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REVIEW ARTICLE

Chemotherapy, targeted therapy and immunotherapy: Which drugs can be safely used in the solid organ transplant recipients?

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SUMMARY

In solid organ transplant recipients, cancer is associated with worse prognosis than in the general population. Among the causes of increased cancer-associated mortality, are the limitations in selecting the optimal anticancer regimen in solid organ transplant recipients, because of the associated risks of graft toxicity and rejection, drug-to-drug interactions, reduced kidney or liver function, and patient frailty and comorbid conditions. The advent of immunotherapy has generated further challenges, mainly because checkpoint inhibitors increase the risk of rejection, which may have life-threatening consequences in recipients of life-saving organs. In general, there are no safe or unsafe anticancer drugs. Rather, the optimal choice of the anticancer regimen results from a careful risk/benefit assessment, from the awareness of potential pharmacokinetic and pharmacodynamic drug-to-drug interactions, and of the risk of drug overexposure in patients with kidney or liver dysfunction. In this review, we summarize general principles that may help the oncologists and transplant physicians in the multidisciplinary management of recipients of solid organ transplantation with cancer who are candidates for chemotherapy, targeted therapy, or immunotherapy.

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Introduction

Mortality from cancer in solid organ transplant (SOT) recipients is increased compared with that expected in the general population [1-3]. Among the various factors affecting the poor prognosis in SOT recipients, are the hurdles in selecting the most efficacious anticancer treatment, namely the risk of graft toxicity and rejection, drug-to-drug interactions (DDI) with concurrent anti-rejection treatment, reduced kidney or liver function, patients' frailty and comorbid conditions [2]. These concerns may lead to suboptimal use of the available therapies and to a generally less aggressive cancer treatment, which at least in part, explain the observed mortality excess in transplant recipients in some studies [2].

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Therefore, it is critical for health-care providers to understand which chemotherapy, targeted therapy, and immunotherapy drugs can be safely used in SOT recipients, what are the best treatment strategies and those that should be avoided. In this review, we provide a concise summary of principles that may help the oncologist and the transplant physician in the decision-making process on selecting the anticancer treatment regimens in SOT recipients.

Chemotherapy and targeted therapy

Graft toxicity

SOT recipients are at increased risk of chemotherapy-induced nephrotoxicity because of the vasoconstrictive effects of calcineurin inhibitors (CNI). This makes SOT recipients more susceptible to volume depletion caused by diarrhea that occurs after chemotherapy, and to other conditions that are precipitated by hypovolemia, such as hyperuricemia, tumor lysis syndrome, precipitations of crystals within tubular lumens, and increased nephrotoxic drug concentration in renal medulla and interstitium. In kidney transplant recipients, the presence of arteriolar lumen narrowing induced by chronic rejection and/or CNI nephrotoxicty, and the presence of renal artery stenosis may further aggravate the consequences of hypovolemic conditions.

The anticancer drugs that most commonly cause nephrotoxic effect by inducing AKI or necrosis include platinum analogs (mainly cisplatin), ifosfamide, zoledronic acid, and the antimetabolite pemetrexed [4]. These drugs can induce cellular toxicity as a result of their transport through tubular cells, induction of mitochondrial injury, oxidative stress, and activation of apoptotic signaling pathways within cells [4]. Only few reports on the use of platinum analogs in kidney transplant recipients have been reported so far. These retrospective series of kidney transplant recipients with urothelial carcinoma or head-neck cancer showed that drug toxicities were acceptable, and nephrotoxicity was mild [5-7], but most cases had preserved graft function.

Hypomagnesemia is the most frequent electrolyte alteration caused by cisplatin, the incidence ranging between 60% and 90% [8]. Hypomagnesemia is also strongly associated with the epidermal growth factor receptor (EGFR) inhibitor cetuximab [9]. More than one-half of cetuximab-treated patients develop hypomagnesemia, and nearly 100% of patients have some decline in serum magnesium concentrations [9]. Kidney transplant recipients may be particularly susceptible to magnesium wasting induced by anticancer drugs because of the high prevalence of hypomagnesemia, which is common early after transplantation, and may persists in at least 20% of recipients, being related to gastrointestinal losses diarrhea and co-medications, including proton-pump inhibitors, loop diuretics, and CNI [9].

The angiogenesis inhibitor bevacizumab and the nucleotides analogs gemcitabine can injure the renal vasculature and cause thrombotic microangiopathy (TMA) [9]. This risk is higher in kidney transplant recipients than in nontransplanted individuals possibly due to the concomitant risk factors for TMA, such as the use of CNI or mTORi, the presence of chronic antibody-mediated rejection, or genetic factors related to the primary renal disease [10].

The anthracyclines (doxorubicin), EGFR inhibitors, Vinca Alkaloids, and BRAF-MEK inhibitors (see Table 1) have cardiotoxic effects that may be particularly risky in heart transplant recipients and in many kidney transplant recipients because of the high prevalence of coronary artery disease in patients with chronic kidney disease.

BRAF-MEK inhibitors, ALK inhibitors, and EGFR inhibitors (see Table 1) are the anticancer drugs with highest hepatotoxic potential, although occasional severe drug-induced hepatotoxicity have been described with other agents, such as sorafenib [42,43]. The BRAF-MEK inhibitors trametinib, ALK inhibitors, EGFR inhibitors, in addition to CDK 4/6 inhibitors may also cause interstitial pneumonia (see Table 1).

In summary, platinum analogs, particularly cisplatin, are the drugs with most toxic potential because they are associated with high risk of acute tubular injury (AKI), particularly in kidney transplant recipients. Because of their high nephrotoxic potential, the choice of a platinum analogs-based chemotherapy should take into consideration the risk-benefit ratio, based on the expected response to treatment, cancer prognosis, and life expectancy, together with the baseline kidney function.

Pharmacokinetic (PK) drug-to-drug interaction (DDI)

There are five «must-know» key principles of DDI that should be considered in managing DDI in SOT transplantation.

The first principle is that most PK DDI are caused by perturbation in the activity/expression of metabolic enzymes and/or drug transporters (efflux or influx

Table 1. Chemotherapy and targeted anticancer drugs: relevant characteristics for solid organ transplant recipients.

Drug	Adjustment for renal dysfunction	Adjustment for hepatic dysfunction	Interactions with CYP 3A4 or P-Glycoprotein	Interactions with immunosuppressive drugs	Warnings for toxicity in transplant patients
Solid cancers					
Platinum analogs	↙ [11]	**X**	**X**		**Myelosuppression Nephrotoxicity**
Cisplatin (iv)				=	Neurotoxicity, ototoxicity
Carboplatin (iv)				=	Peripheral neuropathy
Oxaliplatin (iv)				=	Peripheral neuropathy
Taxanes	X	↙ [12]	**CYP 3A4 inducer**		**Myelosuppression**
Docetaxel (iv)				↓	Fluid retention, hand-foot syndrome
Paclitaxel (iv)				↓	Peripheral neuropathy
Vinca Alkaloids	X	↙ [12]	**CYP 3A4 inhibitor**, P-Glycoprotein	↑	**SIADH, cardiac ischemia**
Vinorelbine (iv)					Neurotoxicity
Vincristine (iv)					
Vinblastine (iv)					Myelosuppression
Vinflunine (iv)				↑ CTM (Cyclosporine [13])	Myelosuppression
Anthracyclines					**Cardiotoxicity**
Epirubicin (iv)	↙	↙ [12]	CYP 3A4 inhibitor	↑	
Doxorubicin (iv)	X	↙ [12]	CYP 3A4 inhibitor P-Glycoprotein	↑ A (Cyclosporine [14])	Hand-foot syndrome
Topoisomerase Inhibitors					**Myelosuppression**
Irinotecan (iv)	X	↙ [12]	CYP 3A4 inhibitor	↑	Increased toxicity in patients with UGT1A1*28 polymorphism
Topotecan (iv)	↙ [15]	X	P-Glycoprotein	↑ A (Cyclosporine [16])	
Antimetabolites					**Myelosuppression, mucositis**
Pemetrexed (iv)	↙ [17]	NA	X	=	Nephrotoxicity, hand-foot syndrome, skin rash
Methotrexate (iv)	↙ [11]	↙ [18]	X	=	Hepatotoxicity, AKI
Nucleotides Analogs					**Myelosuppression**
Gemcitabine (iv)	X	↙ [12]	X	=	Flu-like symptoms, pulmonary toxicity
5-Fluorouracil (iv)	X	X	X	=	Increased toxicity in patients with DPYD polymorphism Coronary artery vasospasms
Capecitabine (po)	↙ [19]	X	X	=	Increased toxicity in patients with DPYD polymorphism Nephrotoxicity, coronary artery vasospasms, hand-foot syndrome
Trabectedin (iv)	X	↙ [20]	CYP 3A4 inhibitor	↑	Hepatotoxicity
Bleomycin (iv)	↙ [21]	X	CYP 3A4 inhibitor	↑	Pulmonary fibrosis, fever
Eribulin (iv)	↙ [22]	↙ [23]	X	=	Myelosuppression, neurotoxicity

Table 1. Continued.

Drug	Adjustment for renal dysfunction	Adjustment for hepatic dysfunction	Interactions with CYP 3A4 or P-Glycoprotein	Interactions with immunosuppressive drugs	Warnings for toxicity in transplant patients
EGFR inhibitors					**Diarrhea, skin rash, dyspnea**
Osimertinib (po)	X	X	CYP 3A4 inducer P-Glycoprotein	↓ CTM (Sirolimus [24])	Interstitial pneumonia
Gefitinib (po)	X	X	CYP 3A4 inhibitor P-Glycoprotein	↑	Hepatotoxicity, Interstitial pneumonia
Erlotinib (po)	X	↙ [25]	CYP 3A4 inhibitor P-Glycoprotein	↑	Interstitial pneumonia
Afatinib (po)	X	X	P-Glycoprotein	↑ CTM (Cyclosporine)	Interstitial pneumonia
MET inhibitors					
Cabozantinib (po)	X	↙ [26]	CYP 3A4 inhibitor P-Glycoprotein	↑	Myelosuppression, electrolyte imbalance
BRAF-MEK inhibitors	**X**	**X**	**CYP 3A4 inducer P-Glycoprotein**	↓	**Drmatological toxicities, hepatotoxicity, thromboembolism, LV dysfunction, acute interstitial nephritis,**
Dabrafenib (po) *Trametinib (po)*					Hyperglycemia, uveitis Retinal detachment, Interstitial pneumonia
ALK inhibitors			**CYP 3A4 inhibitor**	↑	**Hepatotoxicity, bradycardia**
Crizotinib (po)	↙ [27]	↙ [28]		↑ CTM (Sirolimus [29])	Neurotoxicity, pseudo-acute kidney injury
Ceritinib (po)	X	↙ [22]		↑CTM (Cyclosporine, Tacrolimus, Sirolimus [14], Everolimus)	Interstitial pneumonia
Alectinib (po)	↙ [20]	↙ [21]	P-Glycoprotein	↑	Interstitial pneumonia
Angiogenesis inhibitors					**Hypertension, proteinuria, hemorrhage, thrombosis**
Bevacizumab (iv)	X	X	X	=	Wound dehiscence
Sunitinib (po)	X	X	CYP 3A4 inhibitor	↑	Dermatological toxicities, cardiotoxicity
Axitinib (po)	X	↙ [31]	CYP 3A4 inhibitor	↑	Cardiotoxicity, thyroid dysfunction, hepatotoxicity, PRES
Tivozanib (po)	X	↙	CYP 3A4 inhibitor	↑	Cardiotoxicity, hand-foot syndrome, hepatotoxicity, PRES
Sorafenib (po)	X	X	CYP 3A4 inhibitor P-Glycoprotein	↑	Dermatological toxicities, cardiotoxicity, hypoglycemia
Pazopanib (po)	X	↙ [32]	CYP 3A4 inhibitor P-Glycoprotein	↑ A (Cyclosporine [33])	Cardiotoxicity, hepatotoxicity, PRES
EGFR inhibitors					**Cardiotoxicity, hepatotoxicity**

Table 1. Continued.

Drug	Adjustment for renal dysfunction	Adjustment for hepatic dysfunction	Interactions with CYP 3A4 or P-Glycoprotein	Interactions with immunosuppressive drugs	Warnings for toxicity in transplant patients
Trastuzumab (iv)	X	X	X	=	Nephrotoxicity, pneumotoxicity, ototoxicity, cardiotoxicity
Pertuzumab (iv)	X	NA	X	=	Neurotoxicity, cough, dyspnea
Lapatinib (po)	X	↙	CYP 3A4 inhibitor P-Glycoprotein	↑	Hand-foot syndrome, left ventricular dysfunction, Interstitial pneumonia, ototoxicity
Cetuximab (iv)	NA	NA	X	=	Hand-foot syndrome, sudden cardiac arrest, hypomagnesemia
Panitumumab (iv)	NA	NA	X	=	Hand-foot syndrome
CDK 4/6 inhibitors			**CYP 3A4 inhibitor**	↑	**Myelosuppression**
Palbociclib (po)	X	X		↑	
Abemaciclib (po)	X	↙		↑	Interstitial pneumonia, hepatotoxicity
Ribociclib (po)	↙	↙ [34]		↑ CTM (Sirolimus [35])	Interstitial pneumonia
PARP inhibitors					
Olaparib (po)	↙ [35]	X	CYP 3A4 inhibitor	↑	Myelosuppression, central nervous system effects
mTOR-inhibitors					
Everolimus (po)	X	↙ [36]	CYP 3A4 inhibitor P-Glycoprotein	↑ CTM (Cyclosporine [37])	Myelosuppression, hypertension, hemorrhage
Hematologic cancers					
Alkylating agents					**Myelosuppression**
Melphalan (iv;os)	↙	X	X	=	Myelosuppression Mucositis
Cyclophosphamide (iv;os)	↙	X	X	=	Myelosuppression Cystitis
Chlorambucil (os)	X	↙	X	=	Myelosuppression
Ifosfamide(iv)	↙	↙	X	=	Myelosuppression Nephrotoxicity Cystitis Neurotoxicity
Busulfan (iv;os)	X	X	X	=	Myelosuppression
Dacarbazine (iv)	↙	X	X	=	Myelosuppression
Procarbazine (iv)	X	↙	X	=	
Antimetabolites					**Myelosuppression**
Fludarabine (iv; os)	↙	X	X	=	Myelosuppression neurotoxicity
Cytarabine (iv)	↙	↙	X	=	Myelosuppression Mucositis
Bendamustine (iv)	X	X	X	=	Myelosuppression
Hydroxycarbamide (os)	↙	X	X	=	Myelosuppression
Anthracyclines					**Myelosuppression Cardiotoxicity**
Daunorubicin(iv)	↙	↙	X	=	Myelosuppression Cardiotoxicity

Table 1. Continued.

Drug	Adjustment for renal dysfunction	Adjustment for hepatic dysfunction	Interactions with CYP 3A4 or P-Glycoprotein	Interactions with immunosuppressive drugs	Warnings for toxicity in transplant patients
Mitoxantrone (iv)	X	X	X	=	Myelosuppression
Idarubicin (iv)	✓	✓	X	=	Myelosuppression Cardiotoxicity
Topoisomerase Inhibitors II					**Myelosuppression**
Etoposide (iv)	✓	X	CYP 3A4 inhibitor, P-Glycoprotein	↑ CTM (Cyclosporine [38,39])	Myelosuppression Cutaneous
Nucleotides Analogs					**Myelosuppression**
Azacitidine (sc)	X	X	X	=	Myelosuppression
Decitabine (iv)	X	X	X	=	Myelosuppression
Clofarabine (iv)	✓	✓	X	=	Myelosuppression

AKI, acute kidney injury; ALK, anaplastic lymphoma kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CDK, cyclin-dependent kinase; CYP, cytochrome P450; DPYD, Dihydropyrimidine dehydrogenase; EGFR, epidermal growth factor receptor; MEK, mitogen-activated protein kinase enzyme; MET, mesenchymal-epithelial transition; mTOR, mammalian target of rapamycin; PARP, poly adenosine diphosphate-ribose polymerase; SIADH, syndrome of inappropriate antidiuretic hormone secretion; PRES, posterior reversible encephalopathy syndrome.

= no interactions, ↑ increases drug levels, ↓ decreases drug levels.

A: avoid combination; CTM: consider therapy modification.

Bold font represents major drug-to-drug interaction or major drug toxicity.

When all the drugs belonging to the same family have equal features, we reported them on the class line rather than on each drug line. iv: intravenous; po: per os; X : no need for adjustment; ✓ : need for adjustment; NA : not available.

transporters) [44-46]. Among efflux transporters, the most important for DDI in SOT is P-glycoprotein 1 (P-gp) which expels the drug from the body to prevent saturation of the intracellular enzymes; they are mainly located in the enterocytes, in the lymphocytes, in blood barriers (i.e., placenta, brain) and all other excretory systems such as the biliary system [44]. Among the metabolic enzymes, the most important ones are the cytochromes P450 (CYP) 3A isoenzymes (CYP3A4, CYP3A5), the enzymes which metabolize CNI and mTORi; these CYPs are located in the enterocytes and in hepatocytes where they are most abundant [45,46]. The enterocyte CYP3A4 and CYP3A5, along with the enterocyte efflux protein P-gp cause only a fraction of the ingested drug to pass into the bloodstream (the bioavailability of CNI is in fact well below 100%, being approximately 20% for tacrolimus and 33% for cyclosporin) [45,46]. The third group are the influx transporters, such as Organic Anion Transporter Polypeptides (OATP); upon passing into the blood stream, they mediate uptake of the drug into the hepatocytes, the central machinery for drug metabolism [44]. The enterocyte efflux transporter P-gp, and the enzymes CYP3A4 and CYP3A5 in the enterocytes and hepatocytes are responsible for most DDI that involve CNI and mTORi.

The second principle is that there are various polymorphic forms of CYP3A isoenzymes, the most important being CYP3A5*3 [46,47] and CYP3A4*22 [48,49]. The wild-type allele of CYP3A5 (CYP3A5*1) is most common in blacks (>50%) and least common in white/Hispanics (approximately 10%), which most frequently carry the CYP3A5*3 allelic variants. The presence of these alleles may result in significant differences in the tacrolimus dose requirement to reach therapeutic drug concentrations: carriers of the CYP3A5*3 alleles require 50–100% lower doses of tacrolimus [46,47]. Conversely, carriers of the CYP3A5*1 allele are at lower risk of DDIs [50]. Therefore, the extent of DDI may vary across subjects and different ethnicities.

The third principle concerns route of administration. After oral administration, drugs that inhibit enterocytes 'P-gp and CYP3A4 may increase other drugs' bioavailability. Accordingly, DDI is less pronounced in the case of intravenous compared with oral administration [51]. Therefore, orally administered anticancer drugs that engage intestinal P-gp, and CYP3A4, such as epidermal growth factor (EGFR) inhibitors cetuximab [9], MET

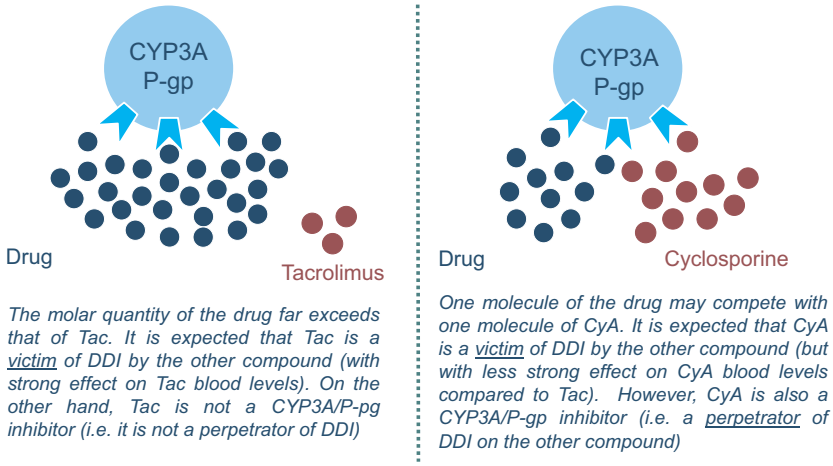

Figure 1 Schematic representation showing that Tac is more victim and less perpetrator of DDI compared with CyA because of the lower molarity of therapeutic doses of Tac compared with CyA. On the other hand, CyA is more often a perpetrator of DDI on the other compound compared with tacrolimus. CYP3A, cytochromes P450 3A; CyA, cyclosporine; DDI: Drug-to-Drug Interaction; P-gp: P-glycoprotein 1; Tac, tacrolimus.

inhibitors, BRAF-MEK inhibitors (dabrafenib and trametinib), ALK inhibitors (crizotinib, ceritinib, and alectinib), CDK 4/6 inhibitors (palbociclib, abemaciclib) (see Table 1) may cause significant DDI with CNI and mTORi.

The fourth principle: Tac is more victim and less perpetrator of DDI compared with cyclosporine A (CyA) because of the lower molarity of therapeutic doses of Tac compared with CyA. The left panel of Fig. 1 explains the case of Tac: the molar quantity of the drug far exceeds that of Tac. It is expected that Tac is a victim of DDI by the other compound (with strong effect on Tac blood levels). On the other hand, Tac is not a CYP3A/P-pg inhibitor (therefore it is not a perpetrator of DDI). The right panel explains the case of CyA: One molecule of the drug may compete with one molecule of CyA. It is expected that CyA is a victim of DDI by the other compound (but with less strong effect on CyA blood levels compared with Tac). However, CyA is also a CYP3A/P-gp inhibitor (that is a perpetrator of DDI on the other compound). In fact, CyA may increase the exposure to anticancer drugs that are metabolized by CYP3A4: cyclosporine has been shown to increase the area under the curve (AUC) of doxorubicin by 50% and of its major metabolite doxorubicinol by more than four times [14]. Accordingly, the anticancer drugs administered orally are more likely to be victims of DDI in patients receiving CyA than in those receiving Tac (see Table 1). In SOT recipients, the concomitant use of CNI and mTORi, may reduce the tolerability to orally administered anticancer drugs that engage the P-gp and are metabolized by CYP3A4 [52]. For the reasons outlined above, the problem is likely to occur more often with CyA compared with Tac and mTORi, and may be further aggravated by the additional use of drugs that are CYP3A/P-gp inhibitors, such as imidazole antifungal agents or macrolide antibiotics, such as clarithromycin [52].

The fifth principle refers to the DDI causing CYP3A induction (they cause a decrease of CNI and mTORi blood levels rather than an increase). Inducers are those drugs that, by penetrating in the nucleus and by binding to so-called Pregnane X (PXR) receptors, are able to activate the transcription machinery of CYP3A isoenzymes. As a consequence, more CYPs are synthesized, and more CNI or mTORi is metabolized [53]. Typical CYP inducers are BRAF-MEK inhibitors (e.g., dabrafenib) and steroids. Unlike CYP inhibition (which occurs in the 24–48 hours following the drug administration), CYP induction occurs slowly over several days to weeks [53]. For instance, in a SOT recipient taking dabrafenib for melanoma, the dose of Tac and of the mTORi everolimus was increased by 3–4-folds over 2–3 weeks with further upward adjustments in the following months to attain the same blood levels [54].

In summary, there is no anticancer drug that is absolutely contraindicated in SOT recipients because of DDI. Anyhow, careful monitoring of CNI and mTORi is recommended in patients starting oral anticancer drugs that are substrate of by CYP3A/P-gp or inductors of CYP3A. Especially with CyA, some anticancer drugs that are substrate of CYP3A/P-gp may be victims of significant DDI, therefore, alternative drugs should be considered whenever possible (see Table 1).

Pharmacodynamic (PD) DDI

Some anticancer therapies may increase the risk of infections or other side effects because they have an adverse effect risk profile that overlap with that of anti-rejection drugs.

Myelosuppression

Anti-proliferative anti-rejection drugs that are commonly used in SOT transplant recipients may cause neutropenia, thrombocytopenia, and anemia. By far, the most common and severe hematologic side effect is mycophenolate-induced neutropenia, which may be severe in the first month post-transplantation, especially in patients treated with lymphodepleting agents and on CMV prophylaxis with valganciclovir [55]. Several anticancer drugs may cause severe myelosuppression (see Table 1), therefore drugs, such as azathioprine and mycophenolate may be reduced or withdrawn before starting treatment with anticancer drugs that may cause severe myelosuppression, such as antimetabolites, platinum analogs, taxanes, topoisomerase Inhibitors, nucleotides analogs, and CDK 4/6 inhibitors (see Table 1). The risk of azathioprine-induced myelosuppression is greatly increased in patients carrying allelic variants in the tiopurine methyltransferase, the polymorphic gene involved in the metabolism of tiopurines [56,57].

QT prolongation

Concerns reported on the Summary of Product Characteristics (SmPC) of the anticancer drugs are related to anticancer drugs as DDI victims (because of CYP3A4 inhibition). The overexposure to some of anticancer drugs may cause prolonged QT interval. Drugs that may be avoided in combination with CNI are the ALK inhibitors crizotinib [58] and the Angiogenesis inhibitor pazopanib [59].

In summary, there is no absolute contraindication related to pharmacodynamic interaction in SOT recipients, but complete azathioprine or mycophenolate withdrawal or dose reduction should be considered in patients undergoing chemotherapy with drugs at high risk of myelosuppression.

Adjustment for renal and/or liver function

SOT recipients, especially kidney transplant recipients have, in general, reduced kidney function [60,61], which exposes them at increased risk of AKI compared with the general population [62,63]. Liver function may also be impaired, especially in liver and heart transplant recipients with graft dysfunction. Dose adjustment indications within the summary of product characteristics (SmPC) document [64] and published tables [65] are available for patients with reduced kidney or liver function based on estimated Creatinine Clearance or GFR, and on serum total bilirubin and aspartate aminotransferase (AST). Examples of anticancer drugs that require major dose adjustment for kidney dysfunction and that are contraindicated with stage IV and V chronic kidney disease (i.e. eGFR < 30mL/min/1.73m^2) are platinum analogs, the antimetabolites pemetrexed and methotrexate, and the nucleotide analog capecitabine. The EGFR inhibitor erlotinib, topoisomerase inhibitor topotecan should be avoided with stage V chronic kidney disease (i.e. eGFR < 15 mL/min/1.73 m^2) [65]. Several anticancer drugs with hepatic metabolism are contraindicated in patients with severe liver failure [65].

Immunotherapy

Cancer immunotherapy engages the patient's own immune system, mainly T cells, against the tumor rather than targeting the cancer directly [66]. T cells can be activated against cancer in three major ways: rejuvenation of tumor-reactive T cells by checkpoint inhibitors (CPI), which are antibodies directed against immune-regulatory checkpoint molecules, adoptive transfer of anticancer T cells (e.g., CAR-T cells or EBV specific T cells), or *in vivo* induction of tumor-reactive T cells [66,67].

Checkpoint inhibitors (CPI)

CPI are increasingly recognized as a very effective treatment in a widening range of cancer types that are resistant to traditional treatments (Table 2) [68]. There are basically two classes of CPI, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, and programmed cell death protein 1 (PD1)/ programmed cell death protein 1 –ligand (PD-L1) inhibitors that uncouple two key mechanisms of T-cell peripheral tolerance [69,70]. CTLA-4 inhibitors promote priming of T cells in lymph nodes, while PD1/PD-L1 prevents exhaustion of T effector-memory cell in peripheral tissues.

CPI are highly efficacious in SOT recipients with cancer as they unleash T-cell immune responses against cancer cells that are inhibited by the anti-rejection treatment [71]. However, PD1 and PDL-1 receptors are not only expressed by the tumor, but also by the graft and

Table 2. Main indications of checkpoint inhibitors.

Checkpoint inhibitors	Main indications	Comment
CTLA-4 inhibitors		
Ipilimumab	• **Melanoma** • **Renal cell carcinoma**	• **Melanoma**: as monotherapy or in combination with nivolumab in patients with advanced (unresectable or metastatic) disease; • **Renal cell carcinoma**: in combination with nivolumab as first-line treatment of patients with intermediate/poor-risk advanced disease.
PD-1 inhibitors		
Nivolumab	• **Melanoma** • **Nonsmall cell lung cancer (NSCLC)** • **Renal cell carcinoma** • **Hodgkin lymphoma** • **Squamous cell cancer of the head and neck** • **Urothelial carcinoma** • **Esophageal squamous cell carcinoma**	• **Melanoma**: as monotherapy for the adjuvant treatment of patients with involvement of lymph nodes or metastatic disease who have undergone complete resection; as monotherapy or in combination with ipilimumab for patients with advanced (unresectable or metastatic) disease; • **NSCLC**: in combination with ipilimumab and 2 cycles of platinum-based chemotherapy for the first-line treatment of metastatic NSCLC in patients whose tumors have no sensitizing EGFR mutation or ALK translocation; as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy; • **Renal cell carcinoma**: as monotherapy for the treatment of patients with advanced carcinoma after prior therapy; in combination with ipilimumab as a first-line treatment of patients with intermediate/poor-risk advanced carcinoma; in combination with cabozantinib as first-line treatment of patients with advanced disease; • **Hodgkin lymphoma**: as monotherapy for the treatment of patients with relapsed or refractory classical lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin; • **Squamous cell cancer of the head and neck**: as monotherapy for the treatment of recurrent or metastatic disease in patients progressing on or after platinum-based therapy; • **Urothelial carcinoma**: as monotherapy for the treatment of locally advanced unresectable or metastatic disease after failure of prior platinum-containing therapy; • **Esophageal squamous cell carcinoma**: as monotherapy for the treatment of patients with unresectable advanced, recurrent or metastatic carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.

Table 2. Continued.

Checkpoint inhibitors	Main indications	Comment
Pembrolizumab	• **Melanoma**; • **NSCLC;** • **Hodgkin lymphoma** • **Urothelial carcinoma** • **Head and neck squamous cell carcinoma** • **Renal cell carcinoma** • **Colorectal cancer**	• **Melanoma**: as monotherapy for the treatment of patients with advanced disease; as monotherapy for the adjuvant treatment of patients with Stage III melanoma and lymph node involvement who have undergone complete resection; • **NSCLC:** as monotherapy for the first-line treatment of metastatic disease in patients whose tumors express PD-L1 with a ≥ 50% tumor proportion score (TPS) with no EGFR or ALK positive tumor mutations; in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous NSCLC in patients whose tumors have no EGFR or ALK positive mutations; in combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of patients with metastatic squamous NSCLC; as monotherapy for the treatment of locally advanced or metastatic disease in patients whose tumors express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen; • **Hodgkin lymphoma:** as monotherapy for the treatment of patients with relapsed or refractory classical disease who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option; • **Urothelial carcinoma:** as monotherapy for the treatment of locally advanced or metastatic disease in patients who have received prior platinum-containing chemotherapy; as monotherapy for the treatment of locally advanced or metastatic disease in patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 with a combined positive score (CPS) ≥ 10; • **Head and neck squamous cell carcinoma:** as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, for the first-line treatment of metastatic or unresectable recurrent disease in patients whose tumors express PD-L1 with a CPS ≥ 1; as monotherapy for the treatment of recurrent or metastatic carcinoma in patients whose tumors express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy; • **Renal cell carcinoma:** in combination with axitinib, for the first-line treatment of patients with advanced disease; • **Colorectal cancer**: as monotherapy for the first-line treatment of patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer.
Cemiplimab	• **Cutaneous squamous cell carcinoma**	• **Cutaneous squamous cell carcinoma:** as monotherapy for the treatment of patients with metastatic or locally advanced disease who are not candidates for curative surgery or curative radiation.
PD-L1 inhibitors		
Atezolizumab	• **Urothelial carcinoma** • **NSCLC** • **Triple-negative breast cancer**	• **Urothelial carcinoma:** as monotherapy for the treatment of patients with locally advanced or metastatic disease, after prior platinum-containing chemotherapy, or who are considered cisplatin ineligible, and whose tumors have a PD-L1 expression ≥ 5%; • **NSCLC:** as monotherapy for the treatment of patients with locally advanced or metastatic disease after prior chemotherapy; • **Triple-negative breast cancer:** in combination with nab-paclitaxel for the treatment of patients with unresectable locally advanced or metastatic disease whose tumors have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.

Table 2. Continued.

Checkpoint inhibitors	Main indications	Comment
Durvalumab	• **NSCLC**	• **NSCLC:** as monotherapy for the treatment of locally advanced, unresectable cancer in adults whose tumors express PD-L1 on ≥ 1% of tumor cells and whose disease has not progressed following platinum-based chemoradiation therapy; in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with extensive-stage cancer.
Avelumab	• **Merkel cell carcinoma** • **Urothelial carcinoma** • **Renal cell carcinoma**	• **Merkel cell carcinoma:** as monotherapy for the treatment of patients with metastatic disease; • **Urothelial carcinoma:** as monotherapy for the first-line maintenance treatment of patients with locally advanced or metastatic carcinoma who are progression-free following platinum-based chemotherapy; • **Renal cell carcinoma:** in combination with axitinib for the first-line treatment of patients with advanced disease.

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, nonsmall cell lung cancer; PD-L1, programmed cell death protein 1 –ligand; PD1, programmed cell death protein 1.
Bold values are used to ease the readibility of the table.

graft-reactive T cells [72]. Therefore, CPI may activate allo-reactive T cells leading to acute rejection and graft loss. The fact that PD-L1 are expressed also in the graft endothelial cell [72], may explain, at least partially, why PD-1/PDL-1 blockade therapy can induce severe vascular rejection [72]. Rejection usually occurs within 6–8 weeks after the beginning of treatment [73,74], but it may occur even earlier. In some patients, rejection occurs immediately after the start of treatment, especially in those who switched from the CTLA-4 inhibitor ipilimumab to a PD1 inhibitor [73,74].

It is unclear whether the onset of graft rejection implies an effective antitumor immune response; in other words, it is unclear whether the break of tolerance against the graft is associated with a break of tolerance against the tumor cells. In all published series, CPI-induced graft rejection has been traditionally managed with CPI discontinuation and administration of pulse steroids or even T-cell depleting therapy. In fact, most rejections were represented by vascular rejection (Banff grade II), often in the absence serological features of antibody-mediated rejection.

Therefore, it is not possible to predict what would have occurred to tumor response and to patient survival had the patients continued CPI despite rejection, and had treatment for acute rejection not done [74]. In fact, virtually all types of antirejection treatment may blunt the antitumor immune response of CPI. Besides pulse steroids and T-cell depleting used as therapies for the treatment of T-cell-mediated rejection, also plasmapheresis, which is used for the treatment of antibody-mediated rejection, by removing CPI from the body, might neutralize the antitumor immune response of CPI.

A recent meta-analysis on check-point inhibitors in SOT recipients showed that acute rejection was the reason for CPI discontinuation in over 40% of the cases [75]. The effect of CPI-induced rejection on patient survival depends on the SOT type [75]. In kidney transplant recipients treated with CPI, the occurrence of graft rejection does not seem to affect patient survival [75]. This is likely the results of two opposite effects that cancel each other out. On one hand, rejection may reflect CPI-induced T-cell recovery and break of tolerance against nonself-antigens promoting tumor response; on the other hand, rejection, by leading to CPI withdrawal, and to immunosuppression increase, may nullify the effect of CPI and eventually cause progressive cancer disease. However, that holds true for SOT recipients of nonlife-saving organs, such as kidney transplant recipients, since patients losing their graft

because of rejection can resort to dialysis. In contrast, rejection can cause death in recipients of life-saving organs [75].

Table 3 summarizes the data from published literature concerning the risk of rejection, risk of death, and probability of tumor response across different SOT, namely, kidney, liver, and heart [75]. So far, approximately, 230 SOT recipients treated with CPI has been reported in the literature. Compared with liver and heart transplant recipients, kidney transplant recipients, despite the highest rate of rejection, have the lower mortality rate [75-90].

How should maintenance anti-rejection treatment be reduced to let CPI fully unleash T cells against cancer while minimizing the risk of graft loss due to rejection? [71] In this regard, emphasis has been placed to the use of mTOR-inhibitors. mTORi may prevent rejection and favor tumor response because of the anticancer properties of mTORi. Protocols have been proposed that are based on high-dose steroids and high-dose mTORi, starting shortly before or at the time of starting CPI treatment [91]. mTORi may be also used as savage therapy. One case report described a transplant patient who developed rejection after starting CPI. The patient had rejection controlled and antitumoral response maintained only after switching to mTORi. The Authors analyzed T-cell responses and concluded that such an optimal and paradoxical effect may have resulted from mTORi eliciting IFN-γ+ CD4+ T cells that uncouple immunological response against the graft (by dampening it) and against the tumor [92]. Anyhow, from published meta-analyses, it seems that rejection is best prevented by maintaining any anti-rejection drugs other than steroids (usually CNI). There is no signal from a multivariable-adjusted regression model in a published meta-analysis that mTORi are superior in preventing rejection compared with other anti-rejection drugs [75]. Rather, the major determinants of rejection were history of rejection and time elapsed from transplantation, CPI-induced rejection being tenfold more frequent in patients with previous history of rejection, and in those treated with CPI within 8 years from transplantation [75]. Nonetheless, upon withdrawal of CNI-based anti-rejection therapy, the absolute risk of rejection remained high even if long time has elapsed after transplantation and the patient has no rejection history. Progression-free survival was highest in patients in whom anti-rejection drugs were withdrawn altogether (with the possible exception for steroids, irrespective of the use of mTOR-inhibitors [75].

Based on what we mentioned above, we contend that one possible strategy to maximize CPI response in kidney transplant recipients may be based on withdrawing immunosuppression altogether, and on performing graft nephrectomy upon development of rejection. That would allow continuing CPI therapy rather than withdrawing it in patients who are developing strong tumor response. This strategy seems feasible since it has been recently shown that CPI can be safely administered in dialysis patients [93]. Evidence is still lacking concerning transplant recipients who start dialysis and who might develop severe reactions, especially if the graft is left in place. Anyhow, this might represent a possible option to include in the process of shared decision-making with the kidney transplant recipients with cancer who are potential candidates to CPI. Unfortunately, the conclusions drawn about the use of CPI in SOT are based on small case series, with obvious publication biases. Prospective and controlled trials are urgently needed.

CAR-T cells

Chimeric antigen receptor (CAR) T cells are genetically engineered autologous T cells that recognize a defined

Table 3. Comparison in outcome after CPI treatment in different organ transplantations.

	KIDNEY	LIVER	HEART
Rejection	45% (74/165)	35% (17/48)	26% (5/19)
Response	40% (64/161)	42% (13/31)	7% (1/13)
Death	43% (63/147)	60% (29/48)	58% (11/19)

CPI, check-point inhibitors.

Rate of rejection, tumor response, and death reported in kidney, liver and heart transplant recipients undergoing treatment with CPI.

Response refers to tumor shrinking. Numbers in the table are extracted from the systematic review by d'Izarny-Gargas [12] updated with published literature beyond 1 November 2019 [75-90].

target antigen (e.g., CD19 in lymphoma). CARs are composed of antibody-binding domains fused to T-cell signaling domains [94,95]. T cells are obtained from the patient by leukapheresis, then the fusion protein CAR is introduced *ex vivo* via a viral vector. After transfection, the CAR-T cells are selected and expanded *ex vivo*, with turnaround times of less than 40 days [94,95]. The CAR-T cells are infused after lymphocyte depletion preconditioning with chemotherapeutic agents to "create room" and permit their expansion *in vivo*. Thus far, CAR-T cells have most often been CD8 cytotoxic T cells, with the capacity to bind to and kill tumor cells [94,95]. Common and concerning side effects of CAR-T-cell treatment include neurological toxicity, including encephalopathy, and cytokine release syndrome, which may induce AKI [94,95]. The cytokine release syndrome can be ameliorated by the anti-interleukin-6 monoclonal antibody, tociluzimab [96]. Other relevant adverse effects that may occur with CAR-T therapy in malignancy include tumor lysis syndrome and electrolyte abnormalities, such as hypokalemia and hypophosphatemia [94-96].

CAR-T cells have provided promising results with recurrent and refractory diffuse large B-cell lymphomas (DLBCL). However, the efficacy of this treatment in SOT recipients with post-transplant lymphoproliferative disorders (PTLD) is unknown, as concurrent use of immunosuppressive agents was prohibited in most CAR-T trials. A recent report [97] showed poor outcomes in three SOT recipients (heart, kidney, pancreas-after-kidney, respectively) with PTLD refractory to immunochemotherapy at 10–20 years after SOT who received CAR-T therapy. All the three patients developed complications of CAR-T therapy, such as cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, and AKI requiring kidney replacement therapy in the two out of three patients. All patients died after withdrawal of care due to lack of response to CAR-T therapy. A pancreas-after-kidney recipient developed acute pancreatitis after CAR-T therapy.

Also with CAR-T-cell therapy, the issue about the optimal management of immunosuppression persists. On one hand, evidence exists that SOT recipients (two kidney- and one liver- transplant recipient) can be safely kept on calcineurin inhibitors during the course of CAR-T-cell collection and administration [98]. However, authors have also attempted to temporarily withdraw it. In another report [99], three kidney transplant recipients received CAR-T-cell- therapy because of relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL) and only one of them developed acute rejection despite temporary interruption of immunosuppression.

Most experience with CAR-T-cell therapy so far has been mostly gained in kidney transplant recipients (seven published cases at the time of writing), but additional supportive data also exist for liver [100] and heart [101] transplant recipients. Despite encouraging results, the overall experience with CAR-T cells in SOT recipients is very limited. More studies are needed to assess the optimal indications and timing for discontinuing and restarting immunosuppressive therapy after CAR-T-cell therapy.

EBV-specific cytotoxic T-lymphocytes

The use of adoptive T-cell therapy for Epstein-Barr virus (EBV)-associated PTLD is an old therapeutic approach that has been started over 25 years in the field of hematopoietic stem cell transplantation (HSCT). Unfortunately, widespread application of this approach has been limited by time constraints in patients with rapidly progressive disease, complex manufacturing protocols, and infrastructural requirements. Therefore, so far adoptive T-cell therapy for EBV-associated PTLD has not been a realistic option for most patients [102]. In an attempt to expand the access to this treatment option, the field has turned to immediately accessible banked and partially matched allogeneic EBV. Recently, a third-party, allogeneic, off-the-shelf bank of EBV-specific cytotoxic T-lymphocyte (EBV-CTL) lines from specifically consented healthy HSCT donors was used to treat 46 recipients of HSCT (n = 33) or SOT (n = 13) with rituximab-resistant EBV-PTLD. Treatment cycles consisted of three weekly infusions of EBV-CTLs and 3 weeks of observation [103]. EBV-CTLs did not induce significant toxicities in the 13 SOT recipients, while achieving complete remission or sustained partial remission in 7 of them. CNI therapy can be continued because of the limited effects that this treatment exerts on CTL, limiting the risk of graft rejection. These results suggest a promising potential therapy for patients with post-transplant rituximab-refractory EBV-associated lymphoma.

Looking into the future

The main goal of personalized precision medicine is the delivery of the correct drug to the right patient at the right time and dose: pharmacogenomics, intratumoral immunotherapy, and gene editing are among the many

strategies closest to implement these principles also in SOT recipients with cancer.

Public resources are already available to implement pharmacogenomics in the clinic. For instance, PharmGKB is a platform which collects, curates, and disseminates information on genetic variation and drug response and provides dosing instructions (https://www.pharmgkb.org/about) [104]; CPIC® (Clinical Pharmacogenetics Implementation Consortium) (https://cpicpgx.org) is another platform that provides publicly available, peer-reviewed, evidence-based, updatable, and detailed gene and drug clinical practice guidelines. In addition, the U.S. FDA's Center for Drug Evaluation & Research and Center for Biologics Evaluation and Research Office have launched an ambitious program to generate informative knowledge from real world data (https://www.fda.gov/about-fda/oncology-center-excellence/oncology-real-world-evidence-program). In this project, aims include exploring counterfactual efficacy and safety of drug-to-drug interactions of the newer drugs for which there is no evidence from clinical trials and in selected patient categories.

Intratumor delivery of neoadjuvant immunotherapy represents a promising strategy to harness the efficacy of immunotherapy while minimizing off-target toxicities [105]. The direct injection of immune stimulating agents into the tumor primes the local tumor-specific immunity to generate a selective, durable clinical response. Currently, more than 20 neoadjuvant clinical trials testing distinct intratumor immune stimulatory agents and their combinations are ongoing. Dang *et al.* [106] showed that intratumor, but not systemic, immunotherapy with anti-PD-1/toll like receptor 9 agonist promoted potent antitumor responses but did not accelerate allograft rejection in mice recipients of heart allografts with cancer, provided that the tumor and cardiac allograft shared major histocompatibility complex (MHC). However, the antitumor effect was compromised by maintenance immunosuppression with CyA, highlighting the importance of finding an optimal balance between antitumor and antigraft immunity.

Gene editing is another major strategy. Currently, the use of CAR-T cells is being extended beyond hematologic malignancies, including skin tumors which are by far the most common type of cancers in SOT recipients. Nagarsheth *et al.* have conducted a first-in-human, phase 1 clinical trial of engineered T cells for the treatment of metastatic human papilloma virus-associated epithelial cancers [107]. The authors showed that engineered T cells can mediate regression of common carcinomas, but defects in critical components of the antigen presentation and interferon response pathways may prevent effective response. Importantly, in SOT recipients, the efficacy of CAR-T cells can be inhibited by the immunosuppressive drugs. To address this relevant issue, strategies are being developed, including removal of glucocorticoid receptor to make these cells unresponsive to steroid therapy as shown by Menger *et al* [108].

Conclusions

In conclusion, there are no anticancer drugs that are intrinsically safe or unsafe. Rather, the optimal choice of the anticancer regimen results from a careful individual risk/benefit assessment, from the awareness of potential PK and pharmacodynamic DDI, and of the risk of drug overexposure in patients with kidney or liver dysfunction. Progresses in basic and translational research are having a major impact in the clinical practice. The potential of recent findings to overcome toxic effects of anticancer drugs in SOT is hard to overstate and the transition to a personalized precision medicine-centric health science and healthcare of SOT tomorrow is inevitable.

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Ethical approval

This article does not report a clinical study in human subjects, therefore, ethical approval was not required.

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