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Corticosteroids in oncology: Use, overuse, indications, contraindications. An Italian Association of Medical Oncology (AIOM)/ Italian Association of Medical Diabetologists (AMD)/ Italian Society of Endocrinology (SIE)/ Italian Society of Pharmacology (SIF) multidisciplinary consensus position paper

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ABSTRACT

Corticosteroids (CSs) are widely used in oncology, presenting several different indications. They are useful for induction of apoptosis in hematological neoplasms, for management of anaphylaxis and cytokine release/hypersensitivity reaction and for the symptomatic treatment of many tumour- and treatment-related complications. If the employment of CSs in the oncological setting results in several benefits for patients and satisfaction for clinicians, on the other hand, many potential adverse events (AEs), both during treatment and after withdrawal of CSs, as well as the duality of the effects of these compounds in oncology, recommend being cautious in clinical practice. To date, several gray zones remain about indications, contraindications, dose, and duration of treatment. In this article, a panel of experts provides a critical review on CSs therapy in oncology, focusing on

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mechanisms of action and pharmacological characteristics, current and emerging therapeutic indications/contraindications, AEs related to CSs treatment, and the impact on patient outcome.

1. Introduction

Synthetic corticosteroids (CSs) are responsible for multiple activities through genomic and non-genomic effects influencing all cells, tissues, and metabolic processes. CSs are one of the most used drug classes in medicine, particularly in cancer patients due to their ability to interfere with multiple biochemical and cellular processes that play a role in inflammation and immune system regulation (Kalfeist et al., 2022).

The main CSs are hydrocortisone, prednisone, prednisolone, methylprednisolone, and dexamethasone (Table 1). To date, CSs are mainly used as supportive treatment for cancer related complications and anticancer treatments side effects, including nausea and vomiting, brain edema and pain flairs, and to treat or prevent hypersensitivity reactions (Aldea et al., 2020). Diabetes mellitus (DM), poorly controlled arterial hypertension, recent acute coronary syndrome, peptic ulcer disease and osteoporosis represent relative contraindications to the treatment with CSs, although their cautious use could be beneficial even in these conditions. The only absolute contraindication to CSs is represented by active infections not controlled by specific therapy as well as hypersensitivity to any component of the formulation.

A recent alert regards a duality of CSs effects in oncology: the signal starting from CSs receptor activation may result both in tumour suppression and progression, according to the molecular pathway involved in the tumourigenesis (Mayayo-Peralta et al., 2021). A specific point concerns CSs and immunotherapy in cancer patients with autoimmune side effects; it has been supposed that CSs can potentially reduce anti-tumour immunity induced by immunotherapy against cancer (Gupta et al., 2021).

Furthermore, adverse events (AEs) could be related to CSs therapy, mainly including metabolic/endocrinological, gastrointestinal, immunological, and cardiovascular effects. These side effects are generally related to dose and treatment duration, as well as to timing of reduction/withdrawal of these drugs. Furthermore, in heavily treated patients the pharmacological interferences can change the consequences to CSs through the modulation of the CYP3A4, the major metabolic pathway of most of the synthetic CSs (Prete and Bancos, 2021).

For these reasons, CSs need to be used with full awareness of their pharmacological properties, modulating type, dose and duration of the therapy according to the indication, tumour type and patient conditions.

In this review, a panel of experts of the Italian Association of Medical Oncology (AIOM)/ Italian Association of Medical Diabetologists (AMD)/ Italian Society of Endocrinology (SIE)/ Italian Society of Pharmacology (SIF) discuss about use and overuse of CSs therapy in oncology, focusing on mechanisms of action and pharmacological characteristics of the available CSs, the current and emerging therapeutic indications and contraindications of CSs in oncology, the side effects related to CSs treatment, and the impact of CSs on patient outcome.

2. Types of drugs and pharmacological characteristics

2.1. Types of drugs

CSs used in clinical practice derive from chemical alterations of the steroid molecule leading to synthetic analogs of cortisol to enhance therapeutic properties while minimizing AEs (Williams, 2018). The pharmacological activity of CSs, as well as the likelihood of adverse drug reactions can be managed by selecting different molecules and routes of administration, along with an appropriate selection of the dose and duration of treatment. High intravenous doses are generally administered for health emergencies, whereas low oral doses are used for chronic diseases (Scherholz et al., 2019). Furthermore, prolonged CSs use (more than two weeks) may induce suppression of the hypothalamic-pituitary-adrenal axis and the consequent need for dose tapering. This is crucial to avoid the CS-induced (tertiary) adrenal insufficiency (Williams, 2018, Prete & Bancos, 2021).

The most used CSs are hydrocortisone, a short-acting agent, prednisone, prednisolone, and methylprednisolone, which are intermediate-acting, and dexamethasone, a long-acting agent (Table 1).

2.2. Mechanisms of action

2.2.1. Pharmacodynamics

CSs possess anti-inflammatory, anticancer, and immunosuppressive properties due to their ability to interrupt multiple biochemical and cellular processes that play a role in inflammation and immune system regulation. In this regard, CSs up-regulate annexin A1 that, in turn, inhibits phospholipase A2 (PLA2) activity and prostaglandin/leukotriene synthesis. Furthermore, CSs decrease cyclooxygenase-2 (COX-2) expression and limit neutrophil migration to inflammatory sites (Ayyar and Jusko, 2020). CSs may also dysregulate glucose, protein, fatty acid metabolism and mobilization, bone and calcium metabolism, cardiovascular, central nervous, and endocrine system (Williams, 2018).

The class effect is due to a similar pharmacological profile; however, some differences in potency, half-lives, and mineralocorticoid activities are worth mentioning. Hydrocortisone has both glucocorticoid and mineralocorticoid activities, while prednisolone and dexamethasone have less or almost no mineralocorticoid activity. Anti-inflammatory activity is much higher for prednisolone and dexamethasone, compared to hydrocortisone (Table 1) (Scherholz et al., 2019). When clinicians need to switch from one CSs to another, therapeutic activity can be maintained using dose equivalence (Table 1) (Scherholz et al., 2019).

CSs can promote both rapid (non-genomic) and delayed (genomic) pharmacological effects (Ayyar and Jusko, 2020; Cohen and Steger, 2017; Panettieri et al., 2019). Pharmacogenomic regulation starts from

Table 1
Pharmacological properties of corticosteroids.

Name	Potency (relative to hydrocortisone)		Equivalent dose (mg)	Duration of action (h)	F (%)	$t_{1/2}$ (h)
	Anti-inflammatory	Mineralocorticoid				
Short acting						
Hydrocortisone	1	1	20	8–12	96	1.8
Intermediate acting						
Prednisone	4	0.3	5	12–36	84	3.3
Prednisolone	4	0.3	5	12–36	99	3.2
Methylprednisolone	5	0.5	4	12–36	88	2.5
Long acting						
Dexamethasone	30	0	0.75	36–54	76	4.0

F: Bioavailability; $t_{1/2}$: Elimination half-life.

binding of the free steroid to the glucocorticoid receptor. This receptor is located in the cytosol as inactive heterocomplex bound to heat shock and FK506 binding proteins (Fig. 1). After dissociation from chaperone proteins, the activated drug-receptor complex translocates into the nucleus and then homodimerizes and binds specific DNA sequences (named glucocorticoid response elements, GRE) in the promoter regions upstream of target genes. Transcriptional changes usually occur in a delayed manner due to intracellular transduction stages (i.e. transactivation and transrepression) as well as mRNA and protein synthesis of several transcriptional factors, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), activator protein 1 (AP-1) and signal transducer and activator of transcription 3 (STAT3) (Ayyar and Jusko, 2020; Cohen and Steger, 2017).

CSs can also trigger a rapid non-genomic response via mechanisms depending on stimuli and cell types (Panettieri et al., 2019). An acute exposure to CSs reduces basal $[Ca^{2+}]_i$ in human bronchial epithelial cells. Such an effect may vary with lipophilicity of CSs and with the direct interactions of drugs with the cell membrane. Collectively, it was found that sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) type Ca^{2+}-ATPase pump, adenylyl cyclase, and protein kinase A (PKA), but not protein kinase C (PKC) may play a role in the inhibitory effects of CSs on $[Ca^{2+}]_i$. Conversely, the acute stimulatory effects on basal $[Ca^{2+}]_i$ levels observed in several cell types suggested a role for PKC. Furthermore, dexamethasone dose-dependently increases phosphorylation and activation of phosphatidylinositol-3-kinase and protein kinase B (PI3K), which in turn promotes the activation of nitric oxide (NO) signaling (e.g., phosphorylation of eNOS) Panettieri et al., (2019). Acute exposure to dexamethasone rapidly inhibits arachidonic acid release triggered by epidermal growth factor (EGF) and suppresses activation of different inflammatory signals (i.e., NFκB and mitogen-activated protein kinase - MAPKs) induced by toll-like receptor (TLR)9 in macrophages. Finally, mitochondrial apoptosis by CSs occurs through the disruption of the mitochondrial membrane potential and the release of cytochrome C (Panettieri et al., 2019).

2.2.2. *Pharmacokinetics*

CSs are lipophilic molecules that are administered orally, intravenously, or intramuscularly usually as pro-drugs. Preparations include the hydrophilic phosphate and succinate esters of glucocorticoids, which are rapidly converted to their active forms. After oral administration and absorption (bioavailability of 60–100%), systemic CSs can distribute rapidly to body tissues, and transporter-mediated membrane influx/efflux proteins appear to play a pivotal role in their tropism, particularly in the liver and brain. CSs can bind to transcortin (i.e., corticosteroid-binding globulin, CBG) and an increase in free CSs fraction usually occurs at 400 μg/L (i.e., a concentration achieved after administering hydrocortisone or prednisolone at doses >20 mg) due to CBG saturation (Czock et al., 2005). Although alterations in protein binding are not usually clinically relevant, low plasma albumin levels were found to be related to AEs in patients taking prednisone (Czock et al., 2005).

The intracellular metabolism of CSs is pivotal in regulating the capability of CSs to bind the glucocorticoid or mineralocorticoid receptors. Such metabolism is mediated by two isoforms of the 11β-hydroxysteroid dehydrogenase (11β-HSD) that act oppositely. 11β-HSD1 is expressed in glucocorticoid target tissues (mainly in the liver) and converts inactive cortisone into active cortisol. On the other hand, 11β-HSD2, which is mainly expressed in mineralocorticoid target tissues (i.e., kidney), transforms cortisol to cortisone in such a way to protect the mineralocorticoid receptor from occupation by cortisol. The fact that the activity of 11β-HSD2 depends on the type of CSs may account for the different mineralocorticoid activities of CSs and high CSs doses are expected to saturate 11β-HSD2 activity and promote enhanced mineralocorticoid effects (Czock et al., 2005).

CSs are extensively metabolized by CYP3A enzymes and some differences among CSs do exist in this process. For example, prednisone is activated to prednisolone regardless of the liver functional status, whereas the transformation of cortisone into its active metabolite, hydrocortisone, is substantially impaired in patients with liver dysfunction, a condition that may limit the therapeutic value of this drug. Furthermore, since CSs are sensitive substrates of CYP450 enzymes, coadministration of potent inducers (e.g., anticonvulsants) or inhibitors (e.g., azole derivatives) increases or decreases drug clearance, respectively, with possible clinical consequences (Czock et al., 2005; Williams, 2018; Prete & Bancos, 2021). The elimination half-life, i.e. the time required for the concentration of a drug to decrease to half of its initial dose, is usually correlated with the duration of response. However, due to the genomic mechanism of CSs action, the effects persist after the drug is cleared from circulation. Therefore, the duration of CSs action is higher than their elimination half-life (Table 1).

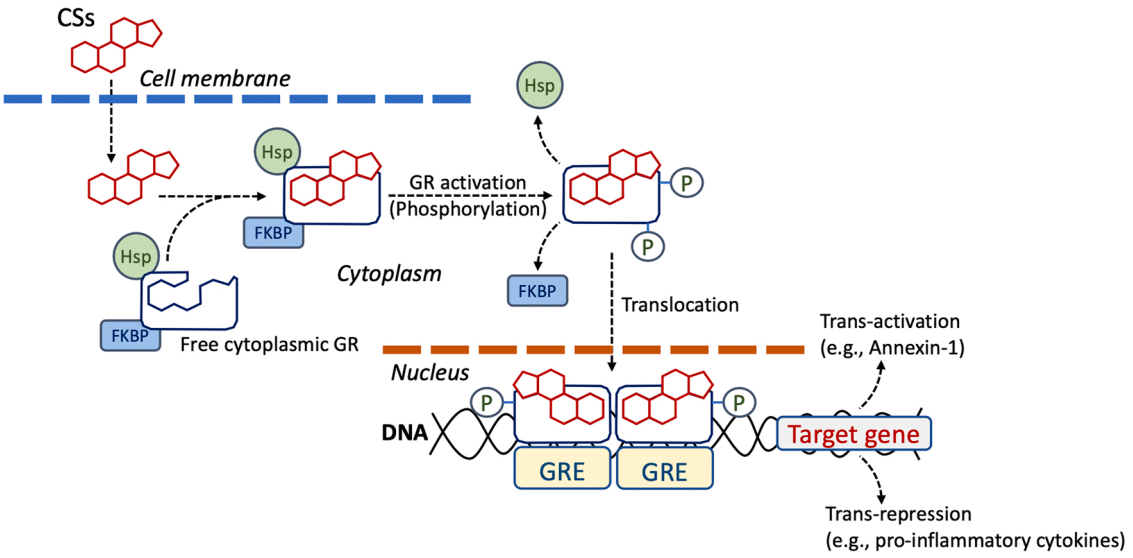

Fig. 1. Genomic effects of corticosteroids (CSs). The CSs receptor is located in the cytosol as inactive heterocomplex bound to heat shock (*Hsp: Heat shock protein*) and FK506 binding proteins (*FKBP: FK506 binding protein*). After dissociation from chaperone proteins, the activated drug-receptor complex translocates into the nucleus and then homodimerizes and binds specific DNA sequences (*GRE: glucocorticoid receptor*).

3. Adverse events of corticosteroids

3.1. Glico-lipidic metabolism

It has been well documented that CSs can cause hyperglycemia ("steroid-induced diabetes") or further aggravate a pre-existing condition of DM (Aldea et al., 2020; Clore & Thurby-Hay, 2009). The effect of CSs on glucose metabolism is dose-dependent, resulting in a mild increase in fasting blood glucose levels, a larger increase in postprandial blood glucose in patients without pre-existing DM (Oray et al., 2016), and reduced sensitivity to exogenous insulin (Hirsch & Paauw, 1997). CS-induced hyperglycemia may be due to increased hepatic gluconeogenesis and inhibited glucose uptake in adipose tissue (McMahon et al., 1988). For these reasons, before initiating CSs therapy, glycemia should be closely monitored, and antidiabetic therapy beginning or adjustment should be considered (Aldea et al., 2020; Caplan et al., (2017)). Importantly, hyperglycemia improves with reduction in the dose of CSs and usually reverses when the medication is withdrawn (Olefsky & Kimmerling, 1976; Oray et al., (2016)); furthermore, the development of *de novo* DM in normal glucose tolerant-patient is uncommon (McMahon et al., 1988; Oray et al., 2016).

With regards to lipid metabolism, CSs induce lipolysis, increase the synthesis of very-low-density lipoprotein (VLDL) and free fatty acids and their accumulation in the liver, leading to a condition of dyslipidemia (Arnaldi et al., (2010); Oray et al., (2016)).

Finally, weight gain is a common AE associated with the use of CSs (Oray et al., (2016)), mainly due to increased appetite or to an increase in food intake to relieve gastrointestinal side effects (Da Silva et al., 2006).

3.2. Endocrine

Cushing syndrome can result from long-term CSs therapy (Oray et al., 2016); the classic characteristics include central obesity, redistribution of body fat to truncal areas, supraclavicular fat pads, *striae distensae*, proximal muscle weakness, fatigue, hypertension, acne, moon face, glucose intolerance or DM, muscle atrophy, and psychologic disturbances (Hopkins & Leinung, 2005; Oray et al., (2016). These effects are directly related to the dose and duration of CSs use (Caplan et al., 2017). On the other hand, prolonged systemic use of CSs can progressively inhibit the hypothalamus-pituitary-adrenal axis and induce adrenal cortex atrophy. As a consequence, an abrupt withdrawal of CSs therapy may lead to adrenal insufficiency, a life-threatening condition (Aldea et al., 2020; Caplan et al., 2017). Therefore, patients should be aware about this possibility and signs and symptoms of adrenal insufficiency (fatigue, low blood pressure, nausea/vomiting, abdominal pain and ion disorders, as well as hypotension, decreased consciousness, lethargy, seizures, coma, and hypoglycemia in case of adrenal crisis) should be closely monitored.

In addition, suppression of growth is a well-recognized AEs of CSs therapy in children (Oray et al., 2016), mainly due to its effects on bone metabolism, nitrogen retention, and on collagen formation, as well as to inhibition of growth hormone release and insulin like growth factor-1 (IGF-1) bioavailability (Braith et al., 1998). Importantly, these defects may not reverse after steroid withdrawal; indeed, growth hormone replacement therapy is sometimes necessary (Braith et al., 1998).

3.3. Hematologic/Immunologic

Hematologic and immunologic AEs s are mainly related to the higher risk for infection due to a reduction in blood cells (Kalfeist et al., 2022). In this regard, patients treated with CSs should be screened for tuberculosis and hepatitis B, and antimicrobial prophylaxis might be indicated in patients who are scheduled to be on high-dose corticosteroids for >4 weeks (>30 mg of prednisone-equivalent dose-PEQ) or in patients chronically treated ($\geq$8 weeks of continuous or intermittent CSs use) with moderate doses ($\geq$15 to <30 mg PEQ). Rarely, autoimmune hemolytic or aplastic anemia, immune thrombocytopenia, and hemophagocytic lymphohistiocytosis could also occur (Shoenfeld et al., 2020).

3.4. Gastrointestinal

CS use is an independent risk factor for gastrointestinal AEs, including gastritis, peptic ulcer and gastrointestinal bleeding Caplan et al., (2017). However, conflicting data are available concerning the risk of peptic ulcer disease in patients treated with CSs alone. Conversely, CSs therapy in association with non-steroidal anti-inflammatory drugs increases the risk of peptic ulcer disease and gastrointestinal bleeding (Caplan et al., 2017). In this context, proton pump inhibitors (PPI) are an effective tool for gastrointestinal prophylaxis (Caplan et al., 2017). However, even if short-term PPI treatment is related to low risk, long-term PPI use may in turn induce AEs, like hypochlorhydria, hypomagnesemia and microscopic colitis (Corleto et al., 2014).

3.5. Neuropsychological

CS chronic use could be associated with neuropsychiatric symptoms, such as minor mood changes, hypomania/mania, depression, euphoria, mood lability, irritability, sleep disorders, akathisia and anxiety (Brown et al., 2001). Furthermore, cognitive impairment and, rarely, psychosis, dementia, and delirium, could also occur (Brown et al., 2001). The incidence and the severity of side effects are dose-dependent, and mainly occur during the first weeks of treatment; the effects are generally reversible with dose reduction or treatment discontinuation (Brown, 2009). The appearance of these side effects is more frequent in female gender, psychiatric background, as well as in people older than 40 years (Brown et al., 2001).

3.6. Muscoloskeletal

CSs have several effects, direct and indirect, on the growth plate and skeletal metabolism (Kobza et al., 2021). The prevalence of secondary osteoporosis is ~ 30–50 %, and the reduction in bone strength mainly occurs during the first 3–6 months of treatment (Kobza et al., 2021). Specifically, CSs reduce osteocyte-mediated mechano-sensing, activate and accelerate bone resorption inducing impaired bone formation (Ward, 2020; Kobza et al., 2021). Furthermore, CSs reduce gastrointestinal calcium absorption and increase vitamin D catabolism. All these events result in bone fragility and an increased risk of bone fractures (Ward, 2020). In this regard, the treatment and prevention of glucocorticoid-induced osteoporosis should be considered in clinical practice, although the lack of clear guideline and recommendations Baschant et al., (2022). This is of particular relevance during the long-term treatment with CGs in childhood (i.e. in case of acute lymphoblastic leukemia), which can induce, beside decreased bone mineral density and increased fracture rate a growth deficit (Velentza et al., 2021).

Finally, muscle cramps and reduced muscle tone may also occur during CSs treatment (Fardet et al., 2007a, 2007b).

3.7. Cardiovascular

CS overuse is associated with adverse cardiovascular outcomes (Pimenta et al., 2012). Risk of hypertension is increased by ~2-fold in patients treated with CSs regardless of treatment duration (Oray et al., 2016). This increase tends to be dose-dependent (Pimenta et al., 2012); it may occur both early, in absence of known risk factors, likely from an imbalance between vasoconstriction and vasodilation (Sato et al., 1995), or as a result of weight gain (Fardet & Fève, 2014). Increased plasma volume, elevated peripheral vascular resistance, and increased

cardiac output are potential contributing mechanisms to the development of hypertension under CSs excess (Pimenta et al., 2012).

Furthermore, it has been reported that the use of CSs increases the risk of coronary heart disease, ischemic heart disease, heart failure and even sudden death (Wei et al., 2004). This may be due to the concomitant occurrence of hypertension, hyperglycemia, and hypertriglyceridemia (Fardet & Fève, 2014). Moreover, triglycerides accumulationin the myocardium can lead to impaired left ventricular filling dynamics (McGavock et al., 2007). Systemic CSs may induce atrial fibrillation and flutter as well (Van Der Hooft et al., 2006). These effects seem to be dose-dependent and the risk decreases after CSs withdrawal (Souverein et al., 2004).

3.8. Skin

CS-related skin AEs include lipodystrophy and cutaneous disorders (Fardet et al., 2007a) Lipodystrophy, which is characterized by selective absence of adipose tissue, mainly occurs in overweight subjects and in women (Fardet et al., 2007a).

Furthermore, skin atrophy, erosions, *striae rubrae*, ecchymosis, as well as acne, hirsutism and hair loss have also been reported (Fardet et al., 2007a).

The risk of these AEs increases with cumulative dosage and duration of treatment (Fardet et al., 2007a).

4. Indications

CSs are extensively prescribed to advanced cancer patients for various specific indications (spinal cord compression, primary and secondary brain tumours, leukemia, lymphomas, etc.), for pain relief, as antiemetics, etc.

4.1. Anti-proliferative treatment

Unlike other steroid hormone receptors, the glucocorticoid receptor is not considered as an oncogene and its activation is linked to anti-proliferative effects.

4.1.1. Lymphoid proliferative diseases

CSs and their receptors perform various functions, including arresting growth or inducing apoptosis in lymphocytes (Pufall, 2015). Efficacy of CSs in this setting is well recognized, thus explaining their fundamental role in lymphoid proliferative diseases treatment. The cytotoxic effect of CSs appears to be mediated through the activation of their receptors. This process inhibits cytokine production, alters the expression of various oncogenes, and induces cell cycle arrest and apoptosis. Anyway, the biological activity of CSs in hematopoietic cells is complex and the mechanism by which they induce cell death in lymphoid cells is not yet clear. Nevertheless, CSs serve as a negative signal in lymphoid development. CSs are also important for T and B cells selection (Mittelstadt et al., 2002; Gruver-Yates and Cidlowski, 2013).

4.1.2. Immune-checkpoint inhibitors

The anti-proliferative effect of CSs when administered concomitantly to immunotherapy with immune-checkpoint inhibitors (ICIs) is controversial. CSs have the capacity to reduce T-cell production, function, and migration in immune and inflammatory processes. Therefore, they are commonly used to manage immune-related AEs associated with the immune response induced by ICIs (Drakaki et al., 2020; Adorisio et al., 2021). However, due to their immunosuppressive effects, legitimate doubts emerged about the possible consequences of CSs on immunotherapy efficacy. Drakaki et al. showed that ICI-treated patients receiving CSs at baseline had shorter time to the next treatment across tumour types Drakaki et al., (2020). Similar results have been reported by other studies (Arbour et al., 2018; Scott and Pennell, 2018; Chasset et al., 2015; Pan et al., 2020). In particular, the use of high-dose steroids in combination with nivolumab or pembrolizumab for the treatment of melanoma, renal cell carcinoma, or non-small-cell lung cancer (NSCLC), appear to be associated with poorer survival outcomes (Pan et al., 2020). Notwithstanding, the authors of this study underlined that many confounders could affect the relationship between steroids treatment and survival (Pan et al., 2020). A possible explanation could be that CSs negatively affect the development of tertiary lymphoid structures, which is associated with improved patient survival, resulting in a reduction in overall survival (OS) in patients with lung cancer (Siliņa et al., 2018). Other studies found no association between CSs and decreased immunotherapy efficacy (Tarhini et al., 2021; Albiges et al., (2019)). In this regard, in a study conducted on 1673 patients with resected high-risk melanoma, no significant associations were found between CSs use and OS (Tarhini et al., 2021).

A systematic review of the literature on this topic concluded that administration of CSs during immunotherapy not necessarily leads to poorer clinical outcomes. In addition, no data on doses and types of steroids emerged to confirm a clear interference with immunotherapy efficacy (Garant et al., 2017). A recent retrospective study evaluating patients with metastatic solid tumours showed no difference between the group early treated with CSs. This study showed that early systemic steroids therapy for managing side-effects of immunotherapy might not have a detrimental effect on outcome Paderi et al., (2021). Ten milligrams daily of prednisone-equivalent is the permitted steroid dose within clinical studies. Even at higher dosage of steroids there is no clear evidence of association with a worse outcome (Paderi et al., 2021). However, given the increasing use of ICIs and the limited evidence on the potential effect of suboptimal use of CSs on patient outcomes, a safe minimum dose after careful considerations should be recommended (Schmitt et al., 2022). Finally, current evidence seems to orient towards less favorable outcomes when CSs administration is related to a palliative intent, while non-palliative ones seem to be associated with stable or neglectable reduced outcomes (Marinelli et al., 2021).

4.1.3. Solid tumours

Beyond the field of immunotherapy, the use of CSs as anti-proliferative agents in solid tumours remains controversial (Kalfeist et al., 2022; Mayayo-Peralta et al., 2021). In fact, depending on the signaling pathways and action targets, the effect of CSs can be stimulatory rather than inhibitory on tumour growth (Kalfeist et al., 2022; Herr et al., 2003). For example, in breast cancer, the expression of estrogen receptors would seem to predict a good response to the addition of CSs, while the absence of estrogen receptors would make the tumour less vulnerable to anti-cancer therapies if CSs are used concomitantly (Mayayo-Peralta et al., 2021).

4.2. Cancer-related symptoms

The cancer-related CSs indications include palliative care for refractory symptoms and oncological emergencies. The widespread use of CSs derives from their rapid effect and broad variety of functions, such as anti-inflammatory, vasoconstrictive, immunosuppressive, and anti-proliferative activities. Systemic CSs use for cancer-related symptoms ranges from fatigue relief, anorexia and cachexia, pain management, dyspnea related to carcinomatous lymphangitis or tumour-dependent airway obstruction, superior vena cava syndrome, peritumoural brain edema, and spinal cord compression (Hardy et al., 2021). However, despite steady side effects, especially following long-term administration, high-quality evidence supporting extensive steroids use for symptom control is still lacking (Pinkerton et al., 2019). Most of the currently available literature results are limited by heterogeneity in steroid type, dosage and routes of administration, comparators, and characteristics of study populations. Therefore, the risk/benefit balance and co-existing clinical conditions must be considered (Pinkerton et al., 2019).

The type, dosage and duration of CSs treatment vary according to the different clinical indications. Dexamethasone is the most commonly

used CSs in palliative care, due to its potency, lower mineralocorticoid effect, and long half-life, allowing once-daily administration. The administered dose of dexamethasone usually ranges from 2 mg to 16 mg daily. ASCO and ESMO guidelines recommend short-term use of low CSs dose (3–4 mg dexamethasone equivalent dose/day) to improve appetite and weight gain, discouraging their prescription for cachexia. Most trials reported a transient benefit in appetite and suggest limiting CSs use to 2–3 weeks for this indication (Roeland et al., 2020; Sacks et al., 2018).

Short-term use for relief of cancer-related fatigue is also recommended based on the results of two clinical studies showing that dexamethasone (4 mg twice a day for 14 days) or methylprednisolone (16 mg b.i.d. for 7 days) are more effective than placebo in improving cancer-related fatigue and quality of life (QoL) (Roeland et al., 2020; Sacks et al., 2018; Paulsen et al., (2013)). Established practice includes steroids as a common therapeutic option for pain management, despite the weak evidence. CSs may be useful as adjuvant analgesics for acute treatment of neuropathic and bone cancer pain due to their anti-inflammatory effects (Haywood et al., 2015; Paice et al., 2016). Recommendation doses range from 1 to 10 mg twice daily (Paulsen et al., 2014; Paulsen et al., 2013). The treatment should be as short as possible and stopped early if a clinical benefit does not occur. Long-term use in cancer survivors is not recommended solely to relieve chronic pain (Paice et al., 2016).

Insufficient quality of evidence supports the clinical practice of using steroids for palliative symptoms of carcinomatous lymphangitis and tumours-induced airway obstruction (Pinkerton et al., 2019; Haywood et al., 2015). Nevertheless, based on clinical experience and biological rationale, systemic CSs may be prescribed for selected patients with cancer-related breathlessness, especially when inflammation is a crucial contributor to dyspnea (Hui et al., 2021).

More solid recommendation exists for CSs systemic use in cancer-related complications, such as spinal cord compression and increased intracranial pressure (Pinkerton et al., 2019). CSs provide analgesia and preserve neurologic function in spinal cord compression by producing prostaglandin E2 and vascular endothelial growth factors (Fallon et al., 2018). Dexamethasone should be prescribed in a dose of 8–16 mg i.v. daily tapered over two weeks (Fallon et al., 2018), considering the unclear benefits and the increased risk of serious AEs in ultra-high dose protocols (up to 96–100 mg/day) (Graham et al., 2006; George et al., 2015). CSs therapy is also a mainstay for the management of symptoms related to increased edema and intracranial pressure secondary to brain lesions. The starting dose ranges between 4 and 16 mg/day, depending on the severity of clinical presentation. Notwithstanding, no clear guidance regarding dose tapering is available, and the dose reduction should occur slowly over 2 weeks, or longer in severely symptomatic patients (Ryken et al., 2010).

Considering the above, the current quality of evidence to support the widespread use of CSs is scanty for most clinical indications. Therefore, caution is recommended in clinical practice and statistically powered, high-quality research is eagerly awaited.

4.3. Drug-related side effects

CSs are frequently prescribed to cancer patients as a supportive therapy to treat side effects derived from anti-tumour treatments (Kalfeist et al., 2022).

4.3.1. Chemotherapy-induced nausea and vomiting

Besides their topical administration to manage skin toxicity from radiotherapy (Kumar et al., 2010) or targeted agents (Kikuchi et al., 2022; Peng et al., 2019), their use in clinical practice is mainly aimed at preventing or counteracting systemic side effects, among which chemotherapy-induced nausea and vomiting (CINV) is one of the most common (Piechotta, 2021).

Indeed, even if their mechanism of action as antiemetics is not entirely clear, CSs administration in CINV dates back to the 1980 s (Van Ryckeghem and Corticosteroids, 2016). The idea to add dexamethasone to antiemetics was probably due to the lower rates of CINV observed in patients receiving steroids in the antineoplastic regimen, but their superiority over placebo in preventing acute and delayed emesis was then established in a meta-analysis of 32 randomized trials including 5613 patients (Ioannidis et al., 2000). At present, both American and European guidelines incorporate dexamethasone in the multi-drug combination of anti-emetics recommended for the prevention of CINV in cancer patients receiving high/medium emetogenic chemotherapy or radiation, while suggesting a single 8 mg dose of the steroid as an alternative option to 5-HT3 receptor antagonists in the presence of low emetic risk (Hesketh et al., 2020; Roila et al., 2016).

Among the proposed mechanisms of action, CSs direct effect on the solitary tract nucleus has been mentioned (Ho et al., 2004), as well as their capability to regulate the hypothalamic-pituitary-adrenal axis (Gupta et al., 2021). Moreover, in addition to the well-known anti-inflammatory properties of this class of agents, interactions with serotonin and neurokinin receptors have been suggested (Chu et al., 2014).

4.3.2. Immune-related adverse events

In recent years, the advent of immunotherapy has revolutionized the management of several malignancies, leading oncologists to face novel immune-mediated side effects, collectively termed immune-related adverse events (irAEs) (Gumusay et al., 2022). IrAEs arise as a consequence of exhausted T cell reactivation which can induce self-tolerance loss (Ramos-Casals et al., 2020), leading to auto-immune manifestations that may potentially involve any organ including the skin Choi et al., 2020, kidney (Seethapathy et al., 2021, Tucci et al., 2019), heart Arangalage et al., 2021, gastrointestinal (Li et al., 2022; Dougan et al., 2020), endocrine (Chang et al., 2019; Silvestris et al., 2020) and central/peripheral nervous (Spain et al., 2017, Feng et al., 2017) systems. Clinical presentations vary according to the agent used: on the one hand, colitis, rash and hypophysitis are more commonly observed during treatment with cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors; on the other hand, hypothyroidism, pneumonitis and vitiligo are generally associated with inhibition of the programmed cell death (PD)− 1 or its ligand (PD-L1) (Ramos-Casals et al., 2020). It is likely that such differences reflect the peculiar mechanisms of action of these agents, while an individual predisposition to autoimmunity has been suggested as a risk factor for irAE onset (Ramos-Casals et al., 2020). Management of irAEs includes the temporary/definitive discontinuation of the drug and introduction of immunosuppressant agents, with CSs being the first-line choice (generally recommended for grade $\geq$2 irAEs) (Schneider et al., 2021). To minimize the risk of acute and long-term steroid-related toxicities, the lowest possible dose should be used for the shortest possible time (Santomasso et al., 2021). For patients receiving at least 20 mg/day prednisone (or equivalent) for a minimum of 4 weeks, the administration of prophylactic antibiotics for pneumocystis pneumonia could be considered, whereas antifungal prophylaxis is recommended in subjects receiving $\geq$ 20 mg prednisone daily for 6–8 weeks or longer (Gumusay et al., 2022; Sørup et al., 2021).

4.3.3. Chimeric antigen receptor T-cells

More recently, immunotherapies with chimeric antigen receptor (CAR) T-cells have been under development in both hematological and oncological fields, raising further concerns related to potentially severe toxicities, including the cytokine release syndrome and the immune effector cell–associated neurotoxicity syndrome (Hou et al., 2021; Brudno and Kochenderfer, 2019). Also in this setting, CSs are currently among the recommended pharmacologic interventions for those patients without adequate response to supportive care and/or life-threatening complications (Santomasso et al., 2021). However, a recent study conducted on 71 patients with relapsed/refractory multiple myeloma treated with CAR-T cell showed that administration of CSs (both considering dose and duration) does not influence the clinical efficacy of therapy (Wang et al., 2022).

4.4. Oncological emergencies

Cancer-related acute complications include spinal cord compression, hypercalcemia, superior vena cava syndrome (SVC), pericardial effusion and acute tumour lysis syndrome (McCurdy and Shanholtz, 2012).

4.4.1. Spinal cord compression

CSs are the mainstay of pharmacologic therapy for pain associated with vertebral metastases and for acute neural deterioration that often accompanies metastatic epidural spinal cord compression. CSs decrease inflammation with an analgesic effect, decrease the associated vasogenic spinal cord edema, and substantially improve short-term neurologic function and decrease pain. Dexamethasone is the most commonly used CS; however, there is no current optimal dosing regimen, and no consensus data are available to recommend high dose steroids.

4.4.2. Hypercalcemia

CSs are also used in the management of tumour-induced hypercalcemia. CSs are generally effective in treating hypercalcemia associated with myeloma and lymphoma. In this context, prednisolone 60–100 mg/day is given. The mechanism of any hypocalcemic effect produced by these steroids is unclear. CSs block the intestinal absorption of calcium; therefore, they could be useful for patients with vitamin D-mediated hypercalcemia where gastrointestinal absorption of calcium is enhanced. However, relatively poor performances do not support the use of CSs as the treatment of choice for hypercalcemia related to most solid tumours (McCurdy and Shanholtz, 2012).

4.4.3. Superior vena cava syndrome and acute tumour lysis

Although commonly prescribed, CSs are of unclear benefit for treatment of SVC syndrome, pericardial effusion, and acute tumour lysis (McCurdy and Shanholtz, 2012). On the other hand, CSs are useful in the management of adverse chemotherapy reaction (Kalfeist et al., 2022). In this regard, some anti-cancer agents (in particular, taxanes, platinum salts, and certain monoclonal antibodies) can induce hypersensitivity reactions during infusion, with clinical presentation varying from skin rash to laryngeal oedema, hypotension, or even anaphylactic shock (Kalfeist et al., 2022). These reactions are mediated by basophils and mast-cells, whose number and activation can be reduced by CSs (Liyanage et al., 2017). In most patients, hypersensitivity reactions can be prevented by pre-treatment with steroids and antihistaminic agents (Boulanger et al., 2014), while high doses of CSs (1–2 mg/kg prednisolone or equivalent) are the mainstay of treatment in cases of severe acute reactions, together with H1/H2 antagonists (Rosellò et al., 2017).

Furthermore, steroids have turned out effective to control taxane side effects, including the development of fluid retention (Markman, 2003) and the so called "taxane-associated pain syndrome" (Clemons et al., 2021).

5. Contraindications

Appropriate use of CSs has been playing a key role in the management of specific and nonspecific manifestations of several malignancies for more than 70 years. Moreover, CSs are a mainstay of palliative treatment for patients with advanced cancer.

In medical and oncological emergencies, no strict contraindications to CSs formally exist. In other settings and when long-term CSs use is expected, precautionary measures for preventing AEs may be advisable (Aldea et al., 2020).

5.1. Absolute contraindications

Absolute contraindications to CSs include hypersensitivity to any component of the formulation, concurrent administration of live or live-attenuated vaccines, and ongoing widespread infections (such as systemic fungal, viral, or bacterial infections) not controlled by anti-infective agents v.

Hypersensitivity and severe allergic reactions to the currently available CSs formulations are well documented. Substitution of succinate with sodium phosphate salts of CSs has been suggested in this case (Twycross, 1994).

5.2. Relative contraindications

CSs should be used with caution in people whose health conditions could worsen with their use (Table 2). In these situations, CSs should be started only when the expected benefits outweigh potential risks of treatment.

Systemic CSs are associated with an increased risk of diabetic and prediabetic conditions, which are more detrimental in patients with cancer. Moreover, these patients are particularly vulnerable to the CSs immunosuppressive effect. In addition, CSs may mask signs and symptoms of infection impairing early recognition, with potential life-threatening consequences. Therefore, CSs are relatively contraindicated in patients with an active infection.

Appropriate testing (e.g., Mantoux, QuantiFERON®-TB Gold, or chest radiography) for excluding systemic tuberculosis infection should be considered, especially in settings where tuberculosis is endemic, before placing cancer patients on long-term, high-dose CSs therapy (Walsh and Avashia, 1992). In high-risk patients such as those undergoing chemo- or radiotherapy, prophylactic treatment for opportunistic infections (such as *Pneumocystis jirovecii* pneumonia) should be evaluated, if prolonged CSs exposure is deemed necessary (Roth et al., 2015). Treatment precautions to prevent reactivation of underlying infections depend on the patient specific risk.

If needed, CSs therapy may be started also in patients with known infections if effective, specific therapy can be administered concomitantly. Similarly, if infection develops during treatment with CSs, the dose may be maintained provided that the best available treatment for the infection is rapidly administered (Goodman and Gilman's, 2018, 10th Editon, 2018, McGraw-Hill Editor).

Increased intraocular pressure (glaucoma) has been observed in prolonged and, to a lesser extent, acute systemic CSs use. Patients with a history of glaucoma (or at increased risk for) should undergo comprehensive eye evaluations, periodically.

When a lymphoma is suspected, the administration of CSs should be delayed until histopathological confirmation of the diagnosis.

In patients with past-medical history of psychiatric conditions, their mood disorder should be under good control before CSs are initiated, and patients should be monitored closely (Aldea et al., 2020). Neuroleptic, sedative, or anti-depressive therapy may need to be adjusted in patient already under treatment with these drugs.

Table 2
Absolute and relative contraindications of corticosteroids (health conditions that may worsen with their use).

Absolute contraindications
Hypersensitivity to any component of the formulation
Concurrent administration of live or live-attenuated vaccines
Ongoing widespread infections not controlled by anti-infective agents
Relative contraindications
Diabetes mellitus
Poorly controlled arterial hypertension
Heart failure, peripheral edema, or recent acute coronary syndrome
Cataract, glaucoma, herpes simplex keratitis
Peptic ulcer disease
Low bone density, osteoporosis, or risk of bone collapse (eg, bone metastases)
Liver disease
Uncontrolled psychosis and behavioral problems, or alcohol dependence
Wound healing problems (recent surgical intervention)
Active fungal, bacterial, or viral disease (especially viral hepatitis, herpes, varicella, shingles)
Uncontrolled/untreated epilepsy

Risk of bone collapse is increased by CSs use, especially when the hips, femoral, or humeral heads are involved from bone metastatic spreading. In this setting, the use of bisphosphonates should be evaluated, as well as vitamin D and calcium supplementation.

The emerging immunotherapeutic approaches may represent a contraindication to CSs therapy in cancer patients, hypothesizing that their administration may dampen the stimulatory activity of ICIs on the immune system (Roth et al., 2015). However, as discussed above, current data are inconclusive about this point, as many studies report no influence of an intercurrent CSs therapy on the anti-tumour response of ICIs.

Conversely, CSs may interfere with boosting an immune response in patients receiving a vaccine for immunotherapy (Finocchiaro and Pellegatta, 2011). Indeed, CSs are among the exclusion criteria for the enrolment in several vaccination trials, with the aim to select only immunocompetent patients.

In palliative care setting, common AEs that limit the use of CSs include oropharyngeal candidiasis, fluid retention, dyspepsia, myopathy, and insomnia. In this setting, it is particularly important to know and properly balance potential harms and benefits of CSs use (Hatano et al., 2018).

6. Corticosteroids and cancer patient outcome

As described above, CSs are widely used in oncology due to anti-inflammatory, cytotoxic and immunomodulatory properties. However, it is known that CSs could have long-term effects which can adversely affect the QoL, among which a psychostimulatory effect. In this regard, patients with previous history of depression, psychotic states or other psychiatric disorders, should be informed and monitored for psychiatric symptoms (VanderWalde et al., 2016). On the other hand, CSs could reduce severe symptoms related to chemo- and radiotherapy, which can impair patient's QoL (Gupta et al., 2021). Finally, specific precautionary measures could be implemented to prevent long- and short-term AEs to CSs and definitely ensure a good QoL while on CSs therapy. In particular, the clinician should consider all strategies to prevent infectious diseases, ion imbalances and hypokalemia, hyperglycemia, adrenal insufficiency, as well as effects on the skeleton and muscle (Aldea et al., 2020).

For this purpose, Adams et al. developed a specific questionnaire aiming at evaluating the physical, behavioral/emotional and cognitive effects of CSs on QoL in children and young adults affected by acute lymphoblastic leukemia Adams et al., (2016). No specific questionnaires are available on other neoplasms.

Considering the impact of CSs therapy on OS, several studies described an improvement in appetite, food consumption (Moertel et al., 1974) and a reduction in cachexia development (Twycross,1994; Lossignol, 2016) related to CSs use, with a final improvement in OS. Other studies reported no or negative impact of CSs therapy on survival. In patients undergoing colectomy for colon cancer, preoperative dexamethasone treatment has been associated with an OS similar to untreated patients (Singh et al., 2014). On the other hand, a study based on a large population (1781 patients) receiving intravenous chemotherapy for different types of cancer showed CSs treatment to be associated with worse 1-year survival in presence of DM (67.3 % vs. 78.3 %) (Zylla et al., 2019). Finally, considering patients treated with immunotherapy, recent evidence suggests that early onset of irAEs leading to the premature administration of high-dose steroids could correlate with reduced clinical benefit and survival, advising for caution when prescribing CSs, especially in the absence of severe and life-threatening irAEs (Bai et al., 2021; Fucà et al., 2019; Scott and Pennell, 2018). Table 3 summarizes pros and cons of CSs use on QoL and OS in cancer patients.

Table 3
Pros and cons of corticosteroids use on quality of life and survival in patients with cancer.

	Pros	*Cons*
QoL	- Prevention and treatment of hypersensitivity reactions - Improvement of appetite and food consumption	- Onset or exacerbation of psychiatric symptoms - Long- and short-term AEs: infectious diseases, ion imbalances, hyperglycemia, adrenal insufficiency
OS	- Reduction in cachexia occurrence - Similar OS in patients with colon cancer treated and untreated with CSs	- Risk of efficacy reduction of anti-cancer treatment in non haematological diseases - Worsened survival in cancer patients treated with chemotherapy plus CSs in presence of DM

QoL: quality of life; OS: overall survival; AEs: adverse events; CSs: corticosteroids; DM: diabetes mellitus

7. Final recommandations

✓ Systemic CSs are a cornerstone in the management of cancer patients, for treatment of cancer- and anti-cancer treatment-related symptoms, for management of anaphylaxis and cytokine release/hypersensitivity reaction and oncological emergencies, and for induction of apoptosis in hematological cells.

✓ Different type of AEs related to CSs treatment can occur; for this reason, several precautionary measures should be performed to prevent long-term and short-term side effects.

✓ To date, some concerns remain on the effects of CSs on tumour growth and response to anti-cancer therapy, especially in patients with solid tumours and in those receiving immunotherapy.

✓ For the clinical management of CSs in oncology, a prudent and vigilant use together with a full knowledge of the available compounds and their pharmacological properties should be recommended.

8. Future perspective

Due to the absence of robust data and prospective trials supporting the use of CSs in oncology, dedicated clinical studies, mainly focusing on clinical outcomes, such as QoL, OS and PFS, are needed to identify the optimal indications, as well as type, dose e duration of therapy of these extraordinary agents for cancer patients. Furthermore, molecular studies should be performed to better understand the mechanisms of action of CSs and their relationship with the pathways responsible for tumour proliferation.

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Conflict of interest

R.D. serves on the scientific advisory board and has consulting

relationship with Ipsen, Novartis, Pfizer, Sanofi Genzyme, AstraZeneca, Janssen, Gilead, Lilly, Gilead, EUSA Pharma; and reports support for travel, accommodation, and expenses from Ipsen, and Sanofi Genzyme. M.G. has received speaking fees from AAA, Boehringer-Ingelheim, EISAI, Eli-Lilly, Lifescan, Novo Nordisk and Sanofi, and served on scientific advisory boards for Boehringer-Ingelheim and Novo Nordisk. F. G. has served as an advisor for AstraZeneca, Eli Lilly, and Novo Nordisk; has served as a research investigator for Eli Lilly and Roche Diabetes Care; has served as a speaker for AstraZeneca and Eli Lilly; has served as a consultant for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Roche Diabetes Care, and Sanofi; and has received grants from Eli Lilly, Lifescan, and Roche Diabetes Care.S.F. serves on the scientific advisory board of, has consulting relationship with, and reports receiving support for travel expenses from Novartis, Teva, Roche, BMS, Lilly, and Ipsen. N.S. received fees for consulting from Roche, Lilly, Servier. All other authors declare no conflict of interest.

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Stella D'Oronzo, MD, PhD: She graduated with honors as a Medical Doctor in 2011 at the University of Bari (Italy) and gained the national certification of the Medical Practice in 2012. At the same University, Dr. D'Oronzo completed her post-graduate residency program in Medical Oncology in 2017 and earned a PhD degree in "Biomolecular, Pharmaceutical and Medical Science". During her PhD course, Dr. D'Oronzo spent about two years at the University of Sheffield (UK) as a Visiting Research Fellow in the "Department of Oncology and Metabolism". In 2018 she gained the "Cancer and Bone Society Young Investigator Award" for her research on osteoporotic malignancies, espe- cially focused on mechanisms of breast cancer homing towards bone, identification of predictive prognostic biomarkers in bone metastatic breast cancer and investigation of cancer-treatment related

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Stefano Fogli, PharmD, MD, PhD: He graduated first in Pharmacy and then in Medicine and Surgery. He received board certifications in Pharmacology and a PhD in Chemotherapy and Pharmacology from the University of Pisa (Italy). He has been an Assistant Professor of Pharmacology since 2007 and is currently an Associate Professor of Pharmacology at the Department of Clinical and Experimental Medicine of the University of Pisa (Italy). His activity includes the evaluation of clinical protocols, pharmacogenetic analyses, therapeutic monitoring of biologicals, and assessment of drug-drug interactions. He is a member of a Phase 1 Clinical Trial Unit at the University Hospital of Parma (Italy) since 2019. He has participated in numerous national and international scientific congresses and meetings as a speaker and collaborated in writing recommendations and guidelines for the appropriate use of immunosuppressive drugs in liver and kidney transplantation and monoclonal antibody drugs in chronic intestinal inflammatory diseases. He was a member of the American Association for Cancer Research, the European Association of Clinical Pharmacology and Therapeutics, and, still today, the Italian Society of Pharmacology and the Italian Society of Toxicology. The research interests of Prof. Fogli include preclinical investigation of anticancer drugs and clinical pharmacokinetics, and he is currently involved in studying biomarkers of response to biologicals. He is the co-author of 81 publications in Pharmacology and Oncology, with an h-index of 29.

Marco Gallo, MD: Head of the Endocrinology and Metabolic Diseases Unit at the "Santi Antonio e Biagio e Cesare Arrigo Hospital" (Alessandria, Italy). Previously, he worked as senior specialist in the Oncological Endocrinology Unit at the AOU Citta` della Salute e della Scienza Hospital of Turin (2005–2020). He received his MD degree in 1992 from the University of Turin (Italy), and his Post Doctoral Specialization in Endocrinology and Metabolic Diseases in 1999 from the same University. His research interest include diabetes, treatment personalization of diabetes, diabetes and cancer, hormones and can- cer, and endocrine cancers. He is author or co-author of more than 150 original papers and reviews (>70 indexed in PubMed) in peer-reviewed scientific journals. He is editorial board member in scientific journals as well as reviewer for many international scientific journals. He has also been a speaker at about 250 national and international conferences. He is member of AMD (Italian Association of Clinical Diabetologists), AME (Italian Association of Clinical Endocrinologists), and SIE (Italian Society of Endocrinology).

Dario Giuffrida, MD: He graduated cum laude in Medicine (1982) at the University of Catania, Italy. He received the post-graduate certification cum laude as specialist in Endocrinology (1985) at the University of Catania and the post-graduate certification cum laude as specialist in Medical Oncology (1989) at the University of Messina. From 2004 until now, he is Director of Medical Oncology Unit and Chief of Department of Oncology at Mediterranean Institute of Oncology (IOM) in Viagrande (CT). He has been Professor of Oncology at Medical School and at School of Specialization in Endocrinology at the University of Catania. He is member of Italian Society of Endocrinology (SIE), Italian Association of Medical Endocrinology (AME), European Society of Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), European Neuroendocrine Tumors Society (ENETs), Italian Association of Medical Oncology (AIOM). He has been Regional Coordinator of Sicilian AIOM section and member of AIOM National Committee. He is author and co-author of more than 100 full papers in international peer reviewed journals. He is reviewer for many scientific journals. He is involved in Phase II and III Clinical Trials as Principal Investigator according to ICH-GCP.

Stefania Gori, MD: Full-time Medical Oncology Director and Department of Oncology Director of IRCCS Sacro Cuore Don Calabria, Negrar di Valpolicella (Italy). She was President of Italian Medical Oncology Association (AIOM) from 2017 to 2019 and President of AIOM Foundation until October 2021. She is President of Rete Oncologica Pazienti Italia- ROPI from December 2020. She is medical oncologist and she focuses on translation oncology, ereditary cancers, breast cancer and ovarian cancer. She is author and co-author of more than 200 scientific papers.

Monica Montagnani, MD, PhD: Associate Professor of Pharmacology at the Department of Biomedical Sciences and Human Oncology, Medical School, University of Bari Aldo Moro. Long-standing research interests are focused on diabetes, insulin resistance and vascular complication, cellular and molecular signaling of endocrine mediators in endothelium. Consultant for Diabetes Unit at the National Institutes of Health (NIH-US) and European Certified Pharmacologist (EuCP). Member of Pharmacology and Hypertension Scientific Societies, and editorial board member in International Journals. Invited speaker and Chairman at National and International congresses; co-author of over 80 scientific publications indexed in PubMed and Scopus (h-index 30, more than 6300 citations).

Alberto Ragni, MD: He graduated in Medicine and Surgery at the University of Pavia in 2016 and entered in 2017 the residency program in Endocrinology and Metabolic Diseases at the University of Turin, being part of the Oncological Endocrinology Unit team of the "Città della Salute e della Scienza" tertiary teaching hospital in Turin, where he completed the residency program in 2021. He is currently working as a specialist in the Endocrinology and Metabolic Diseases Unit at the "Santi Antonio e Biagio e Cesare Arrigo Hospital" (Alessandria, Italy). His clinical interests cover a wide range of oncological endocrinology topics, with a special focus on management of advanced thyroid cancer, diabetes in the oncological setting and endocrine-metabolic complications of cancer patients.

Valerio Renzelli, MD: Received MD degree in 2013 at Sapienza University of Rome and specialized in Endocrinology and Metabolic Disease in 2019 at the same University. He is currently working as a freelance endocrinologist and diabetologist in Rome. He is a member of the AMD (Italian Association of Clinical Diabetologists), AME (Italian Asssociation of Clinical Endocrinologists), and SIE (Italian Society of Endocrinology). His clinical and research activities include type 1 and type 2 diabetes, thyroid disease, gynecological endocrinology, andrology and pediatric endocrinology.

Antonio Russo, MD: Full Professor of Medical Oncology at University of Palermo Medical School, Department of Surgical, Oncological and Oral Sciences (Italy). From 2004 to July 2011, he has been an Adjunct Associate Professor and since August 2011 Adjunct Full Professor at Temple University's College of Science and Tech- nology, Philadelphia (USA). Since February 2012 is Director of Medical Oncology Unit and Director of Regional Reference Center for Prevention, Diagnosis and Treatment of Rare Tumors and Heredofamilial Solid Tumors in Adults, AOUP "P. Giaccone", Palermo (Italy). Since April 2012 to March 2019 and He has been, from April 2012 to March 2019 and from November 2021 to this day, he has been Director of the Specialization School in Medical Oncology, University of Palermo, School of Medicine, Palermo, Italy. Since April 2019 he is Coordinator of the PhD in Experimental Oncology and Surgery at University of Palermo, Department of Surgical, Oncological and Oral Sciences. Since November 2013 Medical Oncology Unit directed by Prof. A Russo has been recognized as a 2013 ESMO Designated Centres of Integrated Oncology and Palliative Care. Since 2001 he has been a coordinator with Prof D. Kerr (University of Oxford, UK) and Prof B. Iacopetta (Western Australia University) of the "CRCP53 International Collaborative Study". Since 2003 he has been an expert member of INSERM (Institut National de la Sant`e et de la Recherche M`edical, France), since 2007 of Scientific Committee INCA (Institut National du Cancer, France) and of NWCRF (North West Cancer Research Fund, UK). He is member of Editorial board of Journal of Carcinogenesis & Mutagenesis and World Journal of Gastrointestinal Oncology and World Journal of Clinical Oncology. He is Associate Editor of Journal of Solid Tumors. Since 2008 he has been Guest Editor of Annals of Oncology (2006, 2007). The central theme of his studies is translational research, meaning the application of molecular ge- netics in cancer management. He is PI in several national and international clinical trials. He is the author of more than 300 peer-reviewed publications listed on Medline-PubMed.

Nicola Silvestris, MD: Full professor in Medical Oncology at the University of Messina (Italy). He has been the Scientific Director of the Cancer Center of Bari until June 2019 and associate professor in medical oncology at the University of Bari until the middle of February 2022. He is National Councilior of the Italian Association of Medical Oncology (AIOM). He is author of over 330 publications in prestigious scientific journals (H-index of 44). Over the past 15 years he has dedicated a large part of his research and assistance to patients suffering from gastrointestinal malignancies, with particular regard to hepatobiliary-pancreatic tumors. He has also been a speaker at over 300 national and international conferences.

Tindara Franchina, MD: Senior researcher of Oncology at the University of Messina and medical oncologist at the University Hospital "G. Martino" (Messina, Italy) with interest in thoracic oncology, gastrointestinal malignancies, and thyroid cancers. She graduated in Medicine at the University of Messina in 2004 and completed the residency in oncology in 2008. She completed a PhD in Clinical Oncology at the University of Messina in 2012. In 2007 she visited the Sbarro Institute for Cancer Research and Molecular Medicine of Temple University in Philadelphia to improve her skills in molecular oncology and translational research. She is member of several national and international scientific societies, including the Italian Association of Medical Oncology (AIOM), the International Association for the Study of Lung Cancer (IASLC), and the European Society for Medical Oncology (ESMO). She is member of the Career Development and Fellowship Committee of the International Association for the Study of Lung Cancer with the role of Deputy Chair for the 2021–2023 term. She is co-author of publications in peer-reviewed international journals and currently involved in clinical research in NSCLC and bilio-pancreatic cancers.

Enzo Tuveri, MD: Full-time MD at the Diabetology, Endocrinology and Metabolic Disease service of the hospital Santa Barbara in Iglesias, ATS Sardegna, Italy. He graduated in medicine and surgery in 2001 at the University of Cagliari and specializated in Endocrinology and Metabolic Disease in 2006 at the same University. He has been performing routine clinical and medical activities in the area of diabetes and diabetic foot. His clinical and research experience include thyroid diseases, type 1 and type 2 diabetes, use of technologies in patients affected by diabetes, gestationale diabetes and diabetic foot.

Saverio Cinieri, MD: Full-time Medical Oncology Director and breast unit Director of Medical Oncology unit of Senatore Antonio Perrino Hospital, Brindisi (Italy). Cinieri is President of Italian Medical Oncology Association (AIOM) from 2021. He is coordinator of Breast Cancer PDTA for Rete Oncologica Pugliese (ROP). He is medical oncologist and she focuses on translation oncology, ereditary cancers, breast cancer and ovarian cancer. Cinieri is author and co-author of more than 200 scientific papers.Annamaria Colao

Annamaria Colao, MD, PhD: Full Professor of Endocrinology at the Department of Clinical Medicine Surgery, University Federico II of Naples. Coordinator of national and international research projects with a scientific activity characterized by the publication of more than 800 original articles in international journals. She has published over one hundred treatises, manuals, chapters of books and monographs. She is at the peak of the Top Italian scientists list and is Italian Top Woman scientist. Head of the European Network ENDO-ERN (European Reference Network) for the study of rare endocrine pathologies in adult of which she is the coordinator of the regional center at the Azienda Universitaria Federico II where she is also responsible for the European center of excellence ENETS (for the study of neuroendocrine tumours) of the centre of excellence for the diagnosis and treatment of obesity CIBO (accredited with SIO and EASO). She was president of the National Council of the Guarantors of Scientific Research at the Ministry for

University and Research. President of the European Society of Neuroendocrinology for the biennium 2016–2018 and President of the Italian Society Endocrinology for the biennium 2021–2023 (first woman in the history of the Society).

Francesco Giorgino, MD, PhD: Full Professor of Endocrinology, Chairman of the Department of Emergency and Organ Transplantation, and Head of the Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, at University of Bari Aldo Moro, Bari, Italy. He received his MD degree from the University of Bari Aldo Moro and his PhD degree from the University of Naples Federico II, in Italy. After completing clinical and research training in endocrinology and metabolism at the University of Catania, Italy, he worked for several years at the Joslin Diabetes Center and Harvard Medical School in Boston, MA, USA, first as a postdoctoral research fellow and then as a visiting scientist. Professor Giorgino has received distinguished scientific awards from various international and national institutions, including the Juvenile Diabetes Research Foundation International (JDRF) Fellowship (New York, NY, USA), the Mary K. Iacocca Foundation Fellowship (Boston, MA, USA), the Glaxo-Wellcome Award from the European Association for the Study of Diabetes (EASD), the Aldo Pinchera and Cassano Awards from the Italian Society of Endocrinology, and the Alcmeone Award from the Italian Society of Diabetology. He has been the Italian Delegate in various European Commission Cooperation in Science and Technology (COST) actions for diabetes research. Professor Giorgino has served on many national commissions and national boards, including the Executive Committee of the Italian Society of Diabetology, and the Scientific Committee of the Italian Society of Endocrinology. He has been President of the Italian Society of Endocrinology (2019–2021). He is or has been a member of the Editorial Boards for numerous. He has published more than 300 original and review articles in prestigious scientific journals (H-index of 55, over 11000 citations) and has been an invited speaker at many national and international meetings. He is named inventor in an approved Italian patent titled "Pharmacological use of a myokine able to preserve the function and mass oh the pancreatic cells under dysmetabolic conditions". Professor Giorgino's research interests include the mechanisms of insulin resistance and beta-cell dysfunction in type 2 diabetes mellitus, the pathophysiology of adipose tissue, and the pharmacological modulation of insulin action and beta-cell function.

Maria Chiara Zatelli, MD, PhD: Professor of Endocrinology at the Department of Medical Sciences, Medical School, University of Ferrara. Long-standing research interests are focused on endocrine oncology, cellular and molecular signaling in endocrine and endocrine-related cancers, chemoresistance. Director of the Endocrine Unit at the University Hospital in Ferrara. Secretary of the European Society of Endocrinology and member of Endocrine Scientific Societies. Editorial board member in International Journals. Invited speaker and Chairman at National and International congresses; co-author of 178 scientific publications indexed in PubMed and Scopus (h-index 44, more than 5700 citations).