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Case Report

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Cyclophosphamide, fluorouracil and low-dose interleukin-2 and salvage combination chemotherapy in advanced cutaneous squamous cell carcinoma

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Abstract

A 70-year-old female with metastatic cutaneous squamous cell carcinoma (cSCC) and low-grade non-Hodgkin's lymphoma, not amenable to cisplatin combination therapy, was treated with cyclophoshamide (Cyc)-fluorouracil (FU)-interleukin-2 (IL-2) in light of high tumor immunogenicity and the potential activity of this regimen. Cyc 300 mg/m^2 and FU 500 mg/m^2 intravenously on day 1 and IL-2 4.5 MIU/day on days 3-6 and 17-20 subcutaneously every 4 weeks; Carboplatin (C) AUC 2 and paclitaxel (P) 85 mg/m^2 on days 1, 8 and 15 ± capecitabine (Cape) every 4 weeks. After partial remission (PR) of lung metastases and local control with two cycles of first therapy followed by PR with five cycles of CP ± Cape, right mastectomy was performed with evidence of viable tumor. Subsequently, the patient underwent 3 cycles of chlorambucil and is alive after 13 months of follow-up. Safety and activity of chemo-immunotherapy and salvage treatment can be achieved in cSCC.

Keywords: Cutaneous squamous cell carcinoma, cyclophosphamide, fluorouracil, interleukin-2, regulatory T cells, myeloid-derived suppressor cells

INTRODUCTION

In 2018, cutaneous squamous cell carcinoma (cSCC) was reported to be the 5th most common type of cancer with 5.8% and 0.7% rates of incidence and mortality respectively[1]. It shows racial and gender differences with greater incidence in white than black subjects and in men than women. The incidence increases with age, with an average age around 60 years[2]. Tumor aggressiveness is associated with histological type. In fact, well-differentiated histologic subtypes such as keratoacanthoma and verrucous carcinoma are associated with low metastatic potential and do not seem related to human papillomavirus (HPV) infection[3]. On the contrary, there are histological variants characterized by greater tumor aggressiveness, metastatic potential and poor prognosis and are represented by desmoplastic[4] and adenosquamous[5] cSCC. However, the absence of negative features such as epithelial dysplasia and stromal invasion in verrucous carcinoma can determine differential diagnostic difficulties with other benign entities[6]. The most important prognostic factors are tumor diameter > 2.0 cm[7], tumor depth (< 2 mm *vs.* > 2 mm)[8] and perineural involvement[9], which are highly associated with local recurrence, nodal metastases and disease-specific death. Sun exposure, age, fair skin, and immunosuppression are the main risk factors. Immunosuppression, associated with organ transplantation[10] or other lymphoproliferative[11] or solid tumors[12], negatively affects the behavior of the disease and probably also the responsiveness to treatments. Surgery and radiotherapy are the main modalities of treatment once the diagnosis has been made or after loco-regional recurrence with good results in terms of relapse-free survival, which is influenced by the state of immunosurveillance[13]. The treatment of metastatic disease up to now has been by chemotherapy[14-19], and it should be noted that cisplatin (DDP)[14] and fluorouracil (FU)[15] are the most active chemotherapeutic agents. Regarding anti-epidermal growth factor receptor (EGFR) therapy, cetuximab[14] seems to be more active than panitumumab[20] with complete response (CR) of 68% and 12.5%, overall response rate (ORR) of 78% and 31% and progression-free survival of 25 and 8 months, respectively.

In comparison, ORR of patients treated with DDP is 45% comprising 22% CR with a median disease-free survival of 14.6 months[14]. One of the mechanisms of DDP resistance could be linked to MiR-3619-5p downregulation, responsible for cell proliferation[19]. To overcome drug resistance, considering the synergistic action between different types of chemotherapeutic agents such as DDP and fluoropyrimidines [e.g., FU[16] or capecitabine (Cape)][17], DDP and taxanes[21], and taxanes and fluoropyrimidines[22], there is a rationale for a combination of these drugs. Recently, we have witnessed an explosion in research on new immunotherapeutic agents that have come into clinical practice both in solid and hematological tumors. In 2018, the US FDA approved cemiplimab-rwlc, a human anti-programmed death 1 (PD-1) monoclonal antibody, which blocks the interaction of PD-1 with programmed death ligand-1 (PD-L1) and represents the first and sole treatment specifically approved and available for advanced cSCC. The approval of cemiplimab-rwlc was based on a combined analysis of data from a phase II trial (EMPOWER-CSCC-1 Study 1540) and a phase I trial with two advanced cSCC expansion cohorts (Study 1423). In 108 patients with metastatic or locally advanced disease, there was a 47.2% objective response, and G ≥ 3 SAE was observed in 29% of cases[14]. Regarding other anti-PD1 agents such as nivolumab[24-28] and pembrolizumab[29-35], there are positive reports with small series [Table 1].

Regarding the negative effect of immunosuppressive cells such as regulatory T lymphocytes (Tregs) and myelo-derived suppressor cells (MDSCs) on resistance to treatment with clinically unfavorable outcome and in light of the possible inhibitory interference of cyclophoshamide (Cyc) and FU on this cell population, the aim of the study was to evaluate an innovative chemo-immunotherapy modality including interleukin-2 (IL-2) in the treatment of cSCC.

Our patient with low performance status had advanced cSCC originating from the right breast and concomitant non-Hodgkin lymphoma (NHL), and was therefore not amenable to combination

Table 1. Anti-PD-1 agents in cSCC

Agent	Study	Drug dose	No. PTS	RR (CR)	PFS (mo)	Toxicity G ≥ 3 SAE
Cemiplimab[23]	1,540		59	41 (7)	(n.r.) MDR > 6 mo 57%	29%
Cetuximab Nivolumab[24]	case	n.d.	1	CR	12+	n.d
Ipilimumab Nivolumab[25]	case	n.d.	1	Path CR	5	Allograft rejection
Nivolumab[26]	case	3 mg/kg/2 weeks	3	PR 2, SD 1	12+	--
Nivolumab[27]	case	3 mg/kg/2 weeks	3	PR 1, SD 2	5.5-7+	--
Nivolumab[28]	case	3 mg/kg/2 weeks	1	PR	4.5	--
Pembrolizumab[29]	cases	2 mg/kg/3 weeks	1	PR	5+	--
Pembrolizumab[30]	cases	2 mg/kg/3 weeks	5	CR 1, PR SD 1, PD 1	3-21	Severe weakness (2)
Pembrolizumab[27]	case	2 mg/kg/3 weeks	2	PR 1, SD 1	4+, 7+	--
Pembrolizumab[31]	case	2 mg/kg/3 weeks	2	PR 2	--	--
Pembrolizumab[32]	case	2 mg/kg/3 weeks	1	PR	11+	--
Pembrolizumab[33]	phase 2	200 mg IV/3 weeks	10	40%	n.r.	hepatitis and pneumonitis
Pembrolizumab[34]	case	2 mg/kg/3 weeks	1	PR	n.r.	--
Pembrolizumab[35]	case	2 mg/kg/3 weeks	1	CR	24+	--

PTS: patients; No.: number; CR: complete remission; PR: partial remission; SD: stable disease; RR: response rate; Path CR: pathological CR; PFS: progression-free survival; MDR: median duration of response; n.d.: not done; n.r.: not reported; SAE: serious adverse event

chemotherapy including DDP. Taking into consideration the high immunogenicity of cSCC, even if burdened by the immunosuppressive effect of NHL, this depletion strategy on Tregs and MDSCs by Cyc and FU could allow effective immune stimulation by IL-2. An alternative treatment with carboplatin, paclitaxel ± Cape was foreseen in case of intolerance or ineffectiveness of the therapy to reach palliative mastectomy.

CASE REPORT

Clinical history and response

A 70-year-old female patient, a teacher by profession and of the Caucasian race, underwent hysterectomy for fibromatosis in 1995. In December 2017, she went to the emergency room because of the presence of exophytic vegetation 10 cm in diameter and localized in the right hemithorax. The lesion had appeared a year before and showed recent bleeding. After biopsy resection, the pathological diagnosis of a cSCC with lymph node metastasis (pT2L1V1N2) was made. A simultaneous marginal low-grade NHL (stage IV) was diagnosed. The patient was treated with radiotherapy on the right chest wall, 50 Gy/20 fractions, which were completed in August 2018. In September 2018, mammography detected local recurrence of a 35-mm nodule with polylobed contours in the right breast. The lesion was confirmed by ultrasound, which detected retroareolar ductal ectasia with dense intraductal content and satellite node of 0.6 cm in the upper internal quadrant of the breast. No significant focal lesions in the left breast were evident. Multiple bilateral axillary lymph nodes were detected. A needle biopsy of the right breast lesion was performed and confirmed the pathological diagnosis of poorly differentiated cSCC, polypoid, ulcerated, initially infiltrating the hypodermis. Thereafter, the immunohistochemistry for programmed death ligand-1 (PDL-1) and microsatellite instability were negative. Considering the new efficacy of anti-PD-1, at present not yet available, the ineligibility for DDP-containing regimen due to weight loss and poor performance status and the chance of low efficacy of alternative chemotherapy, after health authorization of chemo-immunotherapeutic regimen, from November 2018 to January 2019, she was treated with Cyc-FU-IL-2. The treatment was well tolerated, and the only reported problem was flu-like symptoms, which were controlled with paracetamol. On physical examination after two cycles of therapy, the patient showed initial local response [Figure 1A-C, Figure 3A and B] and size reduction of lung metastasis on CT scan [Figure 3D and E]. However, after a short-lasting response [Figure 1C] due to local progression [Figure 1D] from February to March 2019, the patient was treated with weekly low-dose carboplatin (C) AUC 2 and paclitaxel (P) 85 mg/m^2 (CP) on days 1, 8 and 15 every 4 weeks with initial objective response [Figure 2A] followed by progression [Figure 2B]. Thereafter, from March to June 2019, Cape 1000 mg/day for 14 days was combined with CP for 3 cycles. From response evaluation

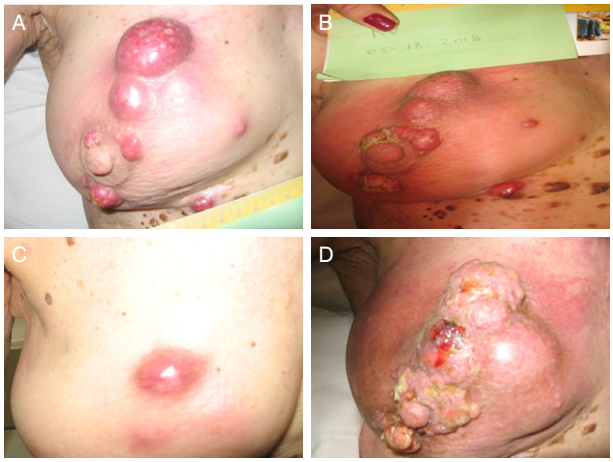

Figure 1. Clinical presentation and course of breast neoplastic lesion during chemo-immunotherapy with cyclophosphamide, fluorouracil and interleukin-2. A: (November 2018): presence of polylobed and ulcerated neoplastic mass of 7 cm × 7 cm and overlying vegetative lesion of 4 cm located on the right breast; B: (December 2018): 2 weeks, after chemo-immunotherapy reduction in size and consistency of the neoplastic mass of 5 cm × 7 cm and of polylobed overlying vegetative lesion of 3 cm located in the right breast; C: (December 2018): 5 weeks after chemo-immunotherapy, further reduction in size and thickness of nodules in the right breast; D: (January 2019): increase in size of the polylobed and ulcerated neoplastic mass of 8 cm × 8 cm with nodules above greater than 4.5 cm located in the right breast after chemo-immunotherapy

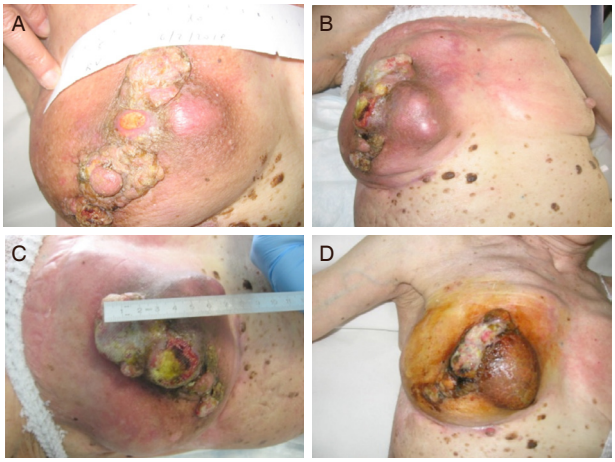

Figure 2. Clinical presentation and course of breast neoplastic lesion during chemotherapy with carboplatin, paclitaxel ± capecitabine. A: reduction in size and thickness of the nodules with ulcerated area and fibrous material in the right breast after chemotherapy (February 2019); B: progression in size and thickness of nodules with ulcerated area and fibrous material within the neoplastic mass in the right breast after chemotherapy (March 2019); C: initial reduction in thickness of the polylobed nodules with ulcerated and necrotic areas and fibrin-hemorrhagic material above the neoplastic mass in the right breast (April 2019); D: reduction in size of the polylobed and ulcerated neoplastic mass of 6 cm × 6 cm located in the right breast after chemotherapy (June 2019)

by physical examination and radiological back-up, there was a reduction in size and thickness of the skin lesion in the right breast [Figure 2C and D, Figure 3C] with good tolerance and a further reduction of lung metastasis [Figure 3F]. After 5 cycles of chemotherapy, in June 2019, the patient was submitted to right simple radical mastectomy and the pathological diagnosis was poorly differentiated cSCC G3 according to WHO. Nipple, margins of resection and muscle level were free from tumor. However, after three months in September 2019, progression of disease was detected in multiple lymph nodes sites, on the chest wall along with the appearance of new pleural and lung metastatic lesions (not shown). Considering the progression and supposed negative impact of NHL, she then underwent three cycles of therapy with chlorambucil, aiming to improve the immunosuppressive role of lympho-proliferative disease. The patient is alive and in a rather good shape after 13 months from the beginning of systemic therapy.

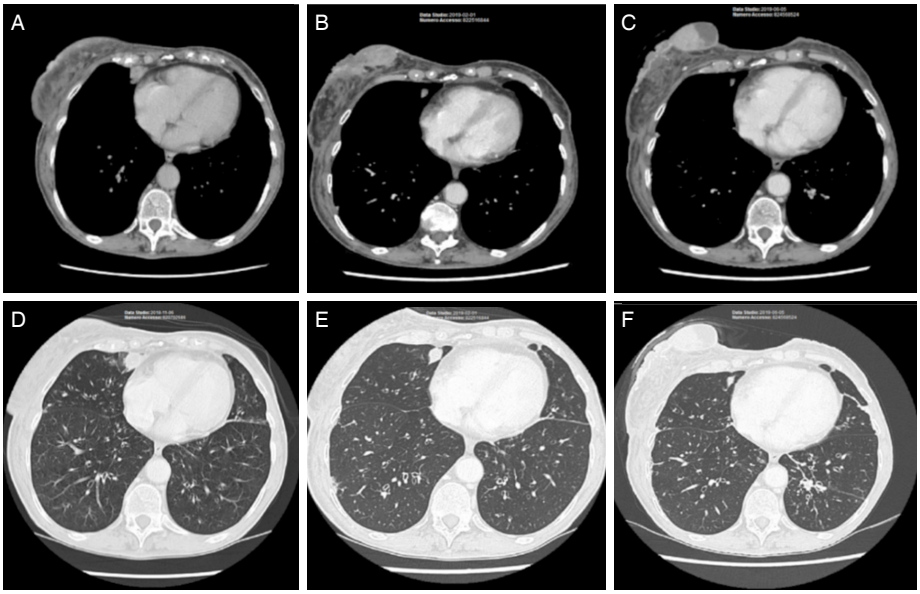

Figure 3. CT scan presentation and clinical course of local and metastatic lesions during chemo-immunotherapy with cyclophosphamide, fluorouracil and interleukin-2 and salvage carboplatin, paclitaxel ± capecitabine regimen. A: neoplastic masses of 19 mm × 13 mm to the infero-lateral quadrant and 40 mm × 35 mm to the medial quadrant of the right breast. Metastatic lesion of 11 mm × 25 mm to the middle lung lobe anteriorly (November 2018); B: dimensional increase of the heterogeneous lesion localized in the right central breast of 63 mm × 34 mm, with current ulcerative aspects of the overlying skin after chemo-immunotherapy (February 2019); C: partial reduction of density due to necrosis and size of the polylobed and ulcerated neoplastic mass of 7 cm located in the right breast after salvage chemotherapy (June 2019); D: metastatic lesion of 11 mm × 25 mm to the middle lung lobe anteriorly (November 2018); E: reduction in size of metastatic lesion of 11 mm × 7 mm to the middle lung lobe anteriorly after chemo-immunotherapy (February 2019); F: further reduction in size of metastatic lesion of 10 mm × 6 mm to the middle lung lobe anteriorly after salvage chemotherapy (June 2019)

Treatment protocol

The chemo-immunotherapy combination included intravenous Cyc 300 mg/m^2 and FU 500 mg/m^2 on day 1 and subcutaneous low-dose IL-2 4.5 MIU/day on days 3-6 and 17-20 every 4 weeks. A premedication with metoclopramide and paracetamol was planned. The cycle was repeated every 4 weeks for three cycles. If an objective response (CR) or PR or disease stabilization was documented upon clinical and radiological back-up every two months, in the absence of serious toxicities or refusal of treatment, the therapy was continued for another three cycles.Blood count, creatinine, alanine aminotransferase (ALT), gamma glutamyl transpeptidase (γ-GT), bilirubin, calcium, lactic dehydrogenase (LD), alkaline phosphatase, peripheral blood lymphocyte immunophenotype CD3$^+$, CD4$^+$, CD8$^+$, CD19$^+$, CD16$^+$, HLA-DR$^+$/CD3$^+$/CD8$^+$ and Treg (CD3$^+$/CD4$^+$/CD25$^+$/CD127$^-$) were determined before every cycle, and blood count, creatinine, ALT, bilirubin and blood lymphocyte immunophenotype (CD3$^+$, CD4$^+$, CD8$^+$, CD19$^+$, CD16$^+$), HLA-DR$^+$/CD3$^+$/CD8$^+$ and Treg (CD3$^+$/CD4$^+$/CD25$^+$/CD127$^-$) on days 3 and 17 of each cycle.

Salvage therapy: carboplatin (C) AUC 2 and paclitaxel (P) 85 mg/m^2 (CP) day 1, 8 and 15 every 4 weeks. In the presence of further disease progression, the addition of Cape 1000 mg/day for 14 days to CP was expected. A premedication with ondansetron during treatment was employed.

Blood count, creatinine, ALT, γ-GT, bilirubin, calcium, LD, alkaline phosphatase were determined before every cycle and blood count, creatinine, ALT, bilirubin on days 1 and 8. Radiological response was determined every 3 months.

DISCUSSION

Advanced cSCC is an orphan disease and the main treatment is represented by radiotherapy, anti-EGFR antibodies and chemotherapy. Unfortunately, these treatments do not offer long-lasting results with a

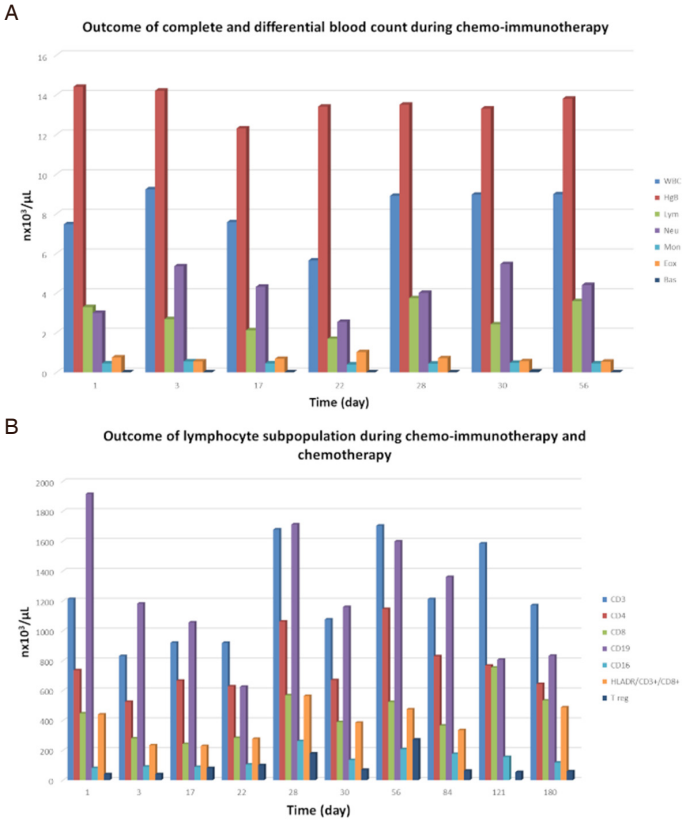

Figure 4. Outcome of complete and differential blood count and immunophenotyping during chemo-immunotherapy and salvage chemotherapy. A: The blood count showed an initial increase in white blood cells (WBC), neutrophilic granulocytes (N) and lymphocytes (Lym) followed by their decrease during chemo-immunotherapy; B: An undulating trend of $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16^+$, HLA-DR^+ and Tregs and a transient decrease in Treg count were observed after chemo-immunotherapy. Subsequently, after an increase in Treg count, there was a decrease during chemotherapy. $CD3^+$: cluster of differentiation 3 T cell; $CD4^+$: $CD4^+$ (helper) T cell; $CD8^+$: $CD8^+$ (cytotoxic) T cells; $CD19^+$: cluster of differentiation 19 B-lymphocyte; $CD16^+$: type I transmembrane receptor mediating antibody-dependent cellular cytotoxicity (ADCC) by NK cells; HLA-DR^+: histocompatibility class II allele T cell; Treg: regulatory T cells CD4(+) CD25(+)Foxp3(+)

range of 8 to 25 months. The disease becomes more resistant especially when it is associated with a state of immunosuppression resulting from post-transplant therapy or neoplastic disease such as lymphomas. This scenario becomes permissive to the immunosuppression exercised above all by Tregs and MDSCs, as well as by tumor-associated macrophages. cSCC shows a high tumor mutation burden (TMB), a condition that makes immunotherapy effectiveness highly possible. Recently, cemiplimab-rwlc, an anti PD-1 checkpoint agent was approved by the FDA for the treatment of cSCC. Regarding other immunotherapeutic agents such as IL-2, which has been shown to be effective in metastatic renal cell carcinoma and cutaneous melanoma, it has not been tested in this disease in human subjects. However, in the animal model, subcutaneous perilesional administration of IL-2 resulted in a high remission rate and long-lasting response, which was significantly satisfactory when administering high doses instead of low ones[36]. IL-2 is a 15.5 kDa cytokine secreted predominantly by CD4+, CD8+ T cells, natural killer cells, and activated dendritic cells[37]. IL-2 can stimulate cells expressing both a high affinity for the trimeric receptor α, β, γ chains or a low affinity dimeric receptor α, γ chains for IL-2. IL-2 can stimulate cell growth in CD8+ cells and differentiation of memory lymphocytes, and maintain and expand the CD41+ Tregs, reducing the risk of uncontrolled immune activity and autoimmunity[38]. Furthermore, it has a differentiating effect on CD4 T cells, and its action can be stimulatory or inhibitory in the different T helper subtypes[39]. The immunosuppressive effect seems to be exerted also by MDSCs. It can occur indirectly through the increase in Tregs and for the expression of indoleamine 2, 3-dioxygenase (IDO) on MDSCs[40] and through the production of TGF-β and retinoic acid[41]. Similarly the overexpression of IDO by the dendritic cells

with consequent depletion of tryptophan determines immunosuppression through their blocking of the maturation and induction of T cell apoptosis[42].

Considering the key immunosuppressive role played by these cells, with Tregs and MDSCs being the most studied, and their negative relationship with tumor stage, prognosis, and resistance to treatment[43], preliminary experience with Cyc and FU, active on both types of suppressive cells, combined with IL-2 was reported in heavily pre-treated solid tumors, with interesting results both from a clinical and laboratory point of view[44].

Our patient with advanced cSCC showed for the first time how a chemo-immunotherapy regimen including IL-2 was able to produce a fleeting response even on the primary and more-lasting tumor response on the metastatic lesion. Furthermore, the blood count and immunophenotype showed an initial increase in white blood cells, neutrophilic granulocytes and lymphocytes followed by their decrease [Figure 4A] and a transient decrease in the Treg count during chemo-immunotherapy [Figure 4B], respectively. In addition, a subsequent decrease in Tregs was observed during salvage chemotherapy [Figure 4B]. This transient effect could be explained by the concomitant presence of lymphomas and Treg stimulation by IL-2 with detrimental effect on the immune system with consequent unfavorable response to chemo-immunotherapy. A more favorable outcome could be hypothesized in the presence of adequate immunosurveillance especially in a high TMB tumor such as cSCC. A confirmation of the poor efficacy of chemotherapy along with the combination of carboplatin and paclitaxel employed after chemo-immunotherapy failure, despite the theoretical synergism and additive antitumor activity for increase of carboplatin-DNA adduct formation[45], has been reported. Noteworthy is the ability of a fluoropyrimidine (Cape) to reverse resistance to the previous carboplatin combination therapy through the upregulation of thymidine phosphorylase activity by paclitaxel and subsequent Cape activation[22,46], the decrease of Treg count and tumor response.

In conclusion advanced spinocellular carcinoma of the skin remains a pathology with severe treatment difficulties due to primary resistance, worsened by a state of immunosuppression resulting from organ transplantation or other tumors. It is desirable to improve our knowledge of the resistance mechanisms and to investigate prospectively innovative therapeutic strategies to improve the therapeutic index and the control of the disease.

DECLARATIONS

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Authors' contributions

Conceptualization: Lo Re G, Doretto P, Lo Re F, Matrone F, Ermacora A
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Formal analysis: Lo Re G, Doretto P, Lo Re F, Matrone F, Ermacora A, Marus W, Pizzichetta MA, Sulfaro S
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Project administration: Lo Re G, Doretto P, Lo Re F, Matrone F, Ermacora A
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Validation: Lo Re G, Doretto P, Lo Re F, Matrone F, Ermacora A, Marus W, Pizzichetta MA, Sulfaro S
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Writing - review and editing: Lo Re G, Doretto P, Lo Re F, Matrone F, Ermacora A, Marus W, Pizzichetta MA, Sulfaro S
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Availability of data and materials

The source of the data is PUBMED and proceeding ASCO.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Informed consent to treatment was accepted and signed by the patient after ethical approval by the competent facility.

Consent for publication

Patient consent for publication.

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