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Current knowledge of immunosuppression as a risk factor for skin cancer development

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ABSTRACT

This review outlines our current understanding of the relationship between immunosuppression and skin cancer. Primary immunodeficiencies increase the incidence of skin cancer, but due to their low frequency, the establishment of accurate risk ratios remains lacking. Regarding secondary immunosuppression, available data demonstrate a significant increase of skin cancer in solid organ recipients, being the most common malignancy of this population. Immunosuppressive drugs have an important role in these patients, with an impact related to both the cumulative dose and the type of regimen used. The association of skin cancer and immunosuppressive drugs in non-transplant patients is conflictive for most of the drugs except for azathioprine. Many cancers lead to secondary immunosuppression as a mechanism for tumor growth and advancement, increasing the risk of progression of the primary tumor. Novel insights related with tumorigenesis and immune-escape mechanisms have led to promising new treatments in melanoma and squamous cell carcinoma.

1. Introduction

The relationship between immunosuppression and skin cancer is well documented, both for primary immunosuppression (genetic) and secondary immunosuppression, which include organ transplant recipients (OTRs), people with human immunodeficiency virus (HIV) infection, chronic users of immunosuppressive drugs (ISDs) and cancer-induced immunosuppression (CII).

2. Primary immunosuppression and skin cancer

Primary immunodeficiencies (PIDs) are inherited disorders characterized by a deficiency or dysfunction of at least one component of the immune system. Currently there are 330 diseases and 320 genetic defects already described (Bousfiha et al., 2018). They are uncommon pathologies, with an incidence of 1:10,000 live births (Salavoura et al., 2008; Mortaz et al., 2016).

PIDs are caused by defects in the innate or adaptive immune system, with abnormalities in the cellular and/or humoral immunity. At the present time, they are classified in 9 main categories, each one with multiple subtypes: 1. Immunodeficiencies affecting cellular and humoral immunity, 2. Combined immunodeficiency with associated or syndromic features, 3. Predominantly antibody deficiencies, 4. Diseases of immune dysregulation, 5. Phagocytes defects, 6. Defects in intrinsic and innate immunity, 7. Auto-inflammatory disorders, 8. Complement deficiencies and 9. Phenocopies of PID (Bousfiha et al., 2018).

Abbreviations: ADCs, Acquired immune deficiency syndrome-defining cancers; AIDS, Acquired immune deficiency syndrome; ART, Anti-retroviral therapy; AZA, Azathioprine; BCC, Basal cell carcinoma; CII, Cancer-induced immunosuppression; CNI, Calcineurin inhibitors; CPA, cyclosporine-A; CTLA-4, cytotoxic T-lymphocyte antigen 4; cSCC, Cutaneous squamous cell carcinoma; DC, Dendritic cells; HL, Hodgkin lymphoma; HPV, Human papilloma-virus; HR, Hazard ratio; IDO, indolamine-2,3-dioxygenase; IR, incidence rate; ISDs, Immunosuppressive drugs; ISF, Immunosuppressive factors; KS, Kaposi's sarcoma; LPD, lymphoproliferative disorders; MCC, Merkel cell carcinoma; MDSCs, Myeloid-derived suppressor cells; MM, Melanoma; MMF, mycophenolate mofetil; mTOR, mammalian target-of-rapamycin inhibitors; MTX, Methotrexate; NADCs, non-AIDS defining cancers; NHL, Non-Hodgkin lymphoma; NMSC, Non-melanoma skin cancer; OTRs, Organ transplant recipients; PD-1, programmed cell death protein 1; PIDs, Primary immunodeficiencies; RA, rheumatoid arthritis; RCT, randomized clinical trials; SMR, Standard mortality ratio; SIR, Standardized incidence ratio; TAMs, Tumor associated macrophages; TC, tacrolimus; TGF- β, Transforming growth factor β; TIL, Tumor-infiltrated lymphocytes; TME, Tumor microenvironment; TNF- α, Tumor necrosis factor alpha; US, United States; VEGF, Vascular endothelial growth factor.

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PIDs present various clinical phenotypes including increased risk of infections, allergy, autoimmunity and malignancies. The association between PIDs and cancer was first described in 1963, and now is considered the commonest cause of death after infections in affected children (Mortaz et al., 2016).

The estimated malignancy risk in PIDs has varied considerably according to different studies. In the early 1970 s it was reported a risk of 4 %, 10.000 times higher than in general population (Loachim, 1990). Recent cohort studies have revealed much smaller risks, varying from 1, 4 to 2,3 times (Satgé, 2018; Mayor et al., 2018; Vajdic et al., 2010; Jonkman-Berk et al., 2015).

Because there are many subtypes of PIDs, the mechanisms that explain their higher incidence of cancer are also multiple and variable. However, the fact that only few subtypes of PIDs have a significant association with cancer puts into doubt that impaired immunosurveillance is the main cause of this phenomenon. Indeed, there are many other factors involved, which have been classified into intrinsic and extrinsic. Intrinsic factors are (1) defects on myeloid and/or lymphoid stem cell development, differentiation or apoptosis, (2), defects on lymphocyte (co-)signaling, cytoskeleton, cytotoxicity and/or metabolism and (3) DNA defects (chromosome stability, telomere maintenance and/or repair). Extrinsic factors are (1) chronic inflammation, (2) infection with oncogenic viruses and (3) impaired immunosurveillance (Hauck et al., 2018).

Since there are many extremely uncommon PIDs, it is difficult to establish their neoplastic predisposing effect. The PIDs most commonly associated with malignancies are common variable immunodeficiency, Wiskott–Aldrich syndrome, ataxia-telangiectasia, Bloom syndrome and severe combined immunodeficiency (Mortaz et al., 2016; Kiykim et al., 2020).

The type of malignancy associated depends on many factors like the subtype of PID and patient's age (Salavoura et al., 2008). However, the spectrum of cancers associated is narrow. The most frequent one is lymphoma, with an incidence 8–13 times higher than in general population (Satgé, 2018). Other cancers associated are leukemia, myelodysplastic syndrome, stomach cancer, carcinomas, medulloblastoma, neuroblastoma and melanoma (Satgé, 2018; Vajdic et al., 2010; Hauck et al., 2018; Kiykim et al., 2020).

To our knowledge, there are no studies that evaluate specifically the association between PIDs and skin cancer. Both Dutch and United States (US) cohorts of 745 and 3685 PIDs patients respectively revealed similar results, in which skin cancer was the second most frequent malignancy after lymphomas, accounting for 15–21 % of all malignancies reported and having 3,3–4,5-fold increased risk compared to general population (Mayor et al., 2018; Jonkman-Berk et al., 2015). Neither of these two studies specified the type of skin cancer evaluated.

Because of their low prevalence, the association between specific subtypes of PIDs and skin cancer is based mostly upon case reports (Table 1). More studies are needed to certainly evaluate the association between PIDs and skin malignancies.

Table 1
Primary Immunosuppression and Skin Cancer.

Disease	Frequency	Global cancer risk (fold increase and/ or prevalence [%])	Skin cancer associated (case reports)
Predominantly antibody deficiency			
CVID (Mayor et al., 2018; Jonkman-Berk et al., 2015)	1/25.000–1/ 50.000 (Resnick et al., 2012). 35 % of PIDs in US registry (Mayor et al., 2018)	10 % (1,5–20,7 %) (Tak Manesh et al., 2017)/12–18 fold greater than in general population (Mortaz et al., 2016) 48,3–70 % of all PID's malignancies (Mayor et al., 2018; Jonkman-Berk et al., 2015)	cSCC (Tak Manesh et al., 2017) MM (Tak Manesh et al., 2017)
Combined immunodeficiency with associated or syndromic features			
Cartilage-hair hypoplasia syndrome	1/1000–2000 in USA, 1/ 23.000 in Finland (Satgé, 2018)	Overall malignancy SIR 6,9 (Mäkitie et al., 1999) SIR of 90 for lymphomas (Mäkitie et al., 1999)	SIR of 35 for BCC (Salavoura et al., 2008; Mäkitie et al., 1999)
Wiskott- Aldrich Syndrome	1/100.000 (Satgé, 2018)	13 % (Satgé, 2018)	KS (Salavoura et al., 2008; Dhouib et al., 2018)
Phagocytic defects			
GATA 2 deficiency	Unknown (Wlodarski et al., 2017)	75 % for myeloid neoplasms (Wlodarski et al., 2017)	HPV-related cSCC (Raje and Dinakar, 2015), (Donadieu et al., 2018) MM (Nguyen et al., 2018) MCC (Crall et al., 2016)
Defects in intrinsic and innate immunity			
WHIM Syndrome	1/4.000.000 (Satgé, 2018)	30 % in 40 years (Satgé, 2018)	Oral and anogenital HPV- related cSCC (Cipriani et al., 2010)
Epidermodysplasia verruciformis	1/1.000.000 (Schierbeck et al., 2019)	50 % for SCC (Patel et al., 2010)	cSCC (90 % positive for HPV 5 or 8) (Schierbeck et al., 2019)
Immunodeficiencies affecting cellular and humoral immunity			
DOCK 8 deficiency (AR- HIES)	Unknown (230 cases reported) (Biggs et al., 2017)	17 % at a median age of 12 years (Aydin et al., 2015)	cSCC (Biggs et al., 2017)
Ox40 deficiency (Raje and Dinakar, 2015)	1/10 million (Byun et al., 2013)		KS (Byun et al., 2013; Jackson et al., 2016)

AR-HIES: Autosomal- Recessive Hyper-igE Syndrome/BCC: basal cell carcinoma/CVID: common variable immunodeficiency/HPV: human papillomavirus/KS: Kaposi's sarcoma/ MM: melanoma/MMC: Merkel cell carcinoma/PID: primary immunodeficiency/sSCC: cutaneous squamous cell carcinoma/ SIR: standardized incidence ratio/WHIM: Warts, Hypogammaglobulinemia, infections, myelokathexis Syndrome

3. Secondary immunosuppression and skin cancer

3.1. Post-transplant immunosuppression

In the last decades there has been a considerable increase in the survival of OTRs, which has led to a higher incidence of cancer and cardiovascular diseases. Malignancy causes a significant proportion of the late mortality in this population (10–47 %) and is expected to become the leading mortality cause in the next decade (Acuna, 2018; Giorgia et al., 2016; Gutierrez-Dalmau and Campistol, 2007).

OTRs have a 3–5 fold overall increase of cancer compared to the general population, especially non-Hodgkin lymphoma (NHL) and non-melanoma skin cancer (NMSC) (Acuna, 2018). Although there is an increase in the overall malignancy risk, the cancer profile of OTRs is different than in general population, in which certain malignancies like breast, prostate and colorectal cancers are frequently seen. In contrast, OTRs have a higher incidence of many virus-related tumors like NHL, Hodgkin lymphoma (HL), Kaposi's sarcoma (KS), cutaneous squamous cell carcinoma (cSCC), anogenital and liver carcinomas (Engels et al., 2011; Grulich et al., 2007; De Fijter, 2017); as well as cancers of organs that are frequently transplanted, like kidney and lung (Engels et al., 2011).

In addition to their higher incidence, cancers in OTRs have also

worse outcomes and increased metastatic risk compared to the general population (Sherston et al., 2014). The overall cancer mortality in OTRs is increased in 3 fold (Bhat et al., 2018).

The pathogenesis that explain the association of organ transplant and the increased risk of cancer is attributed partially to decreased immune-surveillance, but also to the activation of oncogenic viruses, chronic inflammatory state, immunosuppressant medications and pre-existing cancer risk factors (Acuna, 2018).

The severity and duration of immunosuppression are one of the most important risk factors of malignancy (Gutierrez-Dalmau and Campistol, 2007; De Fijter, 2017; Bhat et al., 2018). However, both the incidence and the type of cancer associated vary according to the transplanted organ, being higher for lung and heart recipients (Acuna, 2018; Bhat et al., 2018). This is probably due to the fact that cardio-thoracic transplants are often performed at older ages and require a higher degree of immunosuppression to prevent graft rejection (Kovach and Stasko, 2009; O'Reilly Zwald and Brown, 2011).

Skin cancer is the most frequent malignancy in OTRs (O'Reilly Zwald and Brown, 2011). More than half of the patients will develop at least one, and 44 % two or more, being 95 % of these NMSC, particularly cSCC (Kovach and Stasko, 2009; O'Reilly Zwald and Brown, 2011; Collins et al., 2019). Indeed, the relation of cSCC and basal cell carcinoma (BCC) is inverted in OTRs, favoring cSCC over BCC (4:1) (Kovach and Stasko, 2009). Most skin cancers develop 3–5 years post-transplant and 10–15 years earlier compared to general population (Kovach and Stasko, 2009; Howard et al., 2018).

The largest published registry of malignancies in OTRs (534.472 US OTRs followed from 1987 to 2015) reported a global incidence of cancer of 13,2 %, being 28,1 % and 25,6 % for heart and lung recipients respectively. Of all malignancies, 50 % were cutaneous, followed by solid organs (40 %) and hematological malignancies (10 %). Of the total of skin cancers, 60,2 % were cSCC, 34 % BCC, 4,95 % melanoma (MM) and 0,75 % KS (Bhat et al., 2018).

In addition of the higher incidence, skin cancers in OTRs are locally more aggressive and have an increased risk of metastasis, subclinical extension and mortality (Gutierrez-Dalmau and Campistol, 2007; Gerlini et al., 2005). A retrospective study of 2998 patients revealed that NMSC in OTRs have almost 3 fold increased risk of aggressive subclinical extension, defined by requirement of at least 3 Mohs micrographic surgeries and free margins of at least 10 mm (Song et al., 2016). Skin cancers in OTRs have a metastatic risk of 8 %, which is 1,6–16 times higher compared to general population (Howard et al., 2018).

A US cohort study of 496.951 OTRs revealed a 9-fold increase of skin cancer mortality in this population (35/100.000 vs 4/100.000 person-years), favoring MM (11,48/100.000 person-years) over cSCC (4,94/100.000 person-years) (Giorgia et al., 2016). Another Canadian cohort study of 11.061 OTRs followed for 85.557 person years revealed that NMSC had the highest incremental risk of death of all malignancies evaluated, with a standard mortality ratio (SMR) of 29.85 (18.23–46.10). In this study, MM had a SMR of 3.93 (2.20–6.48) (Acuna et al., 2016). In both studies, mortality due to skin cancer was higher compared to other frequent malignancies like colon and breast cancer. An Australian cohort of heart recipients revealed that 27 % of deaths after 4 years were attributed to skin cancer (Ong et al., 1999).

There are many risk factors associated with the development of skin cancer in OTRs; some related to the patient, others related to the type of transplant and others to the post-transplant period (summarized in Table 2). Most of these factors not only increase the incidence, but also the mortality (Giorgia et al., 2016; Bhat et al., 2018; Howard et al., 2018).

The frequency and characteristics of skin neoplasms in OTRs vary according to the type of skin cancer (Table 3). Interestingly, beta human papilloma-virus (β-HPV) has been identified in 80–100 % of NMSC and pre-malignant lesions in OTRs, compared to 30 % in general population (Gutierrez-Dalmau and Campistol, 2007). In an immunosuppressed setting, active β-HPV contributes in early stages of skin carcinogenesis through the expression of p63 and increased keratinocytes steaminess. However, it is frequently not found in more advanced stages of tumors, probably due to the ability of neoplastic cells to proliferate independently of virus gene expression after acquiring sufficient mutations (Borgogna et al., 2018). Similarly, KS and Merkel cell carcinoma (MCC)-also virus-related skin tumors- are significantly increased in OTRs (Tuttleton Arron et al., 2011). In contrast, when compared to general population, the incidence of BCC and MM -which are not virus-related cancers- is not that high.

Since the introduction of ISDs in 1995, acute graft rejection decreased from 50 % to 10 % (Knoll et al., 2014). However, the post-transplant malignancy is now considered one of the inevitable risks of the long-term use of these therapies (Gutierrez-Dalmau and Campistol, 2007). The most common immunosuppressive regimens used in OTRs include one of the nucleotide inhibitors (mycophenolate mofetil or azathioprine) and one of the calcineurin inhibitors (tacrolimus or cyclosporine-A) (Coghill et al., 2016). A high exposure to these drugs,

Table 2
Significant skin cancer risk factors in organ transplant recipients.

	Risk Factor	Estimated risk
Patient's related risk factors	Male sex	HR = 1,56–1,69 (Bhat et al., 2018; Howard et al., 2018) Mortality HR = 1,85 (Giorgia et al., 2016)
	Age > 50 years	Incidence HR = 2,77 (Garrett et al., 2017) Mortality HR = 2,86 (Giorgia et al., 2016)
	Caucasian	OR = 15 (Ong et al., 1999) Mortality HR = 6,29 (Giorgia et al., 2016)
	Cumulative UV radiation exposure	HR = 19 (total sun burden > 10 points[a]) (Rodríguez-Acosta et al., 2015) 78 % of NMSC develop in sun-exposed areas (Ng et al., 2014) OR = 47 for high cumulative life-time UV exposure vs low (Bouwes, 1993)
	Previous skin cancer	HR = 4,69 (Garrett et al., 2017)
Transplant's related risk factors	Heart or lung transplant	HR = 2–3 vs kidney transplant (Howard et al., 2018) Mortality HR = 2,90 in thoracic vs non thoracic transplant (Giorgia et al., 2016)
	Second transplant	Aggressive cSCC in second and first transplant kidney recipients was 26,4 % vs 9,4 % respectively (Ducroux et al., 2017)
Post- transplant's related factors	Number of immunosuppressant	2,38- fold increase with triple drug therapy (CPA + AZA + prednisolone) vs dual therapy (AZA + prednisolone or CPA + prednisolone) (Jiyad et al., 2016)
	Calcineurin inhibitors	2,81-fold increase for cSCC (Jensen et al., 1999)
	Azathioprine	1,56- fold increase for cSCC (Jiyad et al., 2016) IRR = 1,35 for MM (Robbins et al., 2015)
	Voriconazol	73 % higher risk of developing cSCC, with additional 3 % per 30 days of exposition (Howard et al., 2018)
	Time since transplant	Cumulative incidence of skin cancer in Australian Heart recipients was 8,5 %, 21 %, 31 % and 43 % at 1, 3, 5 y 10 years respectively (Ong et al., 1999)

AZA: Azathioprine/ CPA: cyclosporine-A/HR: Hazard ratio/IRR: incidence rate ratio/MM: melanoma/NMSC: non melanoma skin cancer /OR: Odds ratio/cSCC: cutaneous squamous cell carcinoma.

[a] Based on residency, occupational exposure and recreational exposure.

Table 3
Skin Cancer in Organ Transplant Recipients.

Skin Cancer	IHR	Comments
KS	84–500 times (Mittal and Colegio, 2017)	< 5 % skin cancer in OTRs (Kovach and Stasko, 2009; Gerlini et al., 2005) More aggressive behavior, with extra-cutaneous sites affected more frequently (Gerlini et al., 2005). Latency period of 13 years post transplantation (Collins et al., 2019).
cSCC	65–250 times (De Fijter, 2017; Collins et al., 2019)	Most common neoplasm in OTRs (Collins et al., 2019). cSCC: BCC relation is inverted (from 1:4–4:1) (De Fijter, 2017; Kovach and Stasko, 2009). Metastasis risk in OTRs is 6–9 % vs. 0,5–5 % in general population (Kovach and Stasko, 2009), (Brin et al., 2014). Mortality risk is 10–50 times higher (Howard et al., 2018). Frequent field- cancerization near the lesion (Kovach and Stasko, 2009). 90 % of cSCC in OTR contain HPV DNA (compared with 11–32 % in normal skin) (Mittal and Colegio, 2017). 7,2 fold increase of recurrence (Elghouche et al., 2019).
MCC	5–50 times (Collins et al., 2019; Clarke et al., 2015)	Latency period of 7,5 years post-transplant (Kovach and Stasko, 2009; Brin et al., 2014). Diagnostic is made 15–25 years earlier than general population (Kovach and Stasko, 2009; Gerlini et al., 2005). 1 year-survival of 47 % vs 88 % in general population (Howard et al., 2018). Metastasis in 75 % of patients (Kovach and Stasko, 2009). Mortality risk is 12-fold higher (Garrett et al., 2015). Similar location than in general population (Brin et al., 2014).
BCC	10 times (Collins et al., 2019; Brin et al., 2014)	Similar behavior than in immunocompetent population (Mittal and Colegio, 2017; Brin et al., 2014).
MM	Controversial (0–8 times) (Collins et al., 2019; Robbins et al., 2015; Mittal and Colegio, 2017; Brin et al., 2014; Džambová et al., 2016)	5 % of skin cancer in OTRs (Gerlini et al., 2005). Mean time of diagnosis is 5 years post-transplant (Džambová et al., 2016). More aggressive and worst overall survival rates compared to general population (Collins et al., 2019; Robbins et al., 2015; Dahlke et al., 2014), with a mortality risk 2,98–4,26 times higher (Howard et al., 2018), (Acuna et al., 2016; Robbins et al., 2015). 0–11 % recurrence for MM arising prior to transplantation (Mittal and Colegio, 2017; Brin et al., 2014; Dahlke et al., 2014). 38 % originate from previous melanocytic nevi (vs 25 % in general population) (Džambová et al., 2016).
PCL	Unknown (very rare) (Lok et al., 2005)	Current data regarding the prevalence of CTCL and CBCL in OTRs is not conclusive (Lok et al., 2005; Seçkin et al., 2013; Ravat et al., 2006; Ward et al., 2001)
CTCL		No consistent association with lymphotropic viruses like EBV or HTLV-1 (Lok et al., 2005; Ravat et al., 2006). Clinical appearance, histology and immunohistochemistry are similar to general population, except for an increased frequency of erythroderma (Lok et al., 2005). Mycosis fungoides and CD30+ large PCL are the most frequent variants (Lok et al., 2005). Poor prognosis compared to general population (Lok et al., 2005).
CBCL		Associated with EBV (Ravat et al., 2006). Better prognosis than CTCL (Lok et al., 2005).

CBCL: Cutaneous B-cell lymphoma/ CTCL: Cutaneous T-cell Lymphoma/ BCC: basal cell carcinoma/ EVB: Epstein Barr Virus/ HHV-8: human herpesvirus-8/ HPV: human papillomavirus/ HTLV-1: Human T- cell leukemia virus type 1/ IHR: Incidence hazard ratio/ KS: Kaposi's sarcoma/MCC: Merkel cell carcinoma/ MM: melanoma/ PCL: Primary cutaneous lymphoma/ OTRs: organ transplant recipients /cSCC: cutaneous squamous cell carcinoma

directly related to treatment duration and dose, is strongly associated with both the incidence and mortality of skin cancer (Plasmeijer et al., 2019). However, the estimated risk of each drug varies considerably according to different studies, which reflects differences in geographical distribution and UV-exposure, ethnicities, the immunosuppressive regimen used, the length of follow-up and the transplanted organ (Vial and Descotes, 2003). The following are the most common ISDs used in OTRs.

3.1.1. *Azathioprine*

Azathioprine (AZA) was the main ISD used in the beginning of the transplantation era until the introduction of mycophenolate mofetil (MMF) in the late 1990s. However, nowadays is still employed by 6–69 % of OTRs (Jiyad et al., 2016). The carcinogenic risk of AZA in OTRs is well documented. Indeed, the International Agency for Research on Cancer classifies it as a group I carcinogen, especially for NMSC (Coghill et al., 2016).

A systematic review and meta-analysis that analyzed the risk of skin cancer in OTRs treated with AZA compared to other ISDs found that the risk of cSCC was increased in 56 %, but there was no significant association with BCC (Jiyad et al., 2016). Another case-control study found that AZA increased 2 times the risk of developing one cSCC and 4,9 times the risk of multiple cSCC compared to other ISDs (Coghill et al., 2016).

Regarding the association with MM, the risk of acquiring this malignancy is increased in 35 % (Robbins et al., 2015).

3.1.2. *Mycophenolate Mofetil (MMF)*

Several studies have shown no overall increased risk of cancer in MMF users, (Robson et al., 2005; Funch et al., 2005; Lake et al., 2005; Cherikh et al., 2003); for skin cancer the results are similar. Interestingly, a case control study of 170 OTRs found that MMF was associated with a lower risk of developing cSCC independent on the previous or concomitant ISD used (Coghill et al., 2016). Another study of 392 liver OTRs showed that changing calcineurin inhibitors (CNIs) to MMF monotherapy was also associated with a lower risk of malignancy for both NMSC and non-skin cancers independent of others risk factors (Aguiar et al., 2017).

The possible antitumor effects of MMF are attributed to inhibition of tumor cell growth, angiogenesis and cell adhesion. However, most of these effects have been demonstrated in vitro, with a marginal effect in in vivo studies (Blaheta et al., 2003; Majd et al., 2014).

3.1.3. *Calcineurin inhibitors (CNI): Cyclosporine-A (CPA) and tacrolimus (TC)*

The pro–oncogenic functions of CNI are explained by enhancement of tumor angiogenesis and invasiveness, suppression of immunological clearance of malignant cells (Gutierrez-Dalmau and Campistol, 2007)

and reduced apoptosis and DNA-repair following UVB radiation (Gutierrez-Dalmau and Campistol, 2007; Howard et al., 2018; Sugie et al., 2002).

The association between these drugs and skin cancer in OTRs is well documented. cSCC is the most frequent NMSC in OTRs receiving CPA, with a dose-dependent association (Howard et al., 2018). When comparing the risk of malignancy between CPA and TC in OTRs, there is conflicting data. However, best evidence suggests that there is no significant difference between both drugs (Haddad et al., 2006; Webster et al., 2005; Ye et al., 2009; Penninga et al., 2013; Fan et al., 2009)., an expected result since they share a similar mechanism of action. However, TC has replaced CPA in most post-transplant regimens due to its lower risk of nephrotoxicity, cardiovascular disease and hypertension (Howard et al., 2018).

3.1.4. Mammalian target-of-rapamycin (mTOR)-inhibitors

mTOR-inhibitors have been increasingly used in immunosuppressant regimens in OTRs because of their anti-rejection efficacy and antineoplastic properties, especially when TC is contraindicated or not tolerated (Howard et al., 2018).

Because mTOR pathway contributes to malignant cell proliferation and survival (De Fijter, 2017), its inhibition has an anti-neoplastic role. Indeed, mTOR-inhibitors are considered a validated treatment for some malignancies like KS, renal cell carcinoma, neuroendocrine pancreatic tumors, HER2 negative breast cancers and giant cell astrocytoma (De Fijter, 2017; Yanik et al., 2015) with many clinical trials ongoing for other cancers. Even though the antineoplastic mechanisms of mTOR-inhibitors are well known, results from randomized trials are controversial; most of them have shown modest effects except for specific tumors, like NMSC and KS (De Fijter, 2017; Huang et al., 2015; Paghdal and Schwartz, 2007).

A systematic review and meta-analysis of kidney recipients treated with sirolimus reported a reduction of 56 % in the incidence of NMSC and a 40 % in the incidence of overall malignancies compared to other immunosuppressive regimens. However, after excluding NMSC, there was no association (hazard ratio (HR) 1,05 95 % CI= [0,57−1,94]) (Knoll et al., 2014). Similar findings were delineated in another meta-analysis, in which mTOR-inhibitors decreased the incidence of NMSC but not of other malignancies. The protective effect was more notable when comparing sirolimus with CPA, so it remains unknown if these results were due to CPA removal rather than a direct antineoplastic effect (Yanik et al., 2015).

Sirolimus has shown promising results for both preventing and treating KS in OTRs, which is explained by the ability of this drug to reduce vascular endothelial growth factor (VEGF) levels and inhibit endothelial cell response to VEGF (Paghdal and Schwartz, 2007). A study on15 kidney recipients with KS documented a complete remission in all patients by 3 months of treatment after the discontinuation of their previous regimen (CPA, prednisone and MMF) and prescription of sirolimus. Even though these results could have been attributed to CPA removal; data from Cincinnati Transplant Tumor Registry have revealed remission in only 17 % of patients after the withdrawal, compared to the 100 % of patients of this study (Stallone et al., 2005).

Despite its good efficacy and anti-tumor properties for specific cancers that have been confirmed in most of the studies, the poor tolerability of mTOR-inhibitors limits its use as first line therapy. Indeed, discontinuation rates are as high as 20 %− 30 % (De Fijter, 2017; Howard et al., 2018). There are also reports of a significantly increased risk of death, mainly due to infections and cardiovascular disease (Knoll et al., 2014).

3.2. Immunosuppression in patients with HIV-infection

Compared to general population, the HIV-population has an increased risk of acquired immune deficiency syndrome (AIDS)-defining cancers (ADCs), which include KS, NHL and cervical cancer, as also non AIDS-defining cancers (NADCs) (Chang et al., 2017). However, since the introduction of anti-retroviral therapy (ART) in 1995, the incidence of ADCs has declined by 3 times, while the incidence of NADCs has increased in a similar proportion (Shiels et al., 2011). Despite these changes, ADCs are still the most frequent malignancies in AIDS population in the US (Shiels et al., 2011; Gonçalves et al., 2017) with a total cancer burden that has increased over time (Shiels et al., 2011).

A meta-analysis that compared the incidence of cancer in HIV population and OTRs revealed that the standardized incidence ratio (SIR) and risk profile of both groups was similar and attributed mainly to an infectious etiology, being KS, NHL, HL, HPV-related cancers, liver and stomach cancers commonly seen. These findings support that immunosuppression is an important factor of cancer development (Grulich et al., 2007). As in OTRs, the incidence of most of the epithelial cancers (breast, ovary, colon, rectum and prostate) is not significantly increased in HIV-patients (Grulich et al., 2007; Cobucci et al., 2012).

The explanation of the increased cancer-risk in HIV population is not entirely clear, although several mechanisms have been proposed, such as immunosuppression (which decrease the immune-surveillance and increase the prevalence of oncogenic-viruses), chronic inflammation, ART toxicity and their higher prevalence of pro-oncogenic risk factors like alcohol consumption and smoking (Silverberg et al., 2015; Parka et al., 2016; Deeks, 2011).

Of all skin cancers, KS is the one with the highest incremental risk, followed by MCC. NMSC risk is considerably lower in HIV population compared to OTRs, which suggest that ISDs have a significant role in the development of this malignancy in the second group.

In contrast to KS, the risk of NMSC is similar with or without ART (Zhao et al., 2016; Silverberg et al., 2013; Garlassi et al., 2012), which lead us to assume that the higher risk of skin cancer in this population is not entirely explained by immunodeficiency. People treated with ART for long time persist with higher risk of multiple complications not related to AIDS like cardiovascular disease, osteoporosis, cognitive impairment and cancer. This is explained in part by a phenomenon called immune-senescence, which is caused by immunological alterations (many of them irreversible), secondary to HIV infection. HIV diminish the number and function of hematopoietic and naïve T-cells, favors the thymus involution, increase memory CD28 T-cells (which have pro-inflammatory activity) and pro-inflammatory cytoquines and also diminish CD4 and CD8 T-cells relation. Although ART prevents AIDS-related complications and prolongs survival, it does not restore completely these immunological alterations, especially when initiated late. In fact, the level of inflammation persists elevated independent of the complete suppression of the viral replication (Deeks, 2011). It also should be considered that since the introduction of ART, the survival of patients with HIV had increased considerably, which is also a contributing factor for the development of cancer (Hessol et al., 2018).

Even though the risk of NMSC is not that high (compared to OTRs), it is becoming an important mortality cause in this population (Chang et al., 2017). The most common risk factors for the development of NMSC are; age over 40 years, Caucasian race, history of opportunistic infections and long duration of HIV infection (Brin et al., 2014). Each type of skin cancer in HIV population has its own prevalence and characteristics (Table 4).

3.3. Immunosuppressive drugs in non-transplant patients

ISDs are widely used in many autoimmune diseases and chronic inflammatory disorders. In addition to immunosuppression, there are other mechanisms induced by these therapies that can contribute to the development of skin malignancies: decreased DNA repair, upregulation of cytokines that promote tumor progression and reduction of the immunological clearance of malignant cells (Jiyad et al., 2016).

Because most patients are taken multiple ISDs and some autoimmune disorders have an inherent risk of cancer per se, it is difficult to stablish accurate skin cancer rates associated to these therapies.

Table 4
Skin Cancer in HIV-infected patients.

Skin cancer	IHR	Comments
KS	127–3.640 (Grulich et al., 2007; Hessol et al., 2018; Serraino et al., 2007)	Responsible of 4–7,5 % of all AIDS diagnoses (Mocroft et al., 2004). Since introduction of ART the 2 year- survival increased from 35 % to 81 % (Lodi et al., 2010). After NHL, KS is the second more frequent cancer in HIV patients from the US (Gonçalves et al., 2017). AIDS-related KS is more aggressive compared to classic KS (Gonçalves et al., 2017). Risk factors: MSM (HR of 2,12), lower CD4 count and late start of ART (Mocroft et al., 2004; Lodi et al., 2010).
MCC	13,4 (Engels et al., 2002)	Average time of diagnosis after HIV diagnosis is 9,1 years (Brin et al., 2014). Average survival time after diagnosis is 18 months (Brin et al., 2014).
NMSC	2,1–4,1 (Grulich et al., 2007; Zhao et al., 2016; Silverberg et al., 2013)	Risk is considerably lower in HIV population compared to OTRs (Grulich et al., 2007). Risk is similar independent of ART usage (Zhao et al., 2016; Silverberg et al., 2013; Garlassi et al., 2012). NMSC Affect patients with relatively well-preserved cell immunity (Garlassi et al., 2012). No differences in degree of invasion, subclinical extension, differentiation or localization compared to general population (Song et al., 2016; Silverberg et al., 2013).
BCC	0–2,1 (Collins et al., 2019; Chang et al., 2017; Silverberg et al., 2013; Omland et al., 2018) 2,6–5, 4 (Collins et al., 2019; Silverberg et al., 2013),	More frequent than cSCC, with a relation similar to general population (BCC:cSCC = 4:1)(Chang et al., 2017;Silverberg et al., 2013; Garlassi et al., 2012).
cSCC	(Omland et al., 2018)	The association between NMSC-risk and CD4 cell count is conflictive and apparently only exist for cSCC (Chang et al., 2017; Silverberg et al., 2013; Omland et al., 2018). Recurrence of extragenital SCC is increased in almost 10-times, independent of HIV control (Chang et al., 2017).
MM	Controversial: 0 (Chang et al., 2017; Omland et al., 2018; Yanik et al., 2018)- 2,6 (Patel et al., 2008)	No association with CD4 cell count or viral load (Yanik et al., 2018). Mortality risk is 1,93–10,9 times higher (Coghill et al., 2015; Zucchetto et al., 2016).
PCL	2,4 (Chelidze et al., 2019)	In contrast to systemic NHL, cutaneous NHL are uncommon and more frequently originated from T Cells (Munõz-Pérez et al., 1999). Two main forms: (1) Indolent disease resembling mycosis fungoides/Sezary syndrome with negative EBV-DNA and (2) large cell lymphoma of worse prognosis, frequently of T-cell CD30 + origin and EBV-DNA positive in 73 % of cases (Kerschmann et al., 1995). Increased incidence of CD8+ phenotype in CTCL compared to general population (Burns and Cooper, 1993)

AIDS: acquired immune deficiency syndrome/ ART: antiretroviral therapy/ BCC: basal cell carcinoma/ CTCL: Cutaneous T-cell Lymphoma/ EVB: Epstein Barr Virus/ HR: Hazard Ratio/ IHR: Incidence Hazard Ratio/ KS: Kaposi's sarcoma/ MCC: merkel cell carcinoma/ MM: melanoma/ MSM: men that have sex with men/ NHL: non-hodgkin lymphoma/ NMSC: non melanoma skin cancer/ PCL: Primary Cutaneous Lymphoma/ OTRs: organ transplant recipients/ cSCC: cutaneous squamous cell carcinoma/US: United States.

3.3.1. *Azathioprine*

Available data - mainly in inflammatory bowel disease - show that AZA is associated with an increased risk of NMSC, which seems to be proportional to the treatment duration and dosage (Setshedi et al., 2012; Hagen and Pugliano-Mauro, 2018; Bahi et al., 2018; Abbas et al., 2014). There is also evidence that cSCC-mortality is increased compared to those with no previous exposure to this drug. [HR 8 (95 % CI, 2.0–32.8; P = 0,004)] (Khan et al., 2019). Yet there are studies that have shown that discontinuation of thiopurines returns the risk to baseline (Abbas et al., 2014; Kotlyar et al., 2015; Bressler and Abbas, 2015), others have revealed a residual risk even after the suspension of the drug (Peyrin-Biroulet et al., 2011). Regarding the risk of MM, most of the studies have failed to prove a significant association (Abbas et al., 2014; Bressler and Abbas, 2015).

The increased risk of cancer is not only explained by immunosuppression, but also by the damage of the DNA. The active metabolite of thiopurines (6-thioguanine) is incorporated into the DNA, and after UVA exposure it suffers a photochemical activation that damage the DNA both directly and by the production of reactive oxygen species (Jiyad et al., 2016; Setshedi et al., 2012). This mechanism could explain the eventual residual risk after the discontinuation of the drug.

3.3.2. *Corticosteroids*

Despite the widespread use of systemic corticosteroids, the available data that evaluate their potential oncogenic risk is sparse and conflicting. In addition, most of the studies are retrospective and do not consider the reason of the corticosteroid prescription, so it remains unclear if the higher risk is attributable to the underlying disease or concomitant treatments other than steroids.

A retrospective cohort study that analyzed the relation of skin cancer and NHL with the number of corticosteroid-prescriptions during an 8-year period (excluding other immunosuppressive drugs) found a significantly increased risk of developing cSCC, BCC and NHL (SIR of 2,45, 1,52 and 2,86 respectively) especially in those with higher number of prescriptions. There was no association with MM (Sørensen et al., 2004).

Systemic steroids have been also linked with an increased risk of KS in those herpesvirus seropositive (Hengge et al., 2006; Schwartz et al., 2008; Hoshaw and Schwartz, 1980).

There are other case-control studies that have shown conflictive results, with one showing significant association only with sSCC (Karagas et al., 2001) and other only with BCC (Jensen et al., 2009).

However, there are other studies that have failed to prove an association between corticosteroids and malignancies at all, and have questioned whether the findings of other studies were causal (Askling et al., 2005; Baibergenova and Weinstock, 2012; Baecklund et al., 2006; Troche et al., 2015). Further investigations are needed to certainly asses the association of corticosteroids and cancer.

3.3.3. *Methotrexate*

Whether MTX increases the risk of malignancies or not is again controversial, considering that at higher doses it can be used as a chemotherapy agent for many cancers (including NMSC), due to its antiproliferative action (Salido-Vallejo et al., 2016).

However, probably due to its immunosuppressive properties, there are many case-reports that have associated MTX with an increased risk of malignancies, especially lymphoproliferative disorders (LPD) (Wang et al., 2018). Indeed, the World Health Organization recognized the MTX-LPD among the "immunodeficiency associated LPD", which is supported on multiple reports (mostly in patients with rheumatoid

arthritis) of spontaneous regression of these malignancies after the suspension of the drug (Rizzi et al., 2009).

When analyzing the association between MTX and NMSC, the available evidence is not conclusive. A cohort study of 6806 rheumatoid arthritis (RA)-patients followed for 10 years revealed a malignancy incidence rate (IR) of 10,47 per 1.000 person-years in patients exposed to MTX. Of all the cancers analyzed, NMSC was the most frequent one, with an IR of 5,93 per 1.000 person-years. Non-biologic disease-modifying antirheumatic drugs and a tumor necrosis factor alpha (TNF)-antagonists were associated with a lower risk of cancer compared to MTX (HR of 0,17 and 0,29 respectively). However, the absolute cancer-risk attributable to MTX in this study was very small (Solomon et al., 2014).

When analyzing the association of MTX and MM, again there are conflicting results, with some studies showing significant association (Bhattacharya et al., 2016; Buchbinder et al., 2008) and others showing small or no increased risk at all (Polesie et al., 2017a, 2017b, 2018).

Although the contribution of MTX in cancer development cannot be ruled out, conclusive data is still lacking.

3.3.4. CNI

The association of CNI and skin cancer is less clear in non-transplant patients, specifically in dermatologic diseases like psoriasis and atopic dermatitis, in which treatment is time-limited and with lower doses (Muellenhoff and Koo, 2012).

A review of 60 studies and 7306 patients treated with CPA according to dermatological guidelines (<5 mg/kg/day) reported no significant association with skin cancer. Overall, 14 case reports suggested CPA-induced skin cancer (1 % of total patients), but in most of them dermatologic guidelines were not followed or the patients had pre-existing risk factors like PUVA or exposure to other ISDs. Except for one, all of the affected patients had psoriasis. They concluded that there is no convincing evidence that CPA at 5 mg/kg/day or less, taken for 6 months continuously or intermittently for up to 2 years is associated with considerable risk for skin cancer (Muellenhoff and Koo, 2012).

3.3.5. TNF-α inhibitors

Being the first to be approved, TNF-α inhibitors have been the most studied biologic therapies, specially infliximab, etanercept and adalimumab. When analyzing the overall cancer risk of these drugs, all of the recent meta-analysis and large observational studies (mostly restricted to AR-patients) have reported no significant increased risk of malignancies (Seror and Mariette, 2017).

Regarding the association with NMSC, existing data is controversial. The larger meta-analysis available (74 trials) revealed a HR of 2.02 (95 % CI, 1.11–3.95) (Askling et al., 2011). This finding is in line with a study of long term extension of 71 randomized clinical trials (RCTs) and a pooled analysis of 29 observational studies (Burmester et al., 2013; Mariette et al., 2011). In contrast, three other meta-analyses as well as three observational studies did not report any significant association (Seror and Mariette, 2017).

Even most of the available studies regarding TNF- α inhibitors and skin cancer show no association, there is again conflicting data. As with other ISDs, this may be due to different statistical precision and reported detail of the different trials as well as different baseline cancer risk of the patients evaluated.

3.4. Cancer-induced immunosuppression

Multiple immune reactions occur against tumors to prevent their growth and invasiveness. However, cancers have several mechanisms to evade anti-tumor immunity, which lead to a state of cancer-induced immunosuppression (CII) that facilitates tumor growth and dissemination. The immune system evasion and CII not only occurs in the tumor microenvironment (TME), but also at distant sites like regional nodes and peripheral blood (Hadden, 2003), leading to systemic immunosuppression.

CII is a complex process explained by multiple and interrelated factors and supposed to be stimulated by chronic inflammatory conditions developing in the TME (Umansky and Sevko, 2012). In some tumors like MM and breast cancer, all these immune alterations appear in more advanced stages and increase with tumor development.

The following are the most important contributing factors for CII:

3.4.1. "Immune editing"

Immune editing is the process by which tumors adapt and develop under the selective pressure of the immune system (Ko, 2017). Tumors normally express antigens that are recognized by the immune system, resulting in their elimination. However, the genetic instability of tumor cells leads to constant new cell variants that interfere with the immune system antigen-recognition, facilitating tumor escape (Vinay et al., 2015). MM and cSCC have one of the most highest mutational burden of all tumors, which allows edited and immune-selected variants to evade and suppress the immune system through different mechanisms (Ko, 2017), (Bottomley et al., 2019). Many neoplasms also down-regulate the expression of tumor antigens and costimulatory molecules (Umansky and Sevko, 2012; Vinay et al., 2015) and produce intercellular adhesion molecule 1, which can block the binding of effector cells to their targets (Gross and Walden, 2008).

3.4.2. Cells

CII affects both the innate and adaptive immune system:

3.4.2.1. Lymphocytes. Tumors express antigens and chemokines that induce the presence of tumor-infiltrated lymphocytes (TIL), conformed mainly by cytolytic lymphocytes and regulatory T-cells (T-regs). Under tumor immunosuppressive activity, cytolytic lymphocytes have poor proliferative responses and cytotoxic activity as well as higher apoptotic rates (Hadden, 2003; Vinay et al., 2015).

T-regs are crucial for maintaining the immune-tolerance by the production of immunosuppressive cytokines like IL-10 and transforming growth factor β (TGF-β), the induction of indolamine-2,3-dioxygenase (IDO) in dendritic cells (DCs) and the induction of apoptosis on effector T-cells via granzyme and perforin (Gross and Walden, 2008). The number of T-regs is increased in cSCC compared to normal skin, being even higher in moderately and poorly differentiated tumors (Bottomley et al., 2019).

TIL can be histologically classified into 3 categories: brisk (band-like infiltrate that surround the entire tumor front), non-brisk (a defect in the band-like infiltrate of 0,3 mm or greater) and absent (Ko, 2017). Although the activity of TIL is considerably suppressed by the tumor, brisk infiltrate have been associated with an improved survival in MM, probably because it represent the immunological response against the tumor. For this reason, the College of American Pathologists have recently include the presence and degree of TIL infiltrate as an additional histologic prognosis factor in MM. Interestingly, the proportion of patients with absent TIL is similar to those with metastasis who do not respond to immunotherapy (Ko, 2017).

3.4.2.2. Dendritic cells. DCs initiate and influence both the innate and adaptive immune responses. In MM there are multiple tumor derived factors - VEGF, TGFβ and IL-10- that suppress DCs maturation, migration and their antigen-presentation activity (Mahmoud et al., 2017). These immature and functionally-impaired DCs have lower levels of CD80 and CD86, which also contributes to T-cell anergy by lesser co-stimulatory signals (Vinay et al., 2015). DCs also produces higher levels of IDO, an enzyme that catalyzes the first step of tryptophane degradation leading to the production of kynurenine, which is toxic to T-cells (Gross and Walden, 2008).

3.4.2.3. Myeloid-derived suppressor cells (MDSCs). MDSCs are an

immune suppressive cell population of myeloid origin present in practically all cancers (Ostrand-Rosenberg, 2016). Their production and activation is stimulated by tumor pro-inflammatory cytokines (IL-1B, IL-6) and prostaglandin E2, using different signaling pathways (Umansky and Sevko, 2012; Wang and Du Bois, 2015). They have immune-suppressive activity in both innate and adaptive immune system as also pro-tumor functions by stimulation of angiogenesis and metalloproteinase production. MDSCs are known to be elevated in MM, and the total percentage of these cells is correlated with the overall survival of this cancer (Ko, 2017). Their presence is also a prognostic marker in cSCC, being associated with high risk cSCC (thickness $\geq$5 mm, Clark level V and T-stage 2b/3) (Seddon et al., 2016).

3.4.2.4. Tumor associated macrophages (TAMs). Multiple tumor cell-derived cytokines and chemokines stimulate the conversion of macrophages to M2 phenotype, which induce immunosuppressive responses and favor tumor progression (Li et al., 2020). TAMs synthetize many immunomodulatory molecules like chemokines (CCL2, CXCL8, CXCL12), prostaglandin E2 and inhibitory cytokines (TGF- B, IL-6 and IL-10) which suppress TIL responses (Umansky and Sevko, 2012; Gross and Walden, 2008). TAMs also secrete VEGF and are the main producer of matrix metalloproteases, stimulating directly tumor growth and invasion (Bottomley et al., 2019; Li et al., 2020). A recent study revealed that CCL18 derived from M2 macrophages favors cSCC metastasis by inducing epithelial-mesenchymal transition and stemness (She et al., 2018). As in DCs, there is also an upregulation of IDO activity as well as production of reactive oxygen species that contribute to TIL suppression (Gross and Walden, 2008).

Due to the critical role of TAMs in TME, numerous therapies targeting TAMs are being explored in many tumors, including MM cSCC (Li et al., 2020).

3.4.3. Immunosuppressive factors (ISF)

ISF have been identified in tumor cell extracts as also in the serum or effusions of patients with cancer. They derive from both tumor and stroma cells present in TME and contribute to immunosuppression as well as tumor growth and invasiveness. ISF include cytokines (IL-1, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, INF-Y, TNF-a), chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL12), growth factors (GM-CSF, TGF-B, VEFG) and others factors like Fas-ligand, prostaglandins, reactive oxygen and nitrogen species (Hadden, 2003; Umansky and Sevko, 2012; Vinay et al., 2015). Many of these factors contribute to tumor development by stimulation of tumor mutations, proliferation, neovascularization, resistance to apoptosis and metastasis. ISF can also induce proliferation, migration and activation of various immunosuppressive lymphoid and myeloid cells (Umansky and Sevko, 2012). Some tumors including MM and cSCC release extracellular micro-vesicles which circulate freely through body fluids and contain ISF (Fas-Ligand, TGF-B, PD1-L), tumor antigens and oncoproteins, contributing to generalized immunosuppression and also distant metastasis (Gross and Walden, 2008; Wang et al., 2019; Sharma et al., 2020).

3.4.4. Expression of inhibitory molecules

The chronic activation of the immune system that occurs in MM, cSCC as in other cancers leads to upregulation of programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitory receptors (also known as immune checkpoints) by "exhausted" T- cells. These molecules inhibit the costimulatory signals needed to activate T-cells, leading to a progressive suppression of immune responses directed to the tumor (Seidel et al., 2018).

For this reason, neutralizing antibodies targeting these immune checkpoints are associated with considerable improvement in the outcomes of many cancers including MM, cSCC, renal cell carcinoma and non-small lung carcinoma (Seidel et al., 2018). A recent systematic review revealed that both PD-1 and PD-1 ligand inhibitors are also effective in the treatment of MCC, cutaneous soft tissue sarcomas, malignant peripheral nerve sheat tumors and sebaceous carcinomas (Choi et al., 2020).

Regarding MM treatment, Ipilimumab (anti- CTLA-4 antibody) was the first checkpoint inhibitor approved by the FDA in 2011. PD-1 monoclonal antibodies, nivolumab and pembrolizumab, were approved later in 2014 (Ko, 2017). Both checkpoint inhibitors need an underlying immune response to be effective, which is why tumors with increased number of TIL and mutation rates have better responses (Bottomley et al., 2019; Seidel et al., 2018).

These drugs are effective only in 25 % of patients, probably because of other additional immunosuppressive mechanisms that contribute to T-cell suppression (Sanghera and Sanghera, 2019). In addition, those who initially respond may eventually relapse, which may be explain by the selection of new tumor cells that evade immune-mediated recognition, as also by upregulation of other inhibitory receptors (Seidel et al., 2018).

3.4.5. Other contributing factors

Besides the immunosuppression induced by the tumor itself, there are many other factors implicated in CII, like poor nutrition, radiation (that may stimulate or suppress the immune system) (de et al., 2018), chemotherapy and stress due to surgical resection (Hadden, 2003). Multiple immune imbalances have been described in humans and animals undergoing surgical procedures, like suppression of lymphocyte stimulation, decreased total blood lymphocyte, B cell, and T cell count, decreased leukocyte reactivity and decreased neutrophilic phagocytosis (Pollock et al., 1989). The alteration of gut microbiota in oncology patients also contributes to CII by modulating the expression of inhibitory molecules. Indeed, several studies have shown poor responses to anti-CTLA 4 and anti-PD1 therapies in patients with low levels of specific bacteria (Gopalakrishnan and Spencer, 2018; Vétizou et al., 2015).

4. Discussion

The immune system plays a critical role in the prevention, development and progression of cancer. Its ability to recognize antigens on malignant cells and target them for destruction forms the foundations of immunotherapy. Both primary and secondary immunosuppression are associated with an increased risk of malignancies compared to general population. The association between cancer and immunosuppression is explained in a significant proportion by the impairment of the immune-surveillance, and its importance has been demonstrated by the introduction of immunotherapy and the unprecedented clinical success that has accomplished in many cancers including melanoma.

Although the relation of immunosuppression and skin cancer has been specially studied in the setting of secondary immunosuppression, few studies available in PIDs have also shown an increased incidence of skin neoplasms, being the second most frequent malignancies in this population after lymphomas. However, because PIDs are very uncommon diseases with many different subtypes, the establishment of accurate risk ratios for cancer is still difficult to assess.

In the setting of secondary immunosuppression, the importance of the immune-surveillance is supported by the fact that OTRs, as well as HIV-population, have a higher incidence of virus-related tumors, leading to a different malignancy profile as seen in general population (composed mainly by epithelial tumors). In skin cancer, oncogenic viruses also play an important role and explain the notably higher incidence of certain malignancies like cSCC, KS and MCC when compared to general population. Because pathogenesis of MM and BCC is not related to viruses, their incidence is not significantly increased. Although both OTRs and HIV population have an increased risk of cSCC, this is notably higher in the first group, which suggest that ISDs have a significant role in the development of this malignancy.

In relation to ISDs, it is known that immunosuppression is not the only mechanism that explain their increased risk of malignancy, but also

DNA-repair alteration and upregulation of cytokines that promote tumor progression. However, due to different type of studies and statistical analysis (e.g; baseline cancer risk of patients, length of follow up and types of regimens used), it is difficult to stablish accurate skin cancer risks. AZA and CNI appear to have the highest risk of developing skin cancer in OTRs, while MMF have a neutral effect and mTOR inhibitors have shown a protective role. Similar difficulties are seen in non-transplant patients, in which different studies have revealed conflicting results except for AZA.

The association between cancer and immunosuppression can also be analyzed from a different perspective, such as local and systemic CII. Although MM and cSCC are one of the most immunogenic malignancies -promoting innate an adaptive immune responses at the site of tumor growth- they can also induce immunosuppression by many interrelated factors previously mentioned. The blockage of some of these immune-inhibitory mechanisms with immunotherapy has permitted one of the most successful advances in cancer therapy in the last years.

The management of patients under immunosuppression requires a multidisciplinary approach. A specific preventive dermatologic management with a detailed risk assessment to provide an index for the likelihood of developing subsequent skin cancer would be desirable for each patient.

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María Paz Rollan: Methodology, Investigation, Writing – original draft, Writing – review & editing. **Raul Cabrera:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision. **Robert Schwartz:** Writing – review & editing, Supervision.

Conflicts of interest statement

María Paz Rollan, Raul Cabrera and Robert Schwartz declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

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Slovakia, and Turkey. He has written 5 books, 325 book chapters, 620 full articles, and more than 250 abstracts and other publications.