Managing immunosuppressive therapy in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer): an overview of the available evidence and guidance for shared decision-making

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REVIEW

Managing immunosuppressive therapy in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer): an overview of the available evidence and guidance for shared decision-making

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SUMMARY

Kidney transplant recipients (KTRs) have increased incidence of *de novo* cancers. After having undergone treatment for cancer with curative intent, reducing the overall immunosuppressive load and/or switching to an alternative drug regimen may potentially be of great benefit to avoid cancer recurrence, but should be balanced against the risks of rejection and/or severe adverse events. The TLJ (Transplant Learning Journey) project is an initiative from the European Society for Organ Transplantation (ESOT). This article reports a systematic literature search undertaken by TLJ Workstream 3 to answer the questions: (1) Should we decrease the overall anti-rejection therapy in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer)? (2) Should we switch to mammalian target of rapamycin inhibitors (mTORi) in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer)? The literature search revealed insufficient solid data on which to base recommendations, so this review additionally presents an extensive overview of the indirect evidence on the benefits versus risks of alterations in immunosuppressive medication. We hope this summary will help transplant physicians advise KTRs on how best to continue with anti-rejection therapy after receiving cancer treatment with curative intent, and aid shared decision-making, ensuring that patient preferences are taken into account.

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cancer, immunosuppression, kidney transplantation, mTORi, rejection

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Introduction

Kidney transplant recipients (KTRs) have increased incidence of *de novo* cancers, which contributes to their excess mortality compared with the general population. Cancers at highest risk are those that are virus induced, such as post-transplant lymphoproliferative disease (PTLD) and Kaposi sarcoma; and those caused by

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impaired immune surveillance or via direct DNA damage by anti-rejection drugs themselves, such as skin and lip cancers [1]. However, many other cancer types occur more frequently in KTRs [2].

When an individual is faced with potentially curable cancer, online calculators, using patient and tumour characteristics, provide recurrence risk and survival probability that can guide oncological counselling and inform choice of treatment strategy. Being a transplant recipient, however, adds more complexity and challenges. The impaired immune system may negatively impact cancer control and treatment response. Calculators based on the general population may therefore overestimate their prognosis. The Transplant Cancer Match study, which linked national US transplant and cancer registry data to examine survival after cancer diagnosis among solid organ transplant (SOT) recipients [3], showed that for most cancer types, SOT recipients have an elevated risk of dying from their cancer compared with non-transplant cancer patients, even after adjustment for cancer stage and treatment, suggesting that apparently curable cancers with a seemingly good prognosis could be more susceptible to micro-metastases in immunosuppressed individuals [4]. However, not every tumour is equally susceptible to immunosuppression. In a large US registry study, Yanick *et al* [5] showed that the incidence of kidney and thyroid cancer was not higher during kidney graft function than during graft non-function intervals (when patients are off immunosuppression). Moreover, the Australia/New Zealand study from Au *et al* [6] found that KTRs have an elevated relative risk of dying from several cancer types compared with the general population, whereas mortality from prostate cancer was not increased.

After having undergone treatment for cancer with curative intent, the KTRs and transplant physician face difficult decisions on how to continue with anti-rejection therapy. Although reducing the overall immunosuppressive load and/or switching to an alternative drug regimen may potentially be of great benefit to avoid cancer recurrence, this should be balanced against the risks of rejection and/or severe adverse events. Unfortunately, little is known on the optimal immunosuppressive strategy in KTRs in this setting. During the Transplant Learning Journey (TLJ) 2020 (see Box 1), an initiative by the European Society for Organ Transplantation (ESOT), one of six working groups – including two nephrologists, one haematologist and one methodologist – discussed this topic via an online platform with a large multidisciplinary audience, and reviewed the available evidence. In this paper, we first present the results of a systematic literature search which tried to answer the following two questions:

1. Should we decrease the overall anti-rejection therapy in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer)?
2. Should we switch to mammalian target of rapamycin inhibitors (mTORi) in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer)?

The literature search revealed insufficient solid data to formulate evidence-based recommendations. However, since transplant professionals and their patients would welcome practical advice on the management of immunosuppressive therapy in potentially cured post-transplant cancer, we provide an extensive overview of the indirect evidence on the possible benefit and risks of alterations in immunosuppressive medication, and provide a summary to assist shared decision-making.

Methods

The PICO (Population, Intervention, Comparator and Outcomes) model was used to formulate clinical

Box 1. European Society for Organ Transplantation (ESOT) and the Transplantation Learning Journey (TLJ) project

Workstreams within the TLJ project help to achieve the primary aim of ESOT – to improve patient access to (and outcomes in) transplantation. TLJ workstreams facilitate objective discussion of scientific and clinical research, and expert opinion, to ensure that all perspectives on a topic are considered, with clinically relevant end goals in mind.

ESOT seeks to progress transplantation research, practice and education, and to collaborate with other international bodies, to ensure that policies and regulations are globally consistent and relevant, and based on strong scientific, ethical and clinical foundations.

ESOT TLJ 2.0 TRANSPLANTATION LEARNING JOURNEY

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questions. Separate bibliographic searches were developed for each of the clinical questions by experienced staff from the Centre for Evidence in Transplantation, University of Oxford. Systematic searches were conducted in the Transplant Library (www.transplantlibrary.com), MEDLINE and EMBASE. Full details of the searches, including search dates, can be found in the Appendix S1. Searches consisted of a mixture of free text and controlled vocabulary terms. We included all solid organs, all study designs including systematic reviews, randomized controlled trials (RCTs), registry analyses, observational studies and clinical practice guidelines, and both adult and paediatric populations. Studies in non-melanoma skin cancer were excluded. Search results were limited to the English language and studies published from the year 2000. The draft guideline was posted on ESOT's website to elicit comments from the transplantation community for a consultation period of six weeks.

Results of the systematic literature search

Question 1: Should we decrease the overall anti-rejection therapy in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer)?

The first step of the literature search focussed on solid cancers (Fig. 1). There are no systematic reviews or RCTs on this topic. Only two small ($n = 87$ and $n = 110$), retrospective cohort studies were identified [7,8] comparing outcomes in KTRs with post-transplant cancer between those remaining on standard immunosuppression and those who underwent reduction of immunosuppression. However, no clear conclusions could be drawn from these studies because of the low number of patients, high heterogeneity of cancer types and cancer stages, varying immunosuppressive regimens and a high risk of indication bias, because the patients

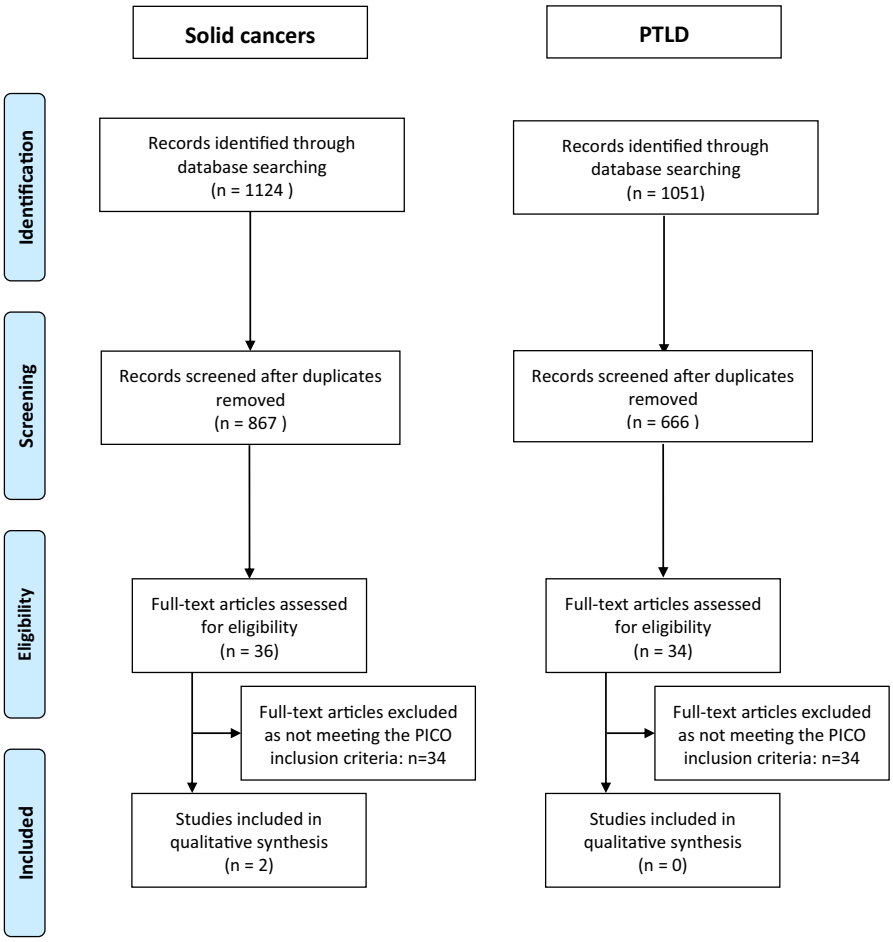

Figure 1 Flow diagram for PICO #1: Identification of studies on reducing overall anti-rejection therapy in potentially cured post-kidney transplant cancer.

who were switched to a reduced immunosuppressive regimen are more likely to be those with an inferior prognosis (Table S1). A second literature search, specifically on PTLD, yielded no studies matching our inclusion criteria (Fig. 1); we found only small, retrospective studies with a large heterogeneity in terms of PTLD type/treatment and immunosuppression reduction at the time of PTLD diagnosis, with no studies specifically examining outcomes based on choice of immunosuppression after completing PTLD treatment.

Question 2: Should we switch to mTORi in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer)?

There are no systematic reviews or RCTs on this topic. Only two small retrospective studies [9, 10]on solid cancers were found that (partly) met the search criteria (Fig. 2). Given their retrospective nature, low number of patients, high heterogeneity in cancer types and stages, varying immunosuppressive regimens and risk of indication bias, no clear conclusions can be drawn from these studies (Table S1). A second literature search, specifically on PTLD, yielded only small retrospective case series that did not match our inclusion criteria, because they do not specifically describe the outcomes of changing to mTORi versus maintaining on a regimen without mTORi after completion of PTLD therapy (Fig. 2).

What do other guidelines or consensus reports say?

Guidelines and consensus reports are largely based on expert opinion (Table 1). It is clear from several consensus documents that reducing the overall immunosuppressive load is often considered, although the possible benefit in terms of reducing cancer recurrence should be balanced against the increased risk of rejection. In addition, some consensus documents suggest switching to a mTORi-based immunosuppressive

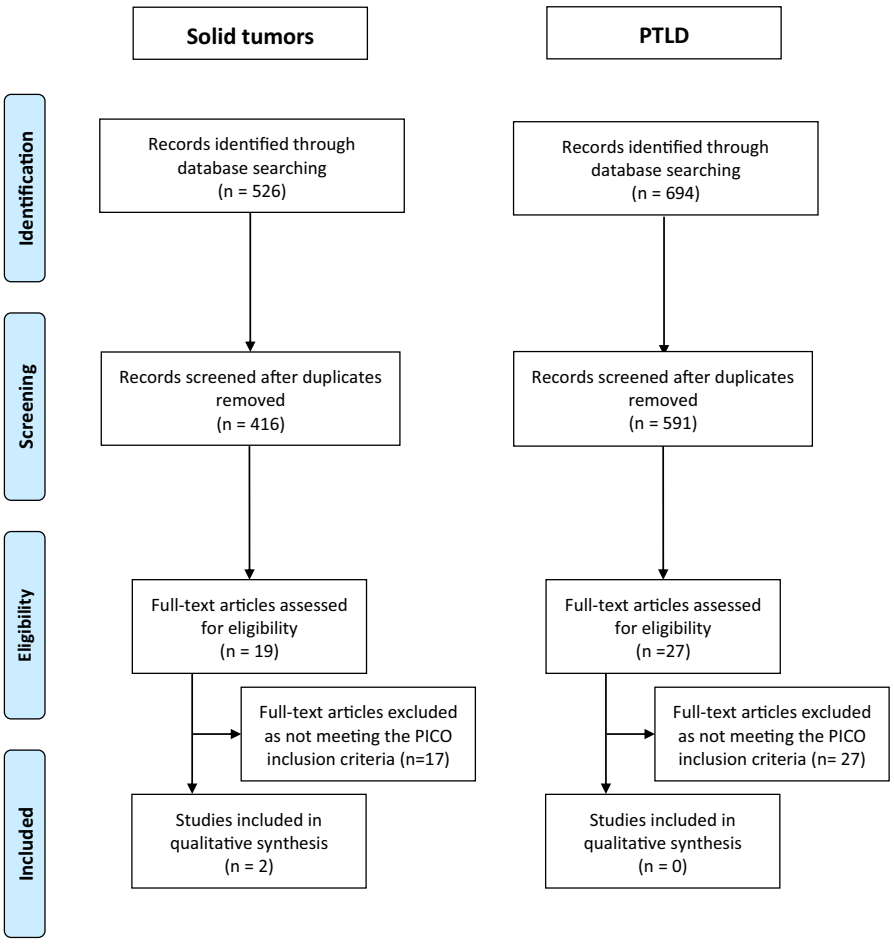

Figure 2 Flow diagram for PICO #2: Identification of studies on switching to mTOR inhibitors in potentially cured post-kidney transplant cancer.

Table 1. Guidelines and consensus reports identified in the literature review.

Guidelines/Consensus/Position paper	Recommendation
Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients [57] *Am J Transplant* 2009; **9** suppl 3: S1–155 Chapter 20: Managing Cancer with Reduction of Immunosuppressive Medication	20.1: We suggest consideration be given to reducing immunosuppressive medications for kidney transplant recipients with cancer. (2C)* 20.1.1: Important factors for consideration include (not graded): • the stage of cancer at diagnosis • whether the cancer is likely to be exacerbated by immunosuppression • the therapies available for the cancer • whether immunosuppressive medications interfere with ability to administer the standard chemotherapy. 20.2: For patients with Kaposi sarcoma, we suggest using mTORi along with a reduction in overall immunosuppression. (2C) * Level 2 'We suggest', C 'Quality of evidence is low'
EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.6.3 Solid organ cancers: prevention and treatment [58]	The European Best Practice Guidelines were produced by the European Renal Association – European Dialysis Transplant Association (ERA-EDTA). The guidance states that it is recommended to reduce immunosuppression whenever possible in transplant patients who are diagnosed with cancer (Evidence level C: guidelines are derived from small or controversial studies or represent the opinion of the group of experts).
Epailly E, et al. Proliferation signal inhibitors and post-transplant malignancies in heart transplantation: practical clinical management questions [59]	The report provides practical guidance from a collaborative group that used literature and personal clinical experience to reach consensus regarding post-transplant malignancies in heart transplant patients. The group proposes a (unvalidated) treatment algorithm that can carefully consider cancer type and patient's risk of acute rejection and can incorporate decisions with minimization or withdrawal of calcineurin inhibitors and introduction of mTORi.
Campistol JM, et al. Use of proliferation signal inhibitors in the management of post-transplant malignancies—clinical guidance [60]	The paper presents guidance regarding immunosuppression for kidney transplant patients diagnosed with cancer following an industry-sponsored workshop. A recommended treatment algorithm based on clinical experience is presented, suggesting to reduce or stop CNIs and start mTORi.
Małyszko J, et al; Conference Participants. KDIGO Controversies Conference on onco-nephrology. Kidney disease in hematological malignancies and the burden of cancer after kidney transplantation [61]	The management of cancer after kidney transplantation is complex. For patients who develop cancer after kidney transplantation, the approach has traditionally focussed on reducing overall immunosuppression, with administration of chemotherapy agents managed by a medical oncologist. Dose reduction of immunosuppression after transplantation is likely to depend upon cancer type, stage and many other factors. However, this approach needs to be balanced carefully with the risk of allograft rejection. Prospective trial-based data to inform immunosuppression management, including dose reduction and/or immunosuppression cessation, are lacking. Mammalian target of rapamycin inhibitors (sirolimus and everolimus) may have a promising role in managing cancer after transplantation (particularly with nonmelanocytic skin cancers and Kaposi sarcomas), owing to their simultaneous immunosuppressive and anti-cancer effects.

regimen, although this might be poorly tolerated by some patients and increase the risk of rejection (see Appendix S1).

Discussion

Should we decrease the overall anti-rejection therapy in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer)?

Reducing overall maintenance anti-rejection treatment, to an extent that depends upon cancer type, stage and other factors, has been the traditional approach used for KTRs with a history of non-skin cancer treated with a curative intent, although robust studies to evaluate the safety and efficacy of such strategies are lacking. When reducing the overall immunosuppressive load, it is unclear which agent should be preferentially reduced or stopped. Kidney transplant recipients are generally treated with multidrug maintenance therapy, and some also receive antibody induction therapy or treatment for rejection. It is therefore extremely difficult to discern the impact of any individual immunosuppressive agent on cancer development/control and to distinguish the effect of a particular drug from the effect of the overall immunosuppressive burden. The calcineurin inhibitors (CNI) cyclosporine A (CsA) and tacrolimus (Tac) have been shown to upregulate TGF-β1 [11] and VEGF [12], both of which are known to contribute to cancer growth and angiogenesis [13]. They also suppress anti-oncogenic genes (p53 via NFAT-ATF3) [12,13]. In fact, a 1990s RCT in KTRs comparing a standard versus reduced dose of CsA showed that CsA had a dose-dependent effect on inducing skin and non-skin cancer [14]. It is unclear whether the risk of developing cancer is different with CsA versus Tac. For example, a large international registry analysis showed a higher risk of post-transplant lymphoma with Tac than with CsA in KTRs, but no difference in risk between Tac and CsA in liver transplant recipients, despite a higher number of cases in the liver transplants [15]. As for mycophenolate mofetil (MMF), recent large registry studies have not found differences in cancer incidence in regimens with/without MMF [16]. Likewise, use of steroids is not associated with increased cancer incidence [17].

Based on available (indirect) evidence, reduction of trough blood levels of CNI below the traditional lower bounds may be the most effective strategy to prevent cancer recurrence, but is probably also the least safe strategy regarding rejection risk. A recent RCT in stable low-risk steroid-free KTRs 4–12 months after transplantation showed that 50% Tac reduction (target trough levels >3 ng/ml) was associated with a sharp increased risk of acute rejection at 1 year (11% vs 2%), and development of donor-specific antibodies (6% vs 0%) [18].

Post-transplant lymphoproliferative disease

Several immunosuppressants have been described as inducing more PTLD than others. In 25,000 renal transplant recipients, in association with an antimetabolite (azathioprine [AZA] or MMF), Tac induced twice as many PTLDs as CsA [15]. In 115,000 renal transplant recipients, mTORi + Tac caused 40% more PTLDs than MMF [19]. In another study, the unfavourable effect of mTORi + Tac was limited to Epstein–Barr virus (EBV)-negative recipients [20]. In general, MMF appears to be less responsible for PTLD after renal transplant than AZA [21]. The current management of PTLDs is fairly codified, and the results are remarkable (median overall survival of >6 years [22]). Standard treatment includes induction with rituximab followed by either rituximab monotherapy in the event of complete remission, or a variation of R-CHOP; however, in rare cases, the decreased immunosuppression alone results in complete remission [23] and it seems preferable to keep the immunosuppression as low as possible throughout follow-up. More typically, further reduction in immunosuppression after remission of PTLD might not be beneficial, the rate of relapse being limited [24]; a re-increase or modification seems possible, since some studies have shown very rare relapses after a new renal transplant [25,26]. However, currently, there is no recommendation on how to modify the immunosuppression, or on optimal timing between the response of PTLD and drug modification.

Should we switch from CNI to a mTORi-based CNI-free regimen?

The mTOR pathway, involved in cellular growth and proliferation [27,28], has a well-described role in carcinogenesis, [27] and mTORi is used for treating some types of cancer. Everolimus (EVL) is FDA-approved for treating certain breast cancers, neuroendocrine tumours and renal cell carcinoma. However, the EVL dose used in oncology is higher than the dose used to prevent transplant rejection. The classical EVL dose for cancer treatment is 5 or 10 mg daily, often yielding EVL blood trough levels >10 ng/ml [29,30]. Indeed, a therapeutic window of 10–26 ng/ml has been proposed [29]. The EVL anti-cancer effect is dose-dependent [30], but

limited by poor tolerability. A recent RCT in KTRs using a CNI-free EVL-based anti-rejection regimen (ZEUS [31,32]) targeted EVL trough levels to 8 ng/ml (range, 6–10 ng/ml) [31]. Of note, in association with CNI, EVL blood trough levels are kept even at lower levels (5.5 ng/ml; range, 3–8 ng/ml) [33]. Despite the lower mTORi doses used in SOT transplantation compared with oncology, evidence from meta-analyses of RCTs [34,35] and large registry analyses [36] indicates that SOT recipients on mTORi have a reduced risk of developing non-melanoma skin cancers.

It is less clear, however, whether mTORi could also decrease the risk of developing other post-transplant cancers. The only individual-level patient data meta-analysis of >5800 KTRs from 21 RCTs on CNI-free mTORi-based maintenance regimens [34] showed no difference in risk of developing other cancers (excluding non-melanoma skin cancer) between patients on sirolimus (SRL) versus controls in the overall study population, although the subgroup analysis on conversion RCTs from CsA to SRL (vs RCTs with *de novo* SRL) did show a 48% reduction in the risk of other cancers (HR 0.52; 95% CI 0.38–0.69) [34]. Concerning observational studies using data from large registries, a US registry study in 32,604 KTRs (5687 SRL exposed) [37] found no significant difference in cancer incidence among KTRs on SRL (excluding non-melanoma skin cancer), and an increased incidence of prostate cancer, although there was a trend towards a beneficial effect of SRL for most other cancer types, with a 26% relative decrease in cancer incidence overall [37]. The authors concluded that this modest association did not provide strong evidence that SRL prevents post-transplant cancer, but it may be advantageous among KTRs with high cancer risk [37]. Finally, a recent worldwide registry analysis by the Collaborative Transplant Study group in 78,146 KTRs (4279 on mTORi) indicated that inclusion of an mTORi in the *de novo* immunosuppressive regimen had no significant influence on incidence of post-transplant cancers other than basocellular carcinoma of the skin [36]. Studies specifically looking at the impact of mTORi on recurrence of post-transplant cancer, however, are lacking.

Post-transplant lymphoproliferative disease

Despite *in vitro* evidence on mTORi inhibiting EBV replication [38], current clinical evidence for the benefit of a CNI-free mTORi regimen is limited to case reports, which might suffer from publication bias. Therefore, currently, there is no evidence that allows to universally recommend a switch to a CNI-free mTORi regimen in KTRs treated for PTLD with a curative intent.

Although mTORi might reduce the incidence of post-transplant cancer in some settings, it should be noted that the meta-analysis of RCTs mentioned earlier showed that CNI-free mTORi-based regimens were associated with a 20% increased risk of death after 4 years post-randomization, mainly due to infection and cardiovascular disease [34]. Moreover, a meta-analysis in KTRs showed that converting from a CNI to a CNI-free mTORi-containing regimen (during the first year post-transplant) almost doubled the risk of rejection [39]. Furthermore, 22% discontinued mTORis because of adverse events [39]. Risk of graft loss might depend on the baseline level of renal function. The CONVERT study [40], the largest RCT on conversion from CsA to SRL ever performed ($n = 830$), showed that conversion was safest in patients with estimated glomerular filtration rate (eGFR) >40 ml/min and urinary protein-to-creatinine ratio ≤0.11 gr/gr. The recent ZEUS RCT on conversion from CsA to EVL (300 patients randomized at 4-month post-transplant on switching from CsA to EVL with target 6–10 ng/ml, or continuing CsA) has not confirmed an increased risk of death, after a follow-up of 5 years [32]. Some concerns remain regarding the risk of rejection: a study carried out in a subset of 127 German patients enrolled in the same or a similar RCT (CRAD001ADE13 trial) showed that, at 5 years after transplantation, the risk of developing donor-specific antibodies was doubled in patients converting from CsA to EVL versus those continuing CsA (23% vs 11%) [41], although another Scandinavian RCT ($n = 202$) showed no increase in dnDSA rates at 3 years post-KT after early conversion to EVL versus continued CsA (15% vs 21%) [42]. The risks of a switch may be low in well-selected patients providing that concomitant therapy with MMF and steroids is sufficiently strong [43].

Should we switch to an immunosuppressive regimen with mTORi and low-dose CNI?

Maintenance regimens using mTORi + CNI rather than CNI-free mTORi-based regimens are increasingly popular, especially in KTRs, since recent publication of results from the TRANSFORM [44] and ATHENA trials [45]. Compared with CNI-free mTORi-based regimens, CNI + mTORi regimens seem better tolerated and more effective in preventing rejection. The TRANSFORM RCT [33,44], in 2037 *de novo* KTRs, showed that a regimen using (EVL [target 5.5 ng/ml] plus low-dose CNI [target Tac, 4 ng/

ml; target CsA, 50 ng/ml]) [33] resulted in similar graft function, GFR and rejection risk at 24 months, and a reduced risk of cytomegalovirus and BK polyomavirus infection, versus a regimen with standard CNI dose and MMF [46]. Despite the relatively low mTORi dose, drug discontinuation was higher in the EVL plus low-dose CNI arm (23% vs 12%), possibly due to side effects such as, primarily, peripheral oedema (37% vs 26%) [46]. Additional side effects that are more common with EVL and might increase rates of drug discontinuation were hyperlipidaemia (35% vs 19%), proteinuria (13% vs 6%), stomatitis/mouth ulcers (8% vs 2%), thrombocytopenia (7% vs 4%) and interstitial lung disease (1.1% vs 0.3%) [46]. No difference in cancer risk was detected in this study, but it is likely that longer follow-up is required to adequately assess this in the TRANSFORM RCT.

Cancer risk was examined in a recent meta-analysis of 7356 participants from 24 RCTs [47], comparing KTRs receiving mTORi + CNI versus regimens containing MMF/MPA or AZA + CNI. That meta-analysis found a 50% decreased risk of cancer among those on mTORi + CNI regimens at long-term follow-up (>2 years; 1466 participants), an effect driven mainly by two studies [48,49]. Analysing data of Australia/New Zealand patients from one of those two studies (A2309), and using the ANZDATA Registry to track patients in the long term follow-up, Lim *et al* [50] compared 7-year risk of incident cancer among KTRs randomized in Australia/New Zealand to mTORi + CNI (pooling two CsA-associated EVL dosage regimens [1.5 mg (n = 35) and 3.0 mg (n = 31) daily] vs MMF/MPA and standard-exposure CsA [n = 29]). Though not statistically significant because of the small sample size, the relative reduction in incidence of non-skin cancer was 65% (HR 0.35; 95% Cl 0.09–1.25); the point estimate of the hazard ratio was virtually identical to that of non-melanoma skin cancer, which was significant because of the larger number of events (HR 0.34; 95% CI 0.13–0.91). However, this effect seems to have been driven mainly by the 3.0 mg daily regimen, again suggesting a dose-dependent anti-cancer effect of EVL. Also in the Australia/New Zealand substudy [50], mTORi + CNI therapy was less well tolerated than MPA/MMF, since only ~50% of patients allocated to EVL continued with their original therapy beyond 2 years.

Most of these RCTs on mTORi + CNI concern *de novo* KTRs. Evidence from RCTs on switching from MMF/MPA to mTORi, however, is scarce. Indirect relevant evidence comes from the HERAKLES study [51,52], which showed that switching to EVL+ CNI was well tolerated: the rate of reported discontinuation due to adverse events was similar, after 4-year follow-up, in 161 CsA-treated patients who switched 3 months post-transplant from MMF/MPA to EVL (target 3–8 ng/ml), compared with the 165 who continued the standard CsA + MMF/MPA regimes [52]. However, details on individual adverse effects or cancer incidence were not reported.

It is unclear whether available evidence on the safety and efficacy of switching to an mTORi-based regimen can be applied to KTRs with a history of cancer treated with curative intent. In such patients, efficacy could depend on residual tumour burden, as demonstrated with skin cancer [53]. In an RCT on squamous cell carcinoma, switching from CNI to mTOR inhibitors halved the risk of cancer recurrence in KTRs with history of squamous cell carcinoma (from 66% to 34%) [53]. However, the effect of mTOR inhibitors could not be demonstrated in the subgroup of patients with extensive disease (>1 tumour) [53].

Summary: Information to guide shared decision-making

Although reducing the overall immunosuppressive load and/or switching to an alternative drug regimen may potentially be of benefit to avoid cancer recurrence, the evidence supporting such a change of immunosuppressive therapy is still weak and should be balanced against the risk of rejection and the risk of other severe adverse events. For these reasons, we contend that patient preference should be taken into account [54]. In this regard, it is worth mentioning the SONG-Tx initiative [55] on kidney transplantation, which was aimed at selecting the outcomes that were critically important to all stakeholders for decision-making, including patients and caregivers. Indeed, patients involved in this initiative felt that graft function was more important than death [56], because they regarded death as inevitable whereas efforts could be made to prevent graft failure. Some regarded graft failure and return to dialysis as being even worse than death [56]. However, this should not be interpreted as a plea against any drug modification in order to, above all, avoid rejection: we rather aimed to provide data to support a balanced decision, and to provide reassurance about settings where drug modifications could be reasonably safe.

Below, we summarize the key points that we believe can be used by transplant physicians as a basis for informed decision-making purposes. In addition, we provide a concise plain-language summary for patients (see Appendix S1).

Potential benefits and risks of the strategy of reducing overall maintenance anti-rejection treatment

Reducing overall maintenance anti-rejection treatment, to an extent that depends upon cancer type, stage and other factors, has been the traditional approach used for KTRs with a history of non-skin cancer treated with a curative intent. This approach needs to be balanced carefully against the risk of allograft rejection and graft loss. Rejection can occur as a result of anti-rejection treatment reduction – either as an acute event, with sudden deterioration of graft function, or, more likely, as a chronic process, with slow graft function deterioration over a period of months or years. The risk of graft rejection can vary among individuals, depending on patient age (the younger the age and the higher the risk), history of rejection and presence of donor-specific antibodies, among other factors. Reduction in trough blood levels of CNI inhibitor below the traditional lower bounds (e.g. halving the dose and/or Tac trough blood levels <5 ng/ml, CsA <100 ng/ml) might be the most effective strategy to prevent cancer recurrence, but also the least safe strategy to prevent rejection – especially if that occurs early after transplantation (it has been shown to cause +10% increased risk of acute rejection at 1 year in steroid-free regimens, even in low-risk individuals, in whom the reduction was carried out 4–12 months after transplantation).

Potential benefits and risks of the strategy of switching from CNI to mTORi

The strategy of replacing the CNI with a mTORi that has both immunosuppressive and anti-cancer effects could be an effective strategy in preventing recurrence of cancer, although the current available evidence on efficacy mainly concerns non-melanoma skin cancers and Kaposi sarcomas. RCTs on conversion from CsA to mTORi (SRL, target blood level 8–20 ng/mL) at various time points after transplantation in non-cancer patients have shown that the conversion from CNI to mTORi halves the risk of non-skin cancer. From studies on cancer patients, it seems that the mTORi anti-cancer effect is dose-dependent. Unfortunately, the mTORi dosage that is most effective against cancer is often poorly tolerated. The studies performed on non-cancer KTRs, in whom the mTORi dosage was in the lower bound of the potential effective dosage, showed that even at such low dosages, the conversion from CsA to sirolimus is associated with an increased risk of SRL withdrawal because of adverse effects. It is worth noting that in the same studies, conversion from CsA to mTORi was associated with increased mortality (up to 20% higher after 4 years in patients undergoing replacement of CsA with SRL). However, the increased risk of death was not confirmed by the most recent study, with 5-year follow-up, on the conversion from CsA to EVL (target 6–10 ng/ml). The risk of graft failure associated with the conversion from CNI to mTORi might depend on baseline graft function: the risk of graft loss is lowest in patients with good graft function at the time of conversion (eGFR >40 ml/min and protein-to-creatinine ratio ≤0.1). There is also some evidence that conversion to CNI to mTORi could be associated with an increased risk of developing chronic rejection, although reports have shown mixed results: the risks may be limited in well-selected patients providing that the concomitant medication (MMF and steroids) is sufficiently strong.

Potential benefit and risks of the strategy of switching from CNI + MPA/MMF to CNI + mTORi

The strategy of replacing the MMF/MPA with a mTORi (EVL target 5.5 ng/ml) while keeping the CNI (Tac or EVL) at low doses (target Tac, 4 ng/ml; target CsA, 50 ng/ml) might be safer in terms of risk of rejection, and of adverse effects, compared with the previous strategy. Compared to regimes on the conversion between CsA and SRL, RCTs on the strategy of replacing MMF/MPA with a mTORi showed that 1) the benefit in reducing the risk of non-skin cancer may be similar, but is currently far less documented than the strategy of replacing CNI with mTORi, especially under the current low-dosage EVL regimes; 2) there is no increased risk of rejection, graft loss or mortality; and 3) mTORi is better tolerated. However, mTORi may still cause some side effects such as peripheral oedema, stomatitis/mouth ulcers and haematological complications that can lead to drug discontinuation. In the RCTs discussed in this article, this has happened in at least 1 in 10 patients.

Authorship

U.M. led the ESOT TLJ 2.0 WS 03. U.M., R.H., S.C. and L.P. engaged in the online discussions involving a multidisciplinary audience. U.M. and R.H. designed the study. L.P. performed the systematic literature search. U.M., R.H. and S.C. interpreted the results. U.M., R.H., S.C. and L.P. wrote the report. All authors approved the final version to be published. U.M. and R.H. agree to be accountable for all aspects of the work in ensuring that questions

related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest

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Ethical approval

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

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 Summary for patients.

Table S1 Should we decrease the overall anti-rejection therapy in potentially cured post-kidney transplant solid organ cancer (excluding non-melanoma skin cancer)?

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