dexamethasone is recommended if co-administered with a CYP 3A4 inhibitor (from 20 to 12 mg) [5,4] Rolapitant has no inhibiting or inducing effect on CYP3A4, thus requiring no dose adjustment [95]. Drugs that reduce the systemic corticosteroids oral absorption include aluminum/magnesium-containing antacids, and strong inducers of CYP 3A4 (e.g., carbamazepine, phenytoin) will decreases drug concentration and efficacy.

In older populations, pharmacodynamic drug-drug interactions with corticosteroid may require monitoring. Corticosteroids, diuretics (e.g., loop and thiazide), and laxatives induce potassium wasting, and concurrent therapy with corticosteroids is likely to be additive. Corticosteroids may enhance the risk of tendonitis and tendon rupture in older

Box 2
The five keys of managing corticosteroid therapy in older patients.

(1) Corticosteroid therapy must be preceded by screening for and stabilization of any disorders and aging-related vulnerabilities that could be aggravated or revealed by the treatment. This includes comorbid conditions, geriatric syndromes, and polypharmacy.
(2) During treatment, regular monitoring for side effects, adjusting of the treatment to the lowest effective dose and regular re-evaluation of the indication are required.
(3) Corticosteroid therapy withdrawal protocols are not evidence-based and the timing is chosen according to the risk of reactivation of the treated condition vs. the risk of adverse events (e.g., quick withdrawal over 2 to 4 weeks vs. slow withdrawal over months). In older patients, slow withdrawal is preferred. It could be monitored according to an adrenocorticotropic hormone (ACTH)-stimulation test to check the function of the adrenal glands in case of acute stress or when a quick withdrawal is necessary.
(4) The risk of adrenal insufficiency increases with the duration of corticosteroid therapy; however, the risk is quite low and does not in itself justify the discontinuation of the treatment.
(5) Evidence suggests that the risk of peptic ulcer disease due to corticosteroids alone is commonly low but increases significantly when these agents are used in combination with non-steroidal anti-inflammatory drugs (NSAIDS), and in patients with polypharmacy, anti-platelet therapy, anticoagulant therapy, and/or selective serotonin reuptake inhibitors. The combination with proton pump inhibitor can be recommended in some specific situations.

patients treated with quinolones. Concomitant treatment with corticosteroids and angiotensin-converting-enzyme (ACE)-inhibitors may lead to an increased risk for hypertension and vascular damage [96]. Patients on stable vitamin K antagonist treatment may show increases in international normalized ratio (INR) after corticosteroid initiation and therefore dose adjustment of vitamin K antagonist should be anticipated and the INR monitored [97,94].

5. Summary of Expert Recommendations

The 'In practice' recommendations of the SIOG Task Force authors (see Box 2), summarizes key principles to consider regarding use of corticosteroids when managing the older adults with cancer.

Declaration of Competing Interest

None.

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