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Management of metabolic adverse events of targeted therapies and immune checkpoint inhibitors in cancer patients: an Associazione Italiana Oncologia Medica (AIOM)/Associazione Medici Diabetologi (AMD)/Società Italiana Farmacologia (SIF) multidisciplinary consensus position paper

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ABSTRACT

The growing insights in the next-generation immunotherapy and the state-of-the-art advancement in targeted-agents significantly improved clinical outcome of cancer patients by pointing towards a unexplored Achilles' heel. Novel toxicity profiles have been uncovered, representing unmet medical needs. Thus, a panel of expert provide comprehensive pharmacological and clinical evidence, to provide a patient-tailored approach to metabolic adverse events associated with novel anti-cancer treatments. Prompted by the need of a multidisciplinary cooperation, a working group of Associazione Italiana Oncologia Medica (AIOM), Associazione Medici Diabetologi (AMD) and Società Italiana Farmacologia (SIF) examined the available literature data. The identification of patient risk profile and the characterization of metabolic effects of novel anti-tumour drugs is clearly a clinical challenge that can be addressed by a multidisciplinary clinical approach. Therefore, this review pinpoints the relevance of the challenging profiling of the patient suffering from dysmetabolic conditions induced by the novel therapeutics in medical oncology.

1. Introduction

The increasing knowledge of underlying biology of tumors allowed the development of targeted therapies with enhanced capability to inhibit aberrant signal transduction and restore immune-competence. However, the novel agents uncovered unexpected and unexplored adverse effects to represent an important medical challenges (Niraula et al., 2012; Bedard et al., 2020; Magee et al., 2020). Despite an improvement in the tolerability over the conventional chemotherapeutic agents, targeted treatments impact on a multitude of biological and homeostatic cell signals (Gharwan and Groninger 2016) resulting in novel adverse events (AEs) and, among them, metabolic alterations whose importance is often underestimated (Kotecki et al., 2015).

Disorders of glucose and lipid homeostasis are reported in a significant number of patients, especially with mTOR-PI3K targeting (Gharwan and Groninger, 2016). Therefore, a deeper knowledge of the

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pathophysiological process underlying the target-therapy related AEs is of paramount importance, to decrease the incidence of potentially severe homeostatic and metabolic implications.

The present AIOM/AMD/SIF consensus statement attempts to provide a patient-oriented pathophysiological approach to the metabolic AEs linked to precision oncology driven therapies and immunocheckpoint inhibition. A panel of specialists in medical oncology, endocrinology, and pharmacology examined the implementation of strategies to streamline a multidisciplinary patient-management.

We considered a stepwise approach, dealing with the most relevant pathogenic aspects and the translational pharmacological implications to provide practical recommendations for the medical practitioners. To this end, a broad spectrum of targeted- and immune-therapeutic agents were examined.

2. Bridging the gap between metabolic AEs and targeted/immune-checkpoint treatments: navigating the patient risk

Although type and stage of disease may predispose for a predictable clinical evolution, the true clinical course is often influenced by several other factors related to overall comorbidity and predisposition profile of the patient.

Among the many conditions that can influence the clinical outcomes, the alterations of the carbohydrate and lipid metabolism are undoubtedly significant (Newton et al., 2015; Samuel et al., 2018). Indeed, diabetes and related metabolic disorders may provide a favourable condition for the development and progression of cancer (Tudzarova and Osman 2015).

Several studies showed that metabolic disorders such as prediabetes, diabetes mellitus (DM) and dyslipidaemia are significant comorbidities impacting on mortality and morbidity of cancer patients. (Barone et al., 2008; Zhou et al., 2010; Rao Kondapally Seshasai et al., 2011; Scappaticcio et al., 2017; Tao et al., 2020). Moreover, several antidiabetic agents are supposed to influence cancer development and progression, or to interfere with anticancer therapies. On the other hand, many oncological therapies may affect the endocrine balance (such as glucose homeostasis, dysthyroidism, hypogonadism) and the cardiovascular risk profile. (Kotecki et al., 2015; Jannin et al., 2019; Weickhardt et al., 2012; Weickhardt et al., 2013) Additionally, AEs related to anticancer therapy, such as anti-EGFR and mTOR inhibitors, may impact the clinical outcome, in turn tipping an equilibrium between the management of toxicities and clinical benefit of treatment (Abola and Prasad, 2014; Reig et al., 2014; Dabydeen et al., 2012; Petrelli et al., 2013; Granito et al., 2016; Lacouture et al., 2018). Likewise, an association between immune-related AEs (irAEs) and improved activity of ICIs has also been reported. It is therefore tempting to envision the early onset of irAEs as a potential predictive clinical marker for improved clinical outcome (Attia et al., 2005; Freeman-Keller et al., 2016; Teraoka et al., 2017; Haratani et al., 2018; Indini et al., 2019; Maher et al., 2019; Ricciuti et al., 2019; Eggermont et al., 2020). However, additional data are discordant, thus pinpointing the complexity underlying the impact on the clinical outcome played by irAEs (Freeman-Keller et al., 2016; Weber et al., 2017). Most likely, methodological caveats might have affected the data consistency and warrant *ad hoc* trials aiming to clarify the role of irAEs as surrogate markers of activity. Ancillary, endocrine toxicity appears to significantly contribute to irAEs. However, scanty shreds of evidence highlighted the relevance of the metabolic effect in this regard (Osorio et al., 2017; Teraoka et al., 2017; Haratani et al., 2018; Eggermont et al., 2020).

There is a lack of high quality evidences on factors able to predict the risk of metabolic toxicity. Nonetheless, patients aged < 65 years, preexisting DM and maximum blood glucose > 8.5 mmol/L (153 mg/dl) at baseline, BMI > 25, Asian race are more likely to develop hyperglycaemia when treated with AKT or dual PI3K/mTOR inhibitors (Aggarwal et al., 2014; Goldman et al., 2016; Khan et al., 2016).

Table 1
Current definitions and acknowledged criteria for diagnosing the main alterations of glucose and lipid metabolism.

Criteria defining prediabetes
• FPG 100 mg/dl to 125 mg/dl (IFG) Or • 2-h Plasma glucose during 75-g OGTT 140 mg/dl to 199 mg/dl (IGT) Or • HbA_{1C} 39-46 mmol/mol (5.7 – 6.4%)
Criteria defining diabetes*
• FPG > 126 mg/dl. Fasting is defined as no caloric intake for at least 8 h. Or • 2-h PG > 200 mg/dl during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. Or • HbA_{1C} > 47 mmol/mol (6.5%). The test should be performed in laboratory using a method that is NGSP certified and standardized to the DCCT assay. Or In Patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose > 200 mg/dl.
Criteria defining Metabolic Syndrome **
Presence of any three or more of the following: Blood glucose greater than 5.6 mmol/L (100 mg/dl) or drug treatment for elevated blood glucose HDL cholesterol < 1.0 mmol/L (40 mg/dl) in men, < 1.3 mmol/L (50 mg/dl) in women or drug treatment for low HDL-C Blood triglycerides > 1.7 mmol/L (150 mg/dl) or drug treatment for elevated triglycerides Waist > 102 cm (men) or > 88 cm (women) Blood pressure > 130/85 mmHg or drug treatment for Hypertension

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *American Diabetes Association, 2020; **NCEP (National Cholesterol Education Program) ATP 2005 – National Institute of Health

Moreover, tyrosine kinase inhibitor (TKI), especially nilotinib, are associated with an increased risk of hyperglycaemia in patients with a history of DM and prediabetes at baseline and age > 60 years; furthermore, dyslipidaemia at baseline was identified as an additional risk factor for development of hyperglycaemia on imatinib treatment (Rea et al., 2012). Interestingly, 76% of patients with ICI-related DM harbour polymorphisms of HLA class II on chromosome 6p21, in particular HLA-DR4 genotype. Remarkably, HLA DRB1*04:05-DQB1*04:01 seems to correlate with greater susceptibility for the development of fulminant type 1 DM (Chang et al., 2019). Collectively, validation on statistically powered studies hold the potential to corroborate these findings.

Notably, early and accurate assessment of the presence of prediabetes, DM and/or dyslipidaemia in each patient is important to put in place appropriate management strategies based on specific needs (Gallo et al., 2020).

Table 1 summarizes the current definitions for the diagnosis of main alterations of glucose and lipid metabolism.

3. Molecular mechanism of metabolic AEs: clinical implications from the pathophysiologic standpoint

Fig. 1 illustrates the current understanding of the network of pathways involved in cancer cell growth, as well as some of the targeted cancer therapies that inhibit them. The PI3K/AKT/mTOR pathway is activated by insulin to regulate blood glucose levels and glucose homeostasis in tissues (Busaidy et al., 2012). Agents that target the PI3K/AKT/mTOR pathway may lead to hyperglycaemia by interrupting the intracellular response to insulin, causing decreased glucose transport and glycogen synthesis, and increased glycolysis. In addition, chronic inhibition of mTOR has been linked to decreased proliferation and reduction of insulin producing pancreatic β-cells, contributing to both hyperglycaemia and the development of insulin resistance (Barlow and Nicholson, 2013).

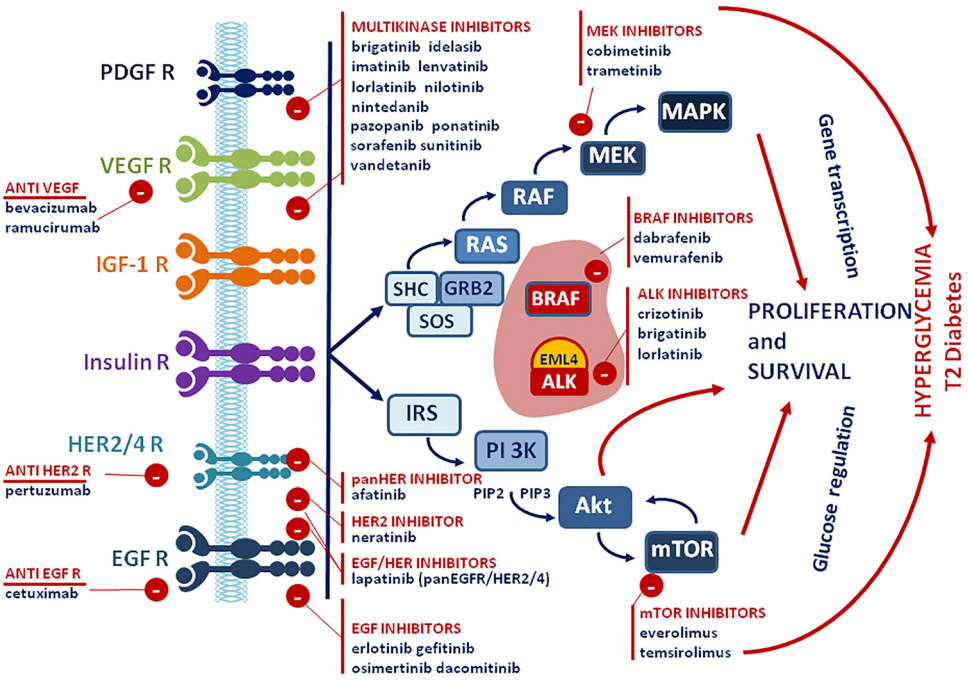

Fig. 1. Schematic diagram showing the main intracellular pathways downstream receptor tyrosine kinases (RTKs) involved in gene transcription, cell growth, differentiation and survival. Specific monoclonal antibodies and targeted therapies designed to inhibit cancer proliferation and promote apoptosis may interfere at multiple points (red circles) on signaling pathways involved in cellular control of glucose homeostasis. Figure reports examples of molecules acting on specific targets.

The search for molecular mechanisms explaining the metabolic effects of multikinase inhibitors is complex since drugs in the same class can be associated with both hypo- and hyperglycaemia. For example, the ABL inhibitor nilotinib causes hyperglycaemia in up to 40% of patients, while imatinib and dasatinib have been reported to cause hypoglycaemia. In part, the effects on glucose metabolism have been related to apoptosis of human β-cells observed *in vitro,* potentially dependent on activation of NFκB secondary to inhibition of PDGFR (Deangelo 2012). The example of rociletinib suggests that hyperglycaemia or even hyperinsulinemia might be caused by a metabolite with targets other than those of the parent molecule (Sequist et al., 2015). On the other hand, hypoglycaemia has been reported for TKIs such as sorafenib, pazopanib, sunitinib, vandetanib, and ponatinib (Ono et al., 2012; Dy and Adjei 2013). For some of these drugs, chemical structure analysis suggests a potential additional mechanism through modulation of farnesoid X receptor (FXR), involved in glucose and lipid homeostasis (Gabler et al., 2018).

ICIs contribute to immune response by modulating either inhibitory or stimulatory pathways that promote T-cell activation and proliferation (Fig. 2). Interestingly, signaling via both CTLA-4 and PD-1 converge on Akt, although the pathways and consequences of antibody inhibition are distinct (Parry et al., 2005). While PD-1 signaling can directly antagonize PI3K, the effects of CTLA-4 occur via a phosphatase called PP2A. This suggests that molecules inhibiting CTLA-4 or PD-1 follow separate cascades and differ in terms of the stage of T cell activation. Accordingly, anti-CTLA-4 and anti-PD-1/PD-L1 antibodies have recently been termed 'immune enhancers' and 'immune normalizers', respectively (Sanmamed and Chen 2018). This implies that a combination therapy with PD-1 and CTLA-4 inhibitors might increase the incidence of irAEs (Weinmann and Pisetsky 2019). Indeed, owing to their ability to unleash T cells to fight cancer, ICIs can also trigger autoimmune-like diseases (Barroso-Sousa et al., 2018). While hypophysitis and thyroid disorders are the most frequent endocrine AEs, autoimmune DM is a rare but potentially life-threatening complication, as diabetic ketoacidosis is often the first presentation (Byun et al., 2017; Quandt et al., 2020). In some cases, the hyperglycaemic events may result from concomitant treatments of irAEs with glucocorticoids; nevertheless, autoimmune destruction of pancreatic islet cells and subsequent type 1 DM can occur, leading to decreased insulin levels and hyperglycaemia (Gaudy et al., 2015; Hughes et al., 2015). Similarities with classic type 1 DM include the presence of islet auto-antibodies and susceptible HLA genotypes (Clotman et al., 2018). According to the mechanisms outlined above, autoimmune DM appears more frequently associated with blockade of PD-1 (nivolumab, pembrolizumab) and PD-L1 (atezolizumab, durvalumab) or combination therapy than with anti-CTLA-4 (ipilimumab) therapy (Haanen et al., 2017; Stamatouli et al., 2018), highlighting the importance of the PD-1/PD-L pathway in maintaining self-tolerance against pancreatic islets. Interestingly, spectrum and grade of irAEs seem to follow a specific time pattern for anti-CTLA-4 and PD-l/PD-L1 inhibitors (Weber et al., 2012; Weber et al., 2016), which may reflect the stage of T cell activation and the overall disease progression. Importantly, recent studies have started to point out differences in early- versus late-effects to this class of drugs, suggesting that late-irAEs might be correlated with progression-free survival and overall survival in long-term responsers (Nigro et al., 2020). The clinical significance of DM resulting from immune checkpoint blockade is expected to increase, as these novel anticancer agents are increasingly employed at an earlier stage of the disease.

4. Novel anti-cancer agents and metabolic toxicities

Despite the strong evidence in the literature regarding the potential AEs of novel anti-cancer agents on lipid and glucose metabolism (Verges et al., 2014; Shariff et al., 2019; Monami et al., 2020), these metabolic toxicities are often underestimated in the clinical practice, with consequent increased risk of inappropriate patient monitoring and late interventions.

The purpose of this section is to explore this phenomenon in a systematic way and summarize clinical data in tables to be quickly consulted by clinicians.

In this regard, we first classified the above-mentioned drugs according to their mechanisms of action and then reviewed the "Summaries of Product Characteristics" (SmPCs) released by the European Medicines Agency (EMA) by October 31, 2019 of the approved drugs belonging to each category.

In particular, we focused on iatrogenic glucose metabolism alterations, including DM, hyper-/hypo-glycaemia and diabetic ketoacidosis (DKA), as well as on the onset of hypercholesterolemia and hypertriglyceridemia as major lipid disorders. Frequencies of such AEs were defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10),

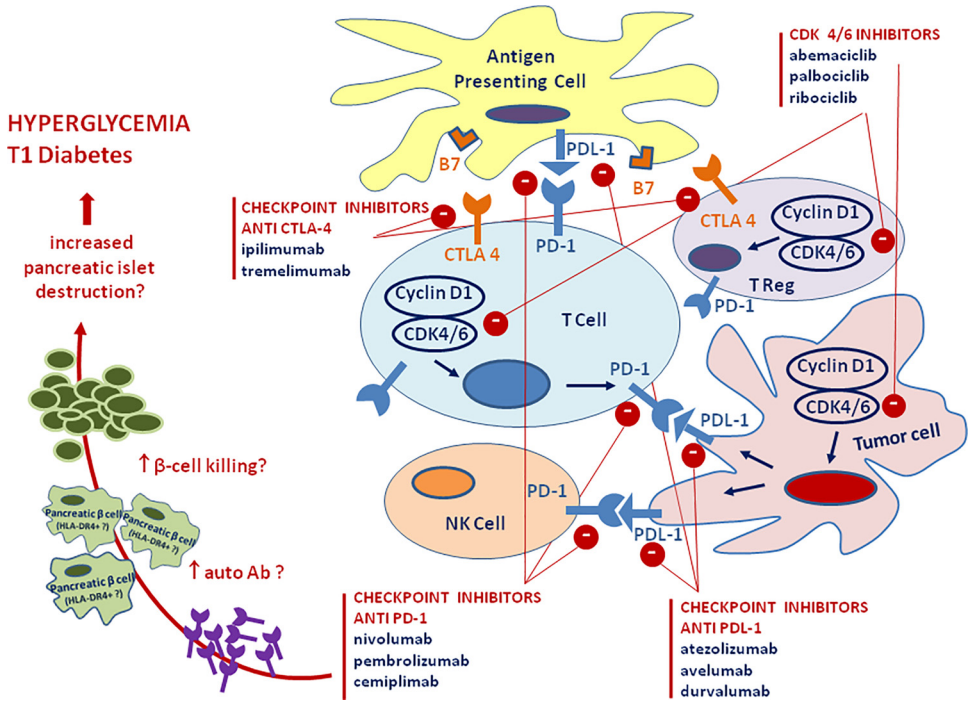

Fig. 2. Schematic diagram recapitulating the main targets of ICIs. These multiple pathways can either trigger immune recognition and killing, or immune tolerance and evasion. Checkpoint inhibitors are regulatory molecules that modulate T cell stimulation or inhibition, thereby preventing inadequate responses and promoting self-tolerance. Some of the most representative molecules and their targets are reported in Fig. 2.

uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) or very rare (< 1/10,000), according to the EMA SmPC's indications. "Not reported" (NR) expression was used to define those AEs whose occurrence was described in the SmPC without frequency specification.

Tables 2–6 summarize the agents for which the SmPCs reported at least one of the selected AEs. Indeed, the drug categories shown in Table 2 were all found to be correlated with the onset of at least one metabolic AE, with multikinase inhibitors being associated with the highest number of explored AEs (6 out of 7); on the other hand, the administration of angiogenesis inhibitors correlated with the occurrence of hyperglycaemia only.

With respect to ICIs (Table 3), the onset of hyperglycaemia and DM, with or without development of DKA, was described for most drugs, even if at variable frequencies. In this regard, the incidences of both DM and DKA reported in the SmPCs were apparently lower than those observed in the clinical practice and described by other authors (Wright et al., 2018; Akturk et al., 2019; Stamatouli et al., 2018; Perdigoto et al., 2019) Interestingly, nivolumab monotherapy was found to be associated with glycidic disorders, while no data were available for ipilimumab used as a single agent; however, the administration of the anti-CTLA4 monoclonal antibody in combination with nivolumab correlated with common DM onset.

When focusing on TKIs, we observed a variable incidence of metabolic toxicities (Table 4); for instance, some agents were associated with common/very common glycidic disorders (i.e. brigatinib, sorafenib, sunitinib, vandetanib), while lipid metabolism alterations were common/very common for ruloxitinib, idelasib, lenvatinib and lorlatinib. Notably, both glycidic and lipid disorders have been described during nilotinib and ponatinib administration. In a similar fashion, the incidence of metabolic AEs turned out extremely variable during treatment with other targeted agents, as shown in Table 5 and 6. However, inhibitors of mTOR pathway were not surprisingly associated with the highest frequencies of metabolic disorders (Sivendran et al., 2014).

Table 3
Metabolic AEs associated with ICIs.

AGENT	DIABETES	HYPER-GLYCEMIA	DKA	HYPO-GLYCEMIA
Nivolumab	**UC**	**VC**	**R**	**C**
Nivolumab + ipilimumab	**C**	**VC**	**UC**	**VC**
Pembrolizumab	**UC**	**NR**	**UC**	-
Cemiplimab	**UC**	**NR**	**UC**	-
Atezolizumab	**UC**	**C**	**UC**	-
Durvalumab	**UC**	-	-	-
Avelumab	**UC**	**C**	**UC**	-

Informations available in EMA's "Summaries of Product Characteristics".
VC, very common (≥ 1/10); C, common (≥ 1/100 to < 1/10); UC, uncommon (≥ 1/1,000 to < 1/100); R, rare (≥ 1/10,000 to < 1/1,000); NR, not reported frequency; -: not reported toxicity.

Table 2
Anti-cancer agents and metabolic AEs.

DRUG CLASS	DIABETES	HYPER-GLYCEMIA	DKA	HYPO-GLYCEMIA	HYPER-CHOLESTEROLEMIA	HYPER-TRIGLYCERIDEMIA
ICIs	**YES**	**YES**	**YES**	**YES**	NO	NO
Monoclonal antibodies	NO	**YES**	NO	NO	**YES**	**YES**
Kinase inhibitors	NO	**YES**	NO	NO	**YES**	**YES**
Multikinase inhibitors	**YES**	**YES**	NO	**YES**	**YES**	**YES**
mTOR inhibitors	**YES**	**YES**	NO	NO	**YES**	**YES**
PARP inhibitors	NO	NO	NO	NO	**YES**	NO
Proteosome inhibitors	**YES**	**YES**	NO	NO	NO	NO
Angiogenesis inhibitors	NO	**YES**	NO	NO	**YES**	NO

Informations available in EMA's "Summaries of Product Characteristics"

Table 4
Metabolic AEs associated with kinase inhibitors.

DRUG CLASS	AGENT	DIABETES	HYPER-GLYCEMIA	DKA	HYPO-GLYCEMIA	HYPER-CHOLESTEROLEMIA	HYPER-TRIGLYCERIDEMIA
MEK inhibitors	**cobimetinib**	-	**C***	-	-	-	-
	trametinib	-	**C***	-	-	-	-
BRAF inhibitors	**dabrafenib**	-	**C**	-	-	-	-
JAK inhibitor	**ruloxitinib**	-	-	-	-	**VC**	**VC**
Multi-kinase inhibitors	**brigatinib**	-	**VC**	-	-	-	-
	idelasib	-	-	-	-	-	**VC**
	imatinib	-	**UC**	-	-	-	-
	lenvatinib	-	-	-	-	**C**	-
	lorlatinib	-	-	-	-	**VC**	**VC**
	nilotinib	**C**	**C**	-	**UC**	**C, VC**	**C, VC**
	pazopanib	-	-	-	**UC**	-	-
	ponatinib	-	**C**	-	-	-	**C**
	sorafenib	-	-	-	**C**	-	-
	sunitinib	-	-	-	**C**	-	-
	vandetanib	-	**C**	-	-	-	-

Informations available in EMA's "Summaries of Product Characteristics".
VC, very common (≥ 1/10); C, common (≥ 1/100 to < 1/10); UC, uncommon (≥ 1/1,000 to < 1/100); NO, not reported toxicity. *AEs described in combination with BRAF-inhibitors.

5. Expert panel recommendations

Many of the commonly used target therapies and ICIs exert different effects on glucose and lipid metabolism, as well as on blood pressure and cardiovascular system (Verges et al., 2014; Ruggeri et al., 2019). As a consequence, diabetologists, oncologists and pharmacologists need to co-operate for early patient care and appropriate management (Gallo et al., 2016). The panel of experts identified by AIOM, AMD and SIF put forward some recommendations on the most relevant metabolic AEs of cancer patients who are candidates or are already on treatment with targeted therapies or ICIs.

5.1. Pre-treatment assessment and ongoing monitoring

Appropriate screening at baseline is highly recommended for every patient starting a target therapy or immunotherapy, to identify subjects requiring close monitoring of glucose and lipid metabolism (Table 7) (Breccia et al., 2014; Iurlo et al., 2015). Any patient without previously known DM, especially if at increased risk for, should control fasting plasma glucose every 2 weeks during the first month and then monthly thereafter for the duration of the treatment, i.e., HbA_{1c} at baseline, at 3 months, and therefore annually if normal. In patients with previously known DM, self-monitoring of blood glucose (SMBG) should be proposed or reinforced, alternating fasting and 2 -hs post-prandial glucose levels measurements (Verges et al., 2014). Patients should also be appropriately educated to recognize symptomatic hypo- or hyperglycaemias, and to manage these events appropriately. In special circumstances, flash glucose monitoring (FGM) or continuous glucose monitoring (CGM) might enable patients to avoid severe hypoglycaemia and glucose deviations from normal values.

Albeit uncommon, the clinical onset of ICIs-induced DM is acute, with an abrupt and steep rise in blood glucose levels, frequently with diabetic ketoacidosis (DKA), manifesting a medical emergency (fulminant diabetes). The median onset of ICI-related DM is 5 months (Stamatouli et al., 2018; Kotwal et al., 2019). Even if blood glucose monitoring for the first 6-12 months of therapy in patients receiving anti-PD-1/PD-L1 therapy is highly recommended by current guidelines, diagnostic delay may be life-threatening. Therefore, patient education for prompt recognition of symptoms of hyperglycaemia (polyuria, polydipsia, blurred vision, weight loss, malaise) and/or DKA (nausea, vomiting, abdominal pain, fatigue) is crucial and urgent medical referral is even more important (Castinetti et al., 2019). Since patients with pre-existing type 2 DM may develop immune-mediated DM when treated with ICIs, this population may benefit from FGM/CGM to early identify a brisk worsening of glucose control (Zezza et al., 2019).

If hyperglycaemia occurs in a patient without well-established risk factors, assessment of urine ketones, auto-antibodies against glutamic acid decarboxylase (anti-GAD), islet cells (ICA) and insulin, as well as serum insulin and C-peptide, is recommended (Ruggeri et al., 2019). Insulin therapy should be promptly started if ICIs-induced DM is suspected, and urgent endocrine consultation is appropriate. Hyperglycaemic hyperosmolar state and diabetic ketoacidosis, which represent the most serious and life-threatening emergencies in subjects with diabetes, should be managed according to the local guidelines. Both disorders are characterized by severe insulinopenia and very high blood glucose levels: as a consequence, aggressive rehydration with intravenous fluids (ie, 0.9% NaCl isotonic saline), insulin therapy, and electrolyte replacement are the cornerstones of their acute management. Pancreatic amylase and lipase may also be of help in cases of fulminant diabetes, whereas diagnostic imaging of the pancreas and

Table 5
Metabolic AEs associated with monoclonal antibodies.

AGENT	DIABETES	HYPER-GLYCEMIA	DKA	HYPO-GLYCEMIA	HYPER-CHOLESTEROLEMIA	HYPER-TRIGLYCERIDEMIA
Brentuximab (anti-CD30)	-	**C**	-	-	-	-
Panitumumab (anti-EGFR)	-	**C**	-	-	-	-
Rituximab (anti-CD20)	-	**C**	-	-	**C**	-
Siltuximab (anti-IL6)	-	-	-	-	**C**	**VC**

Informations available in EMA's "Summaries of Product Characteristics".
VC, very common (≥ 1/10); C, common (≥ 1/100 to < 1/10); NO, not reported toxicity.

Table 6
Metabolic AEs associated with other targeted agents.

CLASS	AGENT	DIABETES	HYPER-GLYCEMIA	DKA	HYPO-GLYCEMIA	HYPER-CHOLESTEROLEMIA	HYPER-TRIGLYCERIDEMIA
PARP inhibitors	**rucaparib**	-	-	-	-	**C**	-
mTOR inhibitors	**everolimus**	**C**	**VC**	-	-	**VC**	**C**
	temsirolimus	**C**	**VC**	-	-	**VC**	**VC**
proteosome inhibitors	**bortezomib**	**UC**	**C**	-	**UC**	-	-
	carfilzomib	-	**VC**	-	-	-	-
angiogenesis inhibitor	**bevacizumab**	-	**NR**	-	-	-	-
	aflibercept	-	-	-	-	**UC**	-

Informations available in EMA's "Summaries of Product Characteristics".
VC, very common (≥ 1/10); C, common (≥ 1/100 to < 1/10); UC, uncommon (≥ 1/1,000 to < 1/100); NR, not reported frequency; NO: not reported toxicity.

Table 7
Recommendations for cancer patients starting a target therapy or immunotherapy.

Pre-treatment assessment
FPG, HbA_{1c}, LDL-C, triglycerides & BP
Ongoing assessment
Patients without previously known DM
FPG & BP every 2 weeks during the 1st month and then once every month for 6-12 months
HbA_{1c} after 3 months and then every year if normal
Education for early recognition of symptoms of hyperglycemia or DKA, if on ICIs
Patients with previously known DM
FPG, HbA_{1c}, LDL-C, triglycerides & BP every 3 months
Reinforce SMBG (FPG & PPG); consider FGM/CGM
Provide diabetes self-management education and support
Consider overall CV risk
Patients who develop hyperglycaemia on ICIs
urine ketones
ICA, anti-GAD, and anti-insulin Ab
Insulin, C-peptide
Pancreatic amylase & lipase

AntiGAD, auto-antibodies against glutamic acid decarboxylase; BP, blood pressure; CGM, continuous glucose monitoring; CV, cardiovascular; DKA, diabetic ketoacidosis; FGM, flash glucose monitoring; FPG, fasting plasma glucose; ICA, anti-islet cells antibodies; ICIs, ICIs; LDL-C, low density lipoprotein cholesterol; PPG, post-prandial glucose; SMBG, self-monitoring of blood glucose.

corticosteroid therapy are not indicated. Patients should not discontinue ICIs therapy while initiating insulin therapy, except in most severe cases (G3-G4), where these drugs could be delayed by a few days until reduction of toxicity to G1 (Haanen et al., 2017; Puzanov et al., 2017; Brahmer et al., 2018; Higham et al., 2018). A 'wallet card' for patients on immunotherapy should be considered to support communication of the risks associated with treatment.

5.2. Glycaemic, blood pressure, and lipid goals

Glycaemic targets for cancer patients with DM should be individualized according to life expectancy, vascular co-morbidities, patient attitude and resources, and expected treatment effects (Inzucchi et al., 2015). Since the prognosis of patients with cancer is longer than in the past, it can be recommended an HbA_{1c} target of 53-58 mmol/mol (7.0-7.5%) for many patients aged less than 75 years, provided that life expectancy will be long enough. In older patients and/or when the prognosis is poor, HbA_{1c} and glucose levels targets should be relaxed with the aim of avoiding symptomatic hypo- hyperglycaemia, DKA, and risk of infection (Gallo et al., 2018). Recommended blood pressure levels for patients with DM are generally < 140 mmHg for systolic and < 90 mmHg for diastolic. Cancer patients with DM and with a prognosis > 1 year may benefit from treatment of hyperlipidaemia, especially if at high risk of cardiovascular AEs based on the SCORE system (https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts) (Busaidy et al., 2012; Breccia et al., 2016).

5.3. Antidiabetic therapy

Metformin is typically the first-line agent for the treatment of type 2 DM also for patients with cancer, provided hyperglycaemia is mild, no contraindications subsist, and the patient is not intolerant to the drug. When choosing second-line agent instead of or in association with metformin, the risk profile of each antidiabetic drug (ADD) should be taken into account, together with the most common AEs of target therapies employed for the underlying oncological disease. To cite the most common examples, metformin and GLP1-receptor agonists should be avoided in patients with already existing nausea, diarrhoea, or abdominal pain, whereas the main drawback of thiazolidinediones (pioglitazone, rosiglitazone) is the occurrence of heart failure or peripheral edema. Conversely, patients at increased risk of fluid depletion should not be treated with SGLT2-inhibitors. Finally, sulphonylureas, meglitinides, but also metformin should be avoided in people with liver or renal failure (Gallo et al. 2018).

A possible algorithm for the management of hyperglycaemia induced by cancer therapy is proposed in Fig. 3, with SGLT2-inhibitors and GLP1-receptor agonists suggested as second line therapies if the risk of heart failure or atherosclerotic cardiovascular disease predominates, respectively. Insulin is always a safe option, especially if hyperglycaemia is severe.

Obviously, life-long insulin treatment is the only available therapy for patients with type 1 or ICI-induced DM (with a basal-bolus regimen), as well as the best option for many patients with secondary DM. Appropriate education on SMBG, insulin conservation and use, and an approach for hyperg- or hypoglycemia, shall be an integral component of DM management.

Finally, since most oral ADDs and some TKIs are metabolised by the cytochrome P450 system (CYP), cancer patients with DM are at enhanced risk of drug-drug interactions. Combination therapies may therefore affect both the anti-diabetic and the anti-cancer drug levels. In patients with DM treated with imatinib, for example, the tissue exposure to glibenclamide, thiazolidinediones, and meglitinides may increase (Haouala et al., 2011). Furthermore, caution must be taken when prescribing fibrates and lipid-lowering agents (Busaidy et al., 2012). Pravastatin and rosuvastatin should be preferred to other statins (due to the risk of competitive inhibition of CYP 3A4), using fenofibrate in case of statin intolerance or hypertrygliceridemia (Haouala et al., 2011; Wiggins et al., 2016). Ezetimibe could represent a reasonable option as an add-on to statins, when cholesterol is not adequately controlled (Breccia et al., 2016).

6. Conclusions

Growing available options in terms of tailored targeted treatment and immunotherapy deeply improved the clinical outcome of cancer patients, though hijacking the toxicity profile to uncovered landscapes. Therefore, deeper insight aiming to a more comprehensive pathophysiological characterization of the mechanism underlying metabolic AEs is needed in order to support patient management. Meanwhile, a

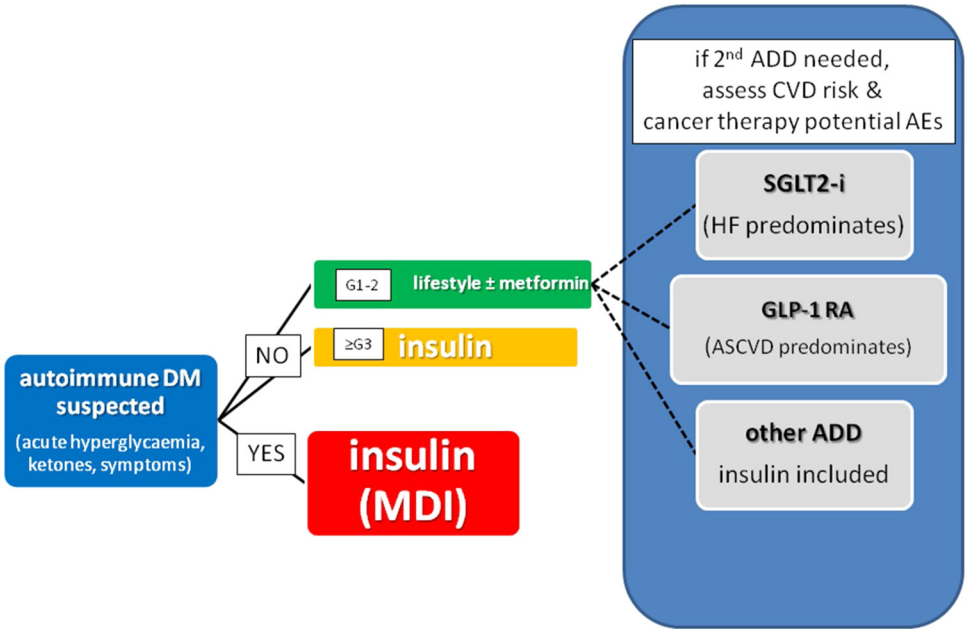

Fig. 3. Management of cancer therapy induced hyperglycaemia.
AES, adverse event; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HF, heart failure; SGLT2-i, sodium-glucose transport 2 inhibitors; MDI, multiple daily injections; G1: glycaemia ULN-160 mg/dL; G2: 160-250 mg/dL; G3: 250-500 mg/dL; G4: ≥500 mg/dL (from: Common Terminology Criteria for Adverse Events, Version 4.03 - http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

stepwise approach to the subjects with targeted- and immune- related metabolic AEs holds the great potential to uncover the complex systemic involvement of novel therapies for optimal management by an integrated multidisciplinary team.

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Declaration of Competing Interest

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