LETTER TO THE EDITOR

Graft rejection after immune checkpoint inhibitor therapy in solid organ transplant recipients

Tor Magnus Smedman[a,b], Pål-Dag Line[b,c], Tormod K. Guren[a] and Svein Dueland[a]

[a]Department of Oncology, Oslo University Hospital, Oslo, Norway; [b]Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [c]Section for Transplantation Surgery, Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway

Introduction

Immune checkpoint therapy, targeting regulatory pathways in T cells, has led to important clinical advances and improved outcomes in patients with malignant diseases [1]. Ipilimumab, a monoclonal human antibody, binds to cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and blocks inhibitory T cell signals. Treatment with ipilimumab has resulted in durable clinical response in patients with metastatic malignant melanoma [2]. Antibodies, e.g., nivolumab and pembrolizumab, targeting the programmed cell death-1 (PD-1) receptor, increase the activity of cytotoxic T cells by blocking inhibitory signals engaged by its two known ligands, PD-L1 and PD-L2. Treatment with anti PD-1 antibodies as monotherapy or in combination with ipilimumab, have also shown substantial and durable responses in several tumor types, including malignant melanoma [3,4]. Immunotherapy with ipilimumab and/or PD-1/PD-1 ligand inhibitors have been approved by FDA/EMEA for treatment of several malignant diseases including renal cancer, lymphoma, non-small cell lung cancer, head and neck cancer, bladder cancer and malignant melanoma. Immunotherapy of these malignancies is now considered standard of care in many countries.

Long-term survival after solid organ transplantation has increased during the last decades. Organ-transplanted patients require lifelong immunosuppression to control the balance between risk of allograft rejection and adverse side effects such as infection. The required level of immunosuppression vary between different organ transplant types with the liver being the organ transplant needing the lowest level [5]. The specific protocols also vary between organ types and centers, but the general principle is to combine 2–3 drugs, thereby minimizing dose-related side effects of any particular agent. Most patients receive corticosteroids. Due to the side effect profile of chronic steroid use, they are either tapered gradually off in the first months or maintained at a low maintenance dose. Calcineurin inhibitors (CNI) like cyclosporine and tacrolimus block the signal-2 of T-cell activation, and these agents are the mainstay of immunosuppression in almost all protocols. Agents that interact with the cell cycle, like mycophenolate mofetil are often added. Due to the nephrotoxicity associated with CNI, agents interacting with the mTOR pathway like sirolimus and everolimus are increasingly used. Chronic immunosuppressive treatment in organ transplant recipients is associated with an increased incidence of *de novo* malignancies, including non-melanoma skin cancer, malignant melanoma, lymphoma, kidney, head and neck cancer, colorectal cancer and lung cancer [6–9].

Organ transplant recipients have been excluded from clinical trials with immune checkpoint inhibitors and the benefit and risks of such treatment have not been evaluated systematically in organ transplant recipients; however, several case reports on outcome have been published [10–32] with acute graft failure or rejection [10,12,15,17,18,20,25,27,28,30,31] as well as unchanged graft function [11,13,14,16,19,21–24,26,29,32]. Immunosuppressive drugs like sirolimus and/or mycophenolate mofetil, which routinely are used after organ transplantation, have also been used to treat serious immune-related side effects of immune checkpoint inhibitor therapy [33]. It is unclear whether these drugs interfere with the antitumor effect, and therefore, the intensity of immunosuppression has often been reduced in patients with an organ graft receiving immune checkpoint inhibitor treatment.

Methods

A literature review was completed on Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present: (Organ Transplantation/or (organ and transplant*).tw,kf. or Liver Transplantation/or (liver and transplant*).tw,kf. or Pancreas Transplantation/or (pancreas and transplant*).tw,kf. or heart transplantation/or heart-lung transplantation/or ((heart and transplant*) or (cardiac and transplant*)).tw,kf. or Lung Transplantation/or (lung and transplant*).tw,kf. or Transplant Recipients/or (transplant* and recipient*).tw,kf. or Kidney Transplantation/or ((kidney and transplant*) or (renal and transplant*)).tw,kf.) and (Ipilimumab/or (ipilimumab or pembrolizumab or nivolumab or immune checkpoint* or checkpoint* inhibit* or pd 1 or pd l1 or ctla 4).tw,kf.) and (exp neoplasms/or (neoplasm or neoplasm or neoplasms or neoplastic or cancer or cancers or carcinom* or adenocarcinom* or melanoma or tumor or tumors or tumor

CONTACT Svein Dueland svedue@ous-hf.no Department of Oncology, Oslo University Hospital, P.O Box 4950 Nydalen, N-0424 Oslo, Norway

https://doi.org/10.1080/0284186X.2018.1479069

or tumors or oncol* or malign* or metastasis or metastatic or metastases).tw,kf.)

A similar search was also performed on EMBASE (OVID). After removing doublets, these searches yielded a total of 235 published articles. Cutoff date for inclusion was set to 1 January 2018, and articles published in non-English language or involving pediatric patients were excluded.

Results

Twenty-three case reports including a total of 26 organ transplant recipients which have received ipilimumab or/and PD-1 inhibitors were identified (Table 1). The majority of these patients were treated with immune checkpoint inhibitors due to metastatic disease from malignant melanoma. Fourteen of the 26 patients had a kidney transplant. The immunosuppressive regimen utilized during immunotherapy varied in the cohort (Table 1).

Ipilimumab

Six case reports including seven patients have been published on immunotherapy with ipilimumab: three kidney transplanted patients [16,28], three liver-transplanted patients [17,19,27] and one patient with a heart transplant [13]. Three patients experienced graft rejection. Two of these patients had a liver graft and metastases in the donor graft. The last patient with rejection on ipilimumab treatment was a patient with a kidney transplant.

The first signs of liver graft rejection will often be elevated levels of ALT/AST as sign of cellular damage before functional impairment with significant elevation in INR and bilirubin values [34]. Elevated transaminases are therefore usually detected before clinical liver dysfunction is observed. Early interventions with steroids and/or anti-thymocyte globulin (ATG) treatment will in most instances halt the rejection process thereby preventing liver graft loss.

The liver-transplanted patient with a biopsy-confirmed rejection received only one dose of ipilimumab resulting in high serum levels of ALT (750 U/L, CTCAE grade 3 toxicity) week 6 [27]. The diagnosis of acute rejection was biopsy confirmed (RAI score 6). In the two other case reports on liver-transplanted patients treated by ipilimumab, one patient [19] had no increase in serum AST/ALT during ipilimumab treatment, whereas the other patient had no elevation of ALT during the four ipilimumab treatments, but a serum ALT level of about 230 U/L was observed at week 16 [17]. No liver biopsy was obtained to confirm rejection histologically in this patient with a transient elevation of ALT [17]. These two patients with no or only late and moderately elevated ALT levels received tacrolimus or sirolimus as immunosuppressive treatment during ipilimumab administration whereas the liver-transplanted patient and the kidney transplanted patient with acute rejection were on prednisolone monotherapy. Two of the liver-transplanted patients had metastatic disease in the liver graft, whereas the liver-transplanted patient with no elevation of ALT [19] had only extra-hepatic metastases. In patients with metastases in the liver graft, increased serum levels of AST and ALT may represent progression of the metastatic disease as well as graft rejection, and this can constitute a diagnostic problem. It is therefore important to obtain a liver biopsy to confirm liver graft rejection in these cases. Furthermore, ipilimumab has also been reported to induce hepatitis in non-transplant livers [35].

The cardiac-transplanted patients treated with ipilimumab and receiving tacrolimus as immune suppressive treatment did not develop rejection [13,22]. Also the two kidney transplanted patients reported by Lipson et al. [16] had unchanged creatinine levels after ipilimumab treatment and prednisolone as immunosuppressive treatment.

PD-1 inhibitors

Eight kidney transplanted patients were treated with PD-1 antibodies [11,12,15,18,24,29,30]. Four of these patients developed graft rejections requiring dialysis. Three of these patients received prednisolone or prednisolone and cyclosporine as immunosuppressive treatment and one patient received azathioprine and everolimus. In the four patients who did not develop kidney graft rejection two patients received sirolimus and prednisolone, one received prednisolone and mycophenolate mofetil, and the last patient received cyclosporine only [11,24,29]. Five liver recipients [21,23,25,26,32] and two patients with heart transplants [29,31] also received PD-1 inhibitor treatment. Of these seven patients, two recipients developed graft rejection [25,31]. One of the liver-transplanted patients treated with PD-1 inhibitor had increase in ALT levels to about 700 U/L after start of immune checkpoint inhibitor treatment [32]. Liver biopsy did not show signs of rejection. The patient had relapse of hepatitis C virus infection with marked elevated hepatitis C RNA levels and responded with normalization of ALT levels on anti-viral treatment. This observation underlines the importance of obtaining a liver biopsy in patients with elevated liver enzymes after start of immunotherapy, particularly in patients with preexisting liver disease that may be re-activated as a consequence of immunotherapy.

Ipilimumab + PD-1 inhibitor

A sequential treatment of ipilimumab and PD-1 inhibitor were administered to three kidney transplant recipients, as well as one heart transplant recipient [10,14,20,22]. Two of these developed kidney graft rejection resulting in dialysis requirement [10,20]. In contrast, one patient had unchanged kidney function, and the heart transplant recipient did not experience any signs of rejection after immune checkpoint inhibitor treatment [14,22]. The latter two patients received tacrolimus alone or combined with prednisolone as immunosuppressive treatment whereas the two other kidney recipients both received prednisolone and cyclosporine or prednisolone alone after starting sequential immune checkpoint inhibitor therapy.

Table 1. Case reports of solid organ recipients receiving treatment with immune checkpoint inhibitors.

Publication, author [reference]	Tx organ	Graft reaction, outcome	Type of immuno-therapy	Time from trans-plantation	Type of immuno-suppression	Malignant disease	Response Ipi	Response PD-1 inhibitor
Lipson et al. [16]								
Case 1	Kidney	None	Ipi	7 years	Prednisolone	Malignant	PR	–
Case 2	Kidney	None	Ipi	11 years	Prednisolone	melanoma	PR	–
Jose et al. [28]	Kidney	Rejection, dialysis	Ipi	16 years	Prednisolone	Ocular malignant melanoma	PD	–
Alhamad et al. [10]	Kidney	Rejection, dialysis	Ipi/ PD-1 inhibitor	15 years	Cyclosporine Prednisolone	Malignant melanoma	PD	N/A
Spain et al. [20]	Kidney	Rejection, dialysis	Ipi/ PD-1 inhibitor	14 years	Prednisolone	Malignant melanoma	PD	PR
Herz et al. [14]	Kidney	None	Ipi/ PD-1 inhibitor	8 years	Prednisolone Tacrolimus	Malignant melanoma	PD	PD
Barnett et al. [11]	Kidney	None	PD-1 inhibitor	6 years	Prednisolone Sirolimus	Duodenal cancer	–	CR
Lipson et al. [15]	Kidney	Rejection, dialysis	PD-1 inhibitor	25 years	Prednisolone	Cutaneous SCC	–	PR
Ong et al. [18]	Kidney	Rejection, dialysis	PD-1 inhibitor	10 years	Prednisolone	Malignant melanoma	–	PR
Boils et al. [12]	Kidney	Rejection, dialysis	PD-1 inhibitor	3 years	Cyclosporine Prednisolone	NSCLC	–	N/A
Kwatra et al. [30]	Kidney	Rejection	PD-1 inhibitor	13 years	Azathioprine Everolimus	Malignant melanoma	–	N/A
Kittai et al. [29]	Kidney	None	PD-1 inhibitor	14 years	Sirolimus Prednisolone	SCC	–	PR
Winkler et al. [24]								
Case 1	Kidney	None	PD-1 inhibitor	13 years	Prednisolone	Malignant melanoma	–	PD
Case 2	Kidney	None	PD-1 inhibitor	32 years	Mycophenolate mofetil Cyclosporine	Ocular Malignant melanoma	–	PD
Morales et al. [17]	Liver	Elevated AST/ALT, recovered	Ipi	8 years	Sirolimus	Malignant melanoma	PR	–
Ranganath and Panella [19]	Liver	None	Ipi	8 years	Tacrolimus	Malignant melanoma	PD	–
Dueland et al. [27]	Liver	Rejection, recovered	Ipi	1.5 year	Prednisolone	Ocular malignant melanoma	PD	–
Biondani et al. [26]	Liver	None	PD-1 inhibitor	13 years	Prednisolone Tacrolimus Everolimus	NSCLC	–	PD
Schvartsman et al. [32]	Liver	None	PD-1 inhibitor	20 years	Tacrolimus	Malignant melanoma	–	CR
De Toni et al. [21]	Liver	None	PD-1 inhibitor	N/A	Tacrolimus	HCC	–	PD
Varkaris et al. [23]	Liver	None	PD-1 inhibitor	8 years	Tacrolimus	HCC	–	PD
Friend et al. [25]	Liver	Rejection, liver failure	PD-1 inhibitor	N/A	Sirolimus	HCC	–	N/A
Gastman et al. [13]	Heart	None	Ipi	15 years	Tacrolimus	Malignant melanoma	SD	–
Quin et al. [22]	Heart	None	Ipi/PD-1 inhibitor	12 years	Tacrolimus	Malignant melanoma	PD	N/A
Owonikoko et al. [31]	Heart	Rejection, recovered	PD-1 inhibitor	19 years	Prednisolone Sirolimus	SCC	–	N/A
Kittai et al. [29]	Heart	None	PD-1 inhibitor	10 years	Cyclosporine Mycophenolate mofetil	NSCLC	–	SD

Tx: transplanted; Ipi: ipilimumab; AST: aspartate transaminase; ALT: alanine transaminase; SCC: squamous cell carcinoma; NSCLC: non-small cell lung cancer; HCC: hepatocellular carcinoma; SD: stable disease; PR: partial response; CR: complete response; PD: progressive disease.

Discussion

Of the 26 solid organ recipients treated with immune checkpoint inhibitors reported in the present review three out of seven had graft rejection on ipilimumab, six of 15 on PD-1 inhibitor and two of the four patients treated with sequential ipilimumab and PD-1 inhibitor administration. Graft rejection was observed in seven of 10 patients receiving prednisolone with or without cyclosporine, and four of 16 patients treated with different immunosuppressive regimens containing any of the following drugs: tacrolimus, everolimus, sirolimus or mycophenolate mofetil. This may suggest that solid organ transplant recipients considered for immune checkpoint inhibitors may need a more intensive immunosuppressive treatment than prednisolone monotherapy. Tumor response was reported in three out of 11 (27%) patients receiving ipilimumab treatment and six out of 19 patients (32%) treated with PD-1 inhibitors (Table 1). These numbers are very small, but are somewhat not in accordance to studies were it is reported that PD-1 inhibitor treatment may have a higher response rate compared to ipilimumab treatment [3]. Of the nine patients obtaining complete response or partial response on immune checkpoint inhibitors, four patients were immunosuppressed with tacrolimus or sirolimus whereas the other five were treated by prednisolone. This might suggest that immunosuppressive regimens containing tacrolimus or sirolimus may be continued when immune checkpoint inhibitors are administered in organ transplant recipients.

Median time from transplantation to start of immune checkpoint inhibitor treatment was 12.5 years (range 1.5–32 years). The two patients with shortest time (1.5 and 3 years) experienced graft rejection. The risk of acute rejection generally tends to diminish with time from transplant and recipients require a lower maintenance immunosuppressive treatment than in the initial post-transplant phase. The incidence of and consequence in terms of functional impact and chronic allograft rejection also varies among organ types [36,37]. Thus, one might therefore be more reluctant to introduce immune checkpoint inhibitor treatment during the first years after solid organ transplantation and particularly in patients that have experienced repeated episodes of acute rejection in their medical history.

Graft loss is a devastating event in organ recipients where no other lifesaving treatment is available. The case reports reviewed in this article showed that graft rejection was observed in seven of fourteen kidney recipients resulting in graft loss. Rejection was also observed in three of eight liver-transplanted patients and one of four heart-transplanted patients. However, there was only one graft loss among these patients. A liver-transplanted patient receiving PD-1-inhibitor experienced elevated transaminases a few days after the second dose of nivolumab developed liver graft loss. The patient died 3 weeks after liver rejection [25]. Furthermore, another patient (14 years old at time of liver transplantation) had relapse of hepatocellular carcinoma about 1 year after receiving a liver transplant. He was treated with nivolumab and passed away 4 weeks after initiation of PD-1 inhibitor treatment [25].

This review is based on published results, we cannot exclude that there are other transplant recipients that may have died due to graft loss after immune checkpoint inhibitor treatment that has not been reported in the medical literature.

Based on these case reports, we suggest that clinicians should be cautious when considering immune checkpoint inhibitor treatment in transplant recipients. If immune checkpoint inhibitor administration is started, careful monitoring of graft function and integrity is required to detect acute rejection early. Graft loss is a life threatening event in recipients of heart, lung and liver, since they will not be eligible for re-transplant, thus probably resulting in a shorter survival compared to the outcome from the metastatic disease, including metastatic malignant melanoma. In contrast, kidney recipients who experience graft loss may be maintained on dialysis and have prolonged survival.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by South-Eastern Norway Regional Health Authority, Oslo University Hospital and the Norwegian Cancer Society.

ORCID

TorMagnus Smedman http://orcid.org/0000-0002-1531-1229
Pål-Dag Line http://orcid.org/0000-0002-5884-9336
TormodK. Guren http://orcid.org/0000-0001-6471-2072
Svein Dueland http://orcid.org/0000-0002-6125-6689

References

[1] Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348:56–61.
[2] Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363:711–723.
[3] Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373:23–34.
[4] Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372:2521–2532.
[5] Moini M, Schilsky ML, Tichy EM. Review on immunosuppression in liver transplantation. World J Hepatol. 2015;7:1355–1368.
[6] Piselli P, Serraino D, Segoloni GP, et al. Risk of *de novo* cancers after transplantation: results from a cohort of 7217 kidney transplant recipients, Italy 1997-2009. Eur J Cancer. 2013;49:336–344.
[7] Zwald FO, Christenson LJ, Billingsley EM, et al. Melanoma in solid organ transplant recipients. Am J Transplant. 2010;10:1297–1304.
[8] Sint Nicolaas J, de Jonge V, Steyerberg EW, et al. Risk of colorectal carcinoma in post-liver transplant patients: a systematic review and meta-analysis. Am J Transplant. 2010;10:868–876.
[9] Verran DJ, Mulhearn MH, Dilworth PJ, et al. Nature and outcomes of the increased incidence of colorectal malignancy after liver transplantation in Australasia. Med J Aust. 2013;199:610–612.
[10] Alhamad T, Venkatachalam K, Linette GP, et al. Checkpoint inhibitors in kidney transplant recipients and the potential risk of rejection. Am J Transplant. 2016;16:1332–1333.
[11] Barnett R, Barta VS, Jhaveri KD. Preserved renal-allograft function and the PD-1 pathway inhibitor nivolumab. N Engl J Med. 2017;376:191–192.

[12] Boils CL, Aljadir DN, Cantafio AW. Use of the PD-1 pathway inhibitor nivolumab in a renal transplant patient with malignancy. Am J Transplant. 2016;16:2496–2497.
[13] Gastman BR, Ernstoff MS. Tolerability of immune checkpoint inhibition cancer therapy in a cardiac transplant patient. Ann Oncol. 2016;27:2304–2305.
[14] Herz S, Hofer T, Papapanagiotou M, et al. Checkpoint inhibitors in chronic kidney failure and an organ transplant recipient. Eur J Cancer. 2016;67:66–72.
[15] Lipson EJ, Bagnasco SM, Moore J Jr, et al. Tumor regression and allograft rejection after administration of anti-PD-1. N Engl J Med. 2016;374:896–898.
[16] Lipson EJ, Bodell MA, Kraus ES, et al. Successful administration of ipilimumab to two kidney transplantation patients with metastatic melanoma. J Clin Oncol. 2014;32:e69–e71.
[17] Morales RE, Shoushtari AN, Walsh MM, et al. Safety and efficacy of ipilimumab to treat advanced melanoma in the setting of liver transplantation. J Immunother Cancer. 2015;3:22.
[18] Ong M, Ibrahim AM, Bourassa-Blanchette S, et al. Antitumor activity of nivolumab on hemodialysis after renal allograft rejection. J Immunother Cancer. 2016;4:64.
[19] Ranganath HA, Panella TJ. Administration of ipilimumab to a liver transplant recipient with unresectable metastatic melanoma. J Immunother. 2015;38:211.
[20] Spain L, Higgins R, Gopalakrishnan K, et al. Acute renal allograft rejection after immune checkpoint inhibitor therapy for metastatic melanoma. Ann Oncol. 2016;27:1135–1137.
[21] De Toni EN, Gerbes AL. Tapering of immunosuppression and sustained treatment with nivolumab in a liver transplant recipient. Gastroenterology. 2017;152:1631–1633.
[22] Qin R, Salama AK. Report of ipilimumab in a heart transplant patient with metastatic melanoma on tacrolimus. Melanoma Manag. 2015;2:311–314.
[23] Varkaris A, Lewis DW, Nugent FW. Preserved liver transplant after PD-1 pathway inhibitor for hepatocellular carcinoma. Am J Gastroenterol. 2017;112:1895–1896.
[24] Winkler JK, Gutzmer R, Bender C, et al. Safe administration of an anti-PD-1 antibody to kidney-transplant patients: 2 clinical cases of the literature. J Immunother. 2017;40:341–344.
[25] Friend BD, Venick RS, McDiarmid SV, et al. Fatal orthotopic liver transplant organ rejection induced by a checkpoint inhibitor in two patients with refractory, metastatic hepatocellular carcinoma. Pediatr Blood Cancer. 2017;64. DOI:10.1002/pbc.26682.
[26] Biondani P, De Martin E, Samuel D. Safety of an anti-PD-1 immune checkpoint inhibitor in a liver transplant recipient. Ann Oncol. 2018;29:286–287.
[27] Dueland S, Guren TK, Boberg KM, et al. Acute liver graft rejection after ipilimumab therapy. Ann Oncol. 2017;28:2619–2620.
[28] Jose A, Yiannoullou P, Bhutani S, et al. Renal allograft failure after ipilimumab therapy for metastatic melanoma: a case report and review of the literature. Transplant Proc. 2016;48:3137–3141.
[29] Kittai AS, Oldham H, Cetnar J, et al. Immune checkpoint inhibitors in organ transplant patients. J Immunother. 2017;40:277–281.
[30] Kwatra V, Karanth NV, Priyadarshana K, et al. Pembrolizumab for metastatic melanoma in a renal allograft recipient with subsequent graft rejection and treatment response failure: a case report. J Med Case Reports. 2017;11:73.
[31] Owonikoko TK, Kumar M, Yang S, et al. Cardiac allograft rejection as a complication of PD-1 checkpoint blockade for cancer immunotherapy: a case report. Cancer Immunol Immunother. 2017;66:45–50.
[32] Schvartsman G, Perez K, Sood G, et al. Immune checkpoint inhibitor therapy in a liver transplant recipient with melanoma. Ann Intern Med. 2017;167:361–362.
[33] Haanen JBAG Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2017;28: iv119–iv142.
[34] Germani G, Rodriguez-Castro K, Russo FP, Senzolo M, Zanetto A, Ferrarese A, et al. Markers of acute rejection and graft acceptance in liver transplantation. World J Gastroenterol. 2015;21(4):1061–1068.
[35] Johncilla M, Misdraji J, Pratt DS, et al. Ipilimumab-associated hepatitis: clinicopathologic characterization in a series of 11 cases. Am J Surg Pathol. 2015;39:1075–1084.
[36] Neuberger J. Incidence, timing, and risk factors for acute and chronic rejection. Liver Transpl Surg. 1999;5:S30–S36.
[37] Wu O, Levy AR, Briggs A, et al. Acute rejection and chronic nephropathy: a systematic review of the literature. Transplantation. 2009;87:1330–1339.

LETTER TO THE EDITOR

Melanoma metastases occuring 40 years after primary melanoma

Gianni Gerlini[a], Lara Tripo[a], Serena Sestini[a], Paola Brandani[a], Vanni Giannotti[a], Riccardo Gattai[b] and Lorenzo Borgognoni[a]

[a]Plastic & Reconstructive Surgery Unit, Regional Melanoma Referral Center and Melanoma & Skin Cancer Unit Tuscan Tumour Institute (ITT), Santa Maria Annunziata Hospital, Florence, Italy; [b]Unit of Emergency Surgery and Surgery of Oncology and Functional Disease, University of Florence, Florence, Italy

Late recurrence of cutaneous melanoma is defined as the onset of metastases more than 10 years after primary melanoma diagnosis [1]. Although its incidence is low, this event is not so rare, even after many years [1,2].

Cutaneous melanoma can develop loco-regional and/or distant metastases in 20% of cases [1,2]. Although most of melanoma recurrences (65–81%) will occur within 3 years after treatment, metastases can also occur after 10 years [3]. The frequency of this event varies from 1.1 to 6.9% of melanoma patients [1,4,5]. Recurrence rates using actuarial analysis were reported to be 6.8 and 11.3%, after 15 and 25 years, respectively, for those patients disease-free for 10 years or more [4]. Instead, late metastases are more common for uveal melanoma, with relapse disease rates of 34% [5].

About 70% of newly diagnosed melanoma today are thin tumors which present a good prognosis [6–8]. However, thin melanoma patients, particularly with high risk factors

CONTACT Gianni Gerlini gianni.gerlini@uslcentro.toscana.it Melanoma & Skin Cancer Unit SM Annunziata Hospital, Via Antella 58, 50011 Florence, Italy

https://doi.org/10.1080/0284186X.2018.1481295