Ther Adv Med Oncol
2020, Vol. 12: 1–11
DOI: 10.1177/1758835920962369

Clinical considerations about the coexistence of melanoma and chronic lymphocytic leukemia in the era of targeted therapies, triggered by rare clinical scenarios. A case series and review of the literature

Panagiotis T. Diamantopoulos, Dimitrios Ziogas, Nora-Athina Viniou, Amalia Anastasopoulou, Georgios Kyriakakis, Konstantina Frangia and Helen Gogas

***Abstract*:** The epidemiologic correlation of melanoma and chronic lymphocytic leukemia (CLL) has been the subject of several population studies. In the present article, through the presentation of five illustrative cases of patients with melanoma and CLL, several aspects of this complex relationship are highlighted, with a focus on the increased incidence of melanoma in patients with CLL, its speculated etiology, and the impact of CLL stage and disease duration on the incidence and prognosis of melanoma. Furthermore, the rare entity of the synchronous diagnosis of melanoma and CLL in biopsied lymph nodes is discussed, along with its implications on the diagnostic and therapeutic procedures. In addition, the available data on the treatment choices in patients with melanoma and CLL are presented and the efficacy and safety of fludarabine, anti-CD20 monoclonal antibodies, new targeted therapies for CLL, and checkpoint inhibitors are further discussed. Finally, since no formal guidelines are available for the management of this group of patients, guidelines are proposed for skin-cancer screening in patients with CLL, for the correct interpretation of *BRAF* mutation analysis in lymph-node specimens with 'collision of tumors,' and for the optimal use of imaging studies in the diagnosis of metastatic disease in patients with CLL and melanoma, while a treatment approach for such patients is also suggested. The information and proposed guidelines provided in the present article comprise a useful guide for physicians managing such patients, focusing on diagnostic challenges and therapeutic dilemmas posed by the coexistence of the two disease entities.

Keywords: *BRAF* mutation, chronic lymphocytic leukemia, immunotherapy, melanoma, targeted therapy

Received: 21 May 2020; revised manuscript accepted: 3 September 2020.

Correspondence to:
Panagiotis T. Diamantopoulos
First Department of Internal Medicine, Laikon General Hospital, National and Kapodistrian University of Athens, Athens 11527, Greece
pandiamantopoulos@gmail.com

Dimitrios Ziogas
Nora-Athina Viniou
Amalia Anastasopoulou
Georgios Kyriakakis
Helen Gogas
First Department of Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece

Konstantina Frangia
Histo-Bio Diagnosis, Athens, Greece

Introduction

In a recent study, the risk of developing a second primary malignancy (SPM) among survivors of common cancers was reported to be 8.1% while more than half of cancer survivors died from their second malignancy.[1] Furthermore, another study reported an 8.1% incidence of a second malignancy in patients with melanoma, with the incidence of lymphoma being 16-fold higher than the expected incidence, adjusted for age, sex, and race.[2] In yet another study, the corresponding cumulative incidence was 6.2%, reporting a higher risk of non-Hodgkin lymphoma and renal cell carcinoma in men.[3] Moreover, the risk of SPM in patients with

chronic lymphocytic leukemia (CLL) as well as the epidemiologic correlation of melanoma with CLL has been studied by several teams.[1–9]

In the present article, several topics referring to the coexistence of melanoma and CLL will be covered, beginning with the presentation of five illustrative cases that highlight several pathogenetic, clinical, diagnostic, and therapeutic aspects of this complex relation. We will then discuss the reported increased incidence of CLL in patients with melanoma, and mainly focus on the increased incidence of melanoma in patients with a history of CLL and its potential causes, the impact of CLL staging, as well as disease duration, on the incidence and prognosis of melanoma. Furthermore, we will consider the rare condition of the synchronous diagnosis of melanoma and CLL and its implications on the diagnostic and therapeutic procedures, the treatment choices in patients with melanoma and CLL; and finally, some established or proposed guidelines for clinicians managing patients with CLL and melanoma.

Case 1: synchronous diagnosis of CLL and melanoma

A 68-year-old man had an almost concurrent incidental diagnosis of CLL and melanoma after being investigated for generalized lymphadenopathy and lymphocytosis. A skin lesion on his scalp was biopsied revealing a T4b nodular melanoma. A bone-marrow trephine biopsy revealed infiltration from a CD20+, CD79+, CD5+, CD23+, cyclin D−, CD10− lymphocytic population, compatible with CLL. On a computerized tomography (CT) scan, several enlarged lymph nodes (bilateral jugular, submandibular, supraclavicular, subcarinal, and axillary) as well as three metastatic lesions in the liver, two osteolytic lesions in the iliac wings, and multiple nodular lesions in both lungs were recognized. The melanoma was found to be *BRAF* wild type and the patient was treated with pembrolizumab at 200 mg/3 weeks. After a short course of pembrolizumab, the patient experienced melanoma progression and died of complications of brain metastases 3 months after diagnosis.

Case 2: CLL after two primary melanomas

A 70-year-old man was diagnosed with a stage IIIc melanoma of the scalp and was treated with adjuvant interferon at 3×10^9 IU three times per week for a year, according to approved guidelines at the time of diagnosis. A year later a second, primary, stage IIIb melanoma was found on his back. At the same time, an enlarged cervical lymph node was detected, and a fine-needle aspiration revealed infiltration by melanoma. A complete lymph-node resection revealed the concomitant presence of melanoma and CLL [CD20+, CD5+, CD43+, CD23+, ZAP70−, lef1 (100%), MUM1+] in the lymph nodes. The patient was found *BRAF*-V600K positive but was started on pembrolizumab at 200 mg intravenously every 3 weeks. At 3 months later, two new satellite lesions were found on his back, while a CT scan identified extensive lymphadenopathy, including enlarged cervical, axillary, mediastinal, iliac, and inguinal lymph nodes, along with metastatic lesions in the lungs and bones. The spleen was also enlarged without focal lesions. Pembrolizumab was replaced with dabrafenib at 150 mg *per os* (PO) twice a day and trametinib at 2 mg daily PO, and upon consecutive imaging studies, he achieved a stable disease. His CLL was Binet stage A; thus, he was offered no treatment. At 18 months from dabrafenib/trametinib initiation he achieved a partial remission but had a fulminant progression of his melanoma and died 2 months later.

Case 3: concurrent diagnosis of a BRAF(−) melanoma and CLL

A 75-year-old man was diagnosed with a stage IIIa skin melanoma. Upon complete lymph-node resection, all resected nodes were found to be infiltrated by small CD5+, CD19+, CD20+, CD23+, cyclin D1− lymphocytes without any evidence of CLL in the peripheral blood. Being *BRAF*−, he was started on adjuvant therapy with pembrolizumab. However, the first imaging reassessment 4 months later revealed extensive melanoma progression with multiple liver metastases, ascites, multiple enlarged lymph nodes in the thorax and abdomen, and the patient died just a month later.

Case 4: newly diagnosed melanoma in a patient with a long history of CLL

A 79-year-old woman was diagnosed with a T4b melanoma of the sole. An enlarged inguinal node was excised and found infiltrated by melanoma cells. The rest of the inguinal nodes were negative for malignant infiltration (stage IIIc). Her past medical history was significant for CLL, diagnosed 20 years earlier. She had been occasionally

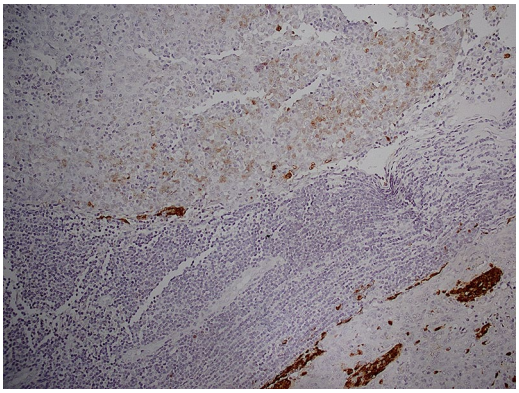

Figure 1. Collision of tumors in a lymph node.
Immunostain for S100 protein, magnification 200×. Chronic lymphocytic leukemia lymphocytes (center) and S100-positive melanocytes, both conglomerates and single cells (upper left and lower right).

treated with chlorambucil while intravenous gamma globulin had been administered in the past due to anosoparesis. Despite the recommendations of her physicians, she refused to receive any adjuvant treatment. At the time of melanoma diagnosis, she had no anemia or thrombocytopenia. Six months later, CT scans revealed mild hepatosplenomegaly, with enlarged axillary nodes bilaterally and an ipsilateral enlarged inguinal lymph node. A positron emission tomography (PET)-CT showed that only the inguinal node had high metabolic activity with a standardized uptake value (SUV) of 9. A complete inguinal lymph-node resection was performed 6 months after the initial diagnosis, and nine of the dissected lymph nodes were found infiltrated by melanoma cells. The lesion was found to be *BRAF* wild type. She was treated with four doses of ipilimumab at 3 mg/kg every 3 weeks, in the adjuvant setting. A year later, she experienced a rapid deterioration of inguinal lymphadenopathy along with pulmonary metastatic lesions and was started on nivolumab at 240 mg/2 weeks, but she died of disease progression just 2 months after treatment initiation. No progression of the CLL was noted during the management of metastatic melanoma.

Case 5: collision of tumors

A 76-year-old man was diagnosed with a T3b melanoma on his back. The histologic evaluation of dissected sentinel lymph node revealed collapse of the lymph-node architecture due to the presence of two distinct malignant cell populations, one with immunophenotypic characteristics compatible with small lymphocytic lymphoma (SLL) and one consisting of middle-sized cells with enlarged nuclei and a prominent eosinophilic nucleolus (Figure 1). The cells of the second population were S100(+), HMB45(+), Melan A(+), MITF(−), revealing the concurrent lymph-node infiltration by melanoma cells. This rare condition of the presence of two malignant populations in the same specimen is termed 'collision of tumors.' The patient, being *BRAF* wild type, was treated with pembrolizumab at 200 mg/3 weeks, at the adjuvant setting (stage IIIb), and has not progressed after 6 months on treatment.

Summary of cases

Through the presentation of these five cases, we have tried to describe several aspects of the coexistence of melanoma and CLL in the same patient, the diagnostic challenges, the clinical dilemmas, the treatment choices, and the poor prognosis that usually characterizes these cases. Patients with both melanoma and CLL are usually elderly (median age was 75 years in our small cohort) mainly due to the fact that CLL is a disease of the elderly with a median age of 70 years at diagnosis.[4] These five cases cover most of the scenarios encountered in clinical practice, such as patients with a synchronous diagnosis of both diseases, including the case of collision of tumors in the lymph nodes, patients with a history of CLL diagnosed with melanoma, and patients with CLL diagnosed after the emergence of melanoma. The patients' characteristics, treatments administered, response, and survival data are all listed in Table 1.

Discussion

Incidence of melanoma in patients with a history of CLL

The risk of SPM in patients with CLL has been assessed in several studies. In a recent study on patients with CLL with a follow up of about 270,000 patient-years, the standardized incidence ratio (SIR) for SPM was 1.2, and was higher between 2 and 5 months after CLL diagnosis and for those patients that had been treated with chemotherapy.[5] The epidemiologic correlation of melanoma with CLL/SLL and other lymphoproliferative disorders is well known and seems to be bidirectional. The SIR for CLL in patients with cutaneous melanoma was found to be 1.29 in a large population study comprising

Table 1. Patient characteristics.

Sex	Age	Stage at diagnosis*	Timing (CLL/melanoma)	Treatment of CLL	*BRAF* status	First-line therapy**	Response	Second-line therapy**	Response	OS (months)
M	68	IV	Synchronous	None	Wild type	Pembrolizumab	PD	NA	NA	3
M	70	IIIc/IIIb	Melanoma first	None	V600K	Pembrolizumab (adj)	PD	Dabrafenib/trametinib	PR	23
M	75	IIIa	Synchronous	None	Wild type	Pembrolizumab (adj)	PD	NA	NA	5
F	79	IIIc	CLL first	IVIG, chlorambucil	Wild type	Ipilimumab (adj)	PD a year later	Nivolumab	PD	14
M	76	IIIb	Synchronous	None	Wild type	Pembrolizumab (adj)	No progression	NA	NA	6$

*Stage of melanoma.
**First- and second-line therapy for melanoma.
$Patient still alive.
adj, adjuvant; CLL, chronic lymphocytic leukemia; F, female; IVIG, intravenous gamma globulin; M, male; NA, not applicable; OS, overall survival; PD, progressive disease; PR, partial response.

16,591 melanoma survivors.[6] On the other hand, in a retrospective study comprising about 129,000 patients with lymphoproliferative disorders (among them 28,964 patients with CLL/SLL), the SIR for melanoma was 2.3, and when invasive melanoma was stratified by patient age and sex, the highest ratio was found in men aged <49 years with CLL ($p < 0.001$).[7] Furthermore, the observed incidence of melanoma among 2028 consecutive patients with CLL/SLL seen from 1985 to 2005 was 8%; much higher than expected.[8] In another study, among 10,993 cases of melanoma, 86 cases occurred in patients with a history of CLL or non-Hodgkin lymphoma (NHL). The majority of the patients were male. The age-adjusted incidence rate of melanoma per 100,000 person-years among patients with CLL or NHL was 107.0 compared with 25.9 among patients without a relevant history ($p < 0.0001$).[9]

Effect of CLL on the prognosis of melanoma

Except for the increased incidence of melanoma in patients with a history of CLL, several studies have shown that patients with melanoma and CLL carry a worse prognosis than patients with melanoma alone. The results of a large population study, including 212,245 patients with melanoma from 1990 to 2006, show that the overall survival (OS) and the melanoma cause-specific survival were lower than expected for patients (1246 patients) with a history of CLL.[10] In the abovementioned study comprising 10,993 cases of melanoma, the overall mortality rate differed significantly among patients with melanoma and a history of CLL or NHL (31.4%), patients without such history (14.4%), and those with CLL or NHL diagnosed after melanoma (28.6%, $p < 0.001$). The hazard ratio (HR) for death for patients with melanoma and a history of CLL or NHL was 1.46 compared with patients without such a history.[9] Another study on 69 patients with CLL and melanoma focused on the progression of melanoma and the progression-free survival (PFS) and OS of the patients.[11] The authors found that the patients had a worse prognosis when CLL preceded the development of melanoma (median OS of 3.8 years *versus* 13.5 years). It should be noted though that, in this study, most (94%) of the patients had stage I or II melanoma; thus, those survival rates overestimate survival of patients with melanoma of any stage. Moreover, there is no mention of the treatments offered to the patients after initial local excision and staging.

Effect of stage and duration of CLL on melanoma prognosis

The effect of CLL stage on the outcome of several skin cancers has been studied in 113 patients (including 22 melanomas) and the authors concluded that patients with high Rai-stage CLL and low T-stage non-basal-cell-carcinoma skin cancers had a significantly higher risk for poor skin-cancer outcomes than patients with low Rai-stage CLL and low T-stage skin cancers.[12] Nevertheless, the authors do not report their results separately for melanoma. Finally, a study on 16,367 patients with CLL evaluating the risk of second malignancies found that in the $<$1-year, 1–4-year, 5–9-year, and $\geqslant$10-year intervals following CLL diagnosis the risk of second malignancies was similar. Moreover, there was no difference in the risk for treatment-naïve patients and those treated with chemotherapy. Lastly, there was no difference in the risk of second malignancies for patients diagnosed between 1973 and 1989 and between 1990 and 1996. The observed-to-expected ratio for melanoma in this cohort was 3.18 ($p < 0.05$), but the authors noted that excess skin cancers in CLL may have been partly due to the increased medical surveillance of the patients.[13]

Speculations about the etiology of the increased incidence of melanoma in patients with CLL

Several studies[14–16] support an association between lymphoproliferative neoplasms with melanoma and speculations for a shared etiology or common risk factors. Apart from the chronic immunosuppression that is an inherent feature of CLL and has been correlated with the development of skin malignancies, the immunosuppressing therapeutic maneuvers in patients with CLL may expose patients to a risk of developing a melanoma. In a study on 202 cases of melanoma developing in 44,870 patients with a history of NHL (91 of them in patients with CLL), fludarabine with or without rituximab was found to be a risk factor for increased melanoma-related mortality (HR, 1.92). The coexistence of a T-cell-activating autoimmune disease, such as rheumatoid arthritis, Grave's disease, psoriasis or localized scleroderma was recognized as another risk factor for increased mortality (HR, 2.30).[17] The speculated increased risk for the development of melanoma in patients under treatment with anti-CD20 antibodies will be discussed later.

Moreover, although there are no data on the effect of prognostic markers for CLL such as *bcl2* and *TP53* on the prognosis of melanoma in patients with both diseases, it should be noted that both overexpression of *bcl2* and *TP53* mutations have been found to have potential prognostic implications in melanoma.

High *bcl2* expression has been found an adverse prognostic factor for OS of patients with early-stage melanoma and has been proposed to contribute as a marker in a model combining *bcl2* expression, nuclear S100 expression, Ki67 proliferation index, and *MITF* immunoreactivity for melanoma risk stratification.[18] Moreover, it has been shown that inhibition of *bcl2* family members increases the efficacy of copper chelation in *BRAF*-V600E-mutated melanoma[19] and that targeting *bcl2* pro-survival proteins may have significant benefit for the treatment of melanoma.[20]

On the other hand, chemotherapy-induced apoptosis in melanoma cell lines has been found to be *TP53* dependent, making mutations of *TP53* an indicator of drug resistance in melanoma.[21] Although it has been shown that *TP53* mutation status has an important role for interferon-gamma-induced programmed-cell-death ligand 1 (PDL1) expression in melanoma cells,[22] in a study of 102 patients with melanoma under treatment with checkpoint inhibitors, pathogenic mutations of *TP53* were not found to significantly alter clinical outcomes.[23]

Finally, it has been shown that ultraviolet (UV) radiation suppresses the immune system both systemically and locally. Thus, there are several epidemiological studies indicating that there is a parallel rise in the incidence of lymphoproliferative disorders and skin cancer with increased levels of UV exposure.[16,24–27]

Concurrent diagnosis of melanoma and CLL

Regarding the rare occurrence of a synchronous diagnosis of melanoma and CLL, in a study of 52 patients, 42% were found to have CLL on the sentinel lymph-node (SLN) biopsy, performed for melanoma staging, and 25% of them had evidence of collision of melanoma and CLL in the SLN. The authors found that the coincidence of CLL and melanoma was 10 times higher than that for colorectal cancer, 8 times higher than for prostate cancer, and 4 times higher than for breast cancer patients.[28]

Anti-CD20 monoclonal antibodies and melanoma

Several case reports and small case series recognize an increased risk of melanoma development in patients that have been treated with anti-CD20 antibodies.[29,30] Moreover, in a large European registry comprising 130,315 patients with rheumatoid arthritis, among whom 287 patients developed a melanoma, pooled SIRs for biologic agent-naïve, tumor necrosis factor inhibitors, and rituximab-exposed patients were 1.1, 1.2, and 1.3, respectively.[31] Nevertheless, it has been shown that melanoma consists of several distinct cell subpopulations, among which one expresses CD20 and has cancer stem-cell properties.[32,33] It seems that these data constitute the rationale for the initiation of two studies with rituximab in patients with metastatic melanoma. In the first one, nine patients were treated with rituximab for 2 years, and after a follow up of 43 months, the median OS was not reached.[34] In the second study, seven heavily pretreated patients with melanoma received rituximab for a maximum of 6 months and the median PFS was 6.3 months,[35] a result that seems more realistic than the one of the first study. Nevertheless, there are no further studies after 2018 with rituximab or other anti-CD20 agents in patients with melanoma.

New targeted therapies for CLL in patients with melanoma

With regard to the new targeted treatments used in patients with CLL and other lymphoproliferative disorders, there are limited data on their use in patients with melanoma and CLL. There is only one case report on the successful treatment of metastatic melanoma with pembrolizumab in a patient with CLL on ibrutinib therapy.[36] Moreover, although there seems to exist no apparent rationale for the use of ibrutinib in patients with melanoma, there are two interventional phase II clinical trials studying the efficacy of ibrutinib alone[37] or in combination with pembrolizumab[38] in patients with advanced or metastatic melanoma, but no results have been reported as of April 2020. Finally, there are no data on the use of idelalisib or venetoclax in patients with melanoma.

BRAF mutations in CLL

Harboring *BRAF* mutations is the molecular hallmark of melanoma to select patients for treatment with *BRAF* (and MEK) inhibitors. Among other malignancies, *BRAF*-V600E mutation is a likely driver mutation in all cases of classic hairy-cell leukemia.[39] This finding prompted the investigation of *BRAF* mutations in CLL. The incidence of *BRAF*-V600E mutations in CLL is found to be low [1/ 23 (4.3%) patients in one study[40] and 4/138 (2.8%) in another study[41]]. In this second study, the authors investigated *in vitro* the possible effect of *BRAF* inhibition on primary CLL cells and found no effect on *BRAF*-positive or -negative CLL cells. Based on the development of CLL in a patient with a Ras-unmutated melanoma under treatment with the *BRAF* inhibitor vemurafenib, another study found that *BRAF* inhibition promoted CLL proliferation in cell culture and murine xenografts and activated the MEK/ERK pathway in primary CLL cells from additional patients, suggesting that *BRAF* inhibitors promote B-cell malignancies in the absence of *Ras* mutations.[42]

A rare but clinically significant pitfall in the interpretation of the *BRAF*-V600E status in patients with collision of melanoma and CLL may arise when in the biopsy specimen, *BRAF*-V600E mutated CLL cells are intermixed with *BRAF*-V600E wild-type melanoma cells. This may result in the erroneous diagnosis of a *BRAF*-V600E-mutated melanoma leading to incorrect treatment choices with *BRAF*/MEK inhibitors in patients with *BRAF* wild-type melanoma. The authors of a case report referring to such a difficult case suggest the use of immunohistochemistry with the monoclonal antibody VE1 (anti-*BRAF*-mutated V600E antibody) against the *BRAF*-V600E-mutant protein as an alternative method for its detection in patients with collision of CLL and melanoma in the same specimen.[43] Collision of CLL and melanoma is an unusual phenomenon first described in 2007[44] that may present puzzling diagnostic problems and warrants the use of alternative diagnostic methods such as immunohistochemistry, or the use of different clinical samples such as skin and bone-marrow samples for the differential detection of *BRAF* mutations.[45]

PD1 and CTLA4 blockade in CLL

The pathogenesis of CLL comprises defects of the regulation of programmed cell death, as well as an altered survival-stimulating microenvironment, resulting in the expansion of the malignant clone. T cells from patients with CLL show features of immune exhaustion that are associated

with the upregulation of surface T-cell receptors, such as the programmed cell-death protein 1 (PD1), a molecule that inhibits T-cell activity by transmitting negative signals to T cells, thus acting as an immune checkpoint. Inhibition of PD1 in a mouse model resulted in correction of leukemia-induced CD8+ T-cell-related immune dysfunction and protected mice from the development of CLL.[46] A flow-cytometry study on the expression of PD1 on CD4+ T cells from 56 patients with newly diagnosed CLL revealed that patients with an advanced-stage melanoma had significantly higher numbers of CD4+PD1+ T cells compared with lower-stage patients. Moreover, higher numbers of PD1+ cells were correlated with significantly shorter time to first treatment.[47] In another study, patients with CLL and increased PD1 expression on T cells from lymph-node samples had poorer OS.[48] On the other hand, one study reported weak expression of PD1 on B neoplastic cells in the majority of patients with CLL.[49] Although the expression profile of PD1 in T cells from CLL clinical samples is still somewhat vague, the PD1/PDL1 axis seems to be functionally active in CLL.[50] The amount of information was large enough so that clinical trials with PD1/PDL1 inhibitors have been carried out in CLL. Thus, in a phase II trial on CLL with Richter transformation (RT), the overall response rate with pembrolizumab was 44% (11% complete response), but it was 0% in relapsed CLL.[51] In the same study, baseline PD1 expression in cells of the microenvironment was associated with response to pembrolizumab. Nivolumab combined with ibrutinib was also clinically active in a small number of patients with relapsed/refractory CLL or RT.[52] In conclusion, it seems that PD1 inhibition has moderate efficacy in patients with RT.[53] Another three clinical trials on CLL with PD1 inhibitors as monotherapy or in combination with ibrutinib,[54] idelalisib,[54] or copanlisib[55] are ongoing and in the phase of recruitment.

Regarding the expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA4), preclinical studies have shown that it is significantly increased in T cells from patients with CLL compared with healthy donors. Moreover, overexpression of CTLA4 has been correlated with a favorable prognosis.[56,57] On the other hand, CTLA4 expression in CLL B cells is inversely correlated with CD38 expression, while CLL cells with down-regulated CTLA4 demonstrated significant increase in proliferation and survival and increased expression of signal transducer and activator of transcription 1 (STAT1), c-Myc, Ki67, and Bcl-2.[58] CTLA4 blockade resulted in enhanced T-cell proliferation in response to autologous or allogeneic CD40-activated CLL B cells. Two phase I studies on the use of ipilimumab in patients with hematologic malignancies after allogeneic bone-marrow transplantation (among them, patients with CLL) have no published results, while there are no other ongoing studies as of April 2020.

Proposed guidelines for patients with CLL with and without melanoma

The management of patients with CLL and melanoma poses several challenges to the treating physicians, especially in patients who need to be treated for both neoplasms. Since there are no formal guidelines for the management of such patients, we have tried to address some of these challenges based on already published data, as well as our own clinical experience with both diseases.

Given the increased incidence of melanoma and non-melanoma skin cancer in patients with a history of CLL, all patients with CLL should have a yearly full-body skin examination, in order to diagnose melanoma at an early stage. There are reports proposing the first skin examination to be performed within the first 6 months of CLL diagnosis,[59] while most authors support a yearly full-body skin examination for all patients.[60,61] It seems though that the penetration of such guidelines in the medical community is still low, as evidenced by the low percentage (36%) of patients with CLL who had a whole-body skin examination within 6 months of diagnosis as reported in a study evaluating compliance with guidelines for skin-malignancy screening in a community-dwelling cohort in the United States of America.[59] We propose a standardized institutional-based approach to increase compliance with melanoma screening guidelines in patients with CLL. Moreover, we propose that patients with CLL who are at higher risk for melanoma, such as those with dysplastic nevi, an advanced CLL stage, or those who have been treated with heavy immunosuppressive regimens such as fludarabine or anti-CD20 antibodies, should be actively screened even at shorter intervals. In a recent article, patient education, implementation of sun protection measures, and self-examination have been proposed as additive strategies for the prevention or early detection of skin cancer in

patients with CLL. The authors emphasize once again on the importance of a dermatological evaluation at least annually by a doctor who has expertise in skin-cancer diagnosis.[62]

Nonetheless, in patients with CLL and melanoma there are several pitfalls for the clinician that should be pointed out. As already mentioned, in the rare cases of collision of tumors in lymph nodes biopsied to stage a melanoma, detection of *BRAF* mutations should be performed on skin and bone-marrow samples to avoid the possibility of a *BRAF* wild-type melanoma being misdiagnosed as a *BRAF*-mutated melanoma in cases of *BRAF*-mutated CLL. This strategy should eliminate the possibility of mistreating a patient with a *BRAF* wild-type melanoma with *BRAF* and MEK inhibitors and depriving the patient of the beneficial effects of immunotherapy.

A more commonly encountered problem in patients with coexistence of CLL and solid tumors, however, is the detection of metastatically infiltrated lymph nodes among the usually large number of enlarged lymph nodes due to CLL. In this direction, the diagnostic accuracy of CT scans is limited while PET-CT is a commonly used imaging technique in patients with melanoma for the detection of fluorodeoxyglucose (FDG)-avid lesions. In patients with CLL and melanoma, PET-CT outweighs CT scans for another reason, too. CLL-involved lymph nodes usually have a relatively low glucose metabolic rate (low SUV). In a study of 526 PET-CT scans performed in patients with CLL, 472 (89.7%) were reported as abnormal and only 120 (22.8%) tests (performed in 83 patients) were found to have lesions with an SUV above 5. A biopsy was undertaken in 80 (96.0%) of them, and in 32 (40%) of the performed biopsies a new malignancy was detected, usually a diffuse large B-cell lymphoma or other solid tumors, among them, six cases of malignant melanoma.[63] Therefore, in patients with melanoma and CLL, PET-CT could help detect highly FDG-avid lymph nodes that should be further investigated as suspicious for metastatic infiltration by melanoma. Lymph nodes with higher SUV, in turn, should be investigated aggressively with invasive techniques (i.e. core or surgical biopsy) in order to accurately stage the melanoma. The same could apply for visceral lesions, although the infiltration pattern is more distinct for the two conditions.

Finally, although there is no evidence based on randomized trials, and although data on the effect of novel agents for CLL such as ibrutinib, idelalisib, and venetoclax on the course of melanoma are very limited, due to the existing data on the detrimental effect of fludarabine and anti-CD20 antibodies on melanoma prognosis,[17,29,30] it would be more prudent to use novel, less immunosuppressant agents to treat CLL in patients with CLL and melanoma instead of fludarabine and anti-CD20 monoclonal antibodies. This strategy could reduce immunosuppression in CLL, allowing the patient's immune system to fight against the melanoma. On the other hand, PD1 inhibitors may be used preferentially to treat melanoma in patients with both melanoma and CLL since they may be effective against both diseases. As already mentioned, combinations of PD1 inhibitors with novel agents such as ibrutinib, idelalisib, and copanlisib are currently under investigation.[54,55] It is more than evident that further clinical trials are needed to optimize the therapeutic approach and improve outcomes in this special population of patients with CLL and melanoma.

Acknowledgements

We would like to thank Ms Evita C. Alexopoulos for copy-editing the final manuscript.

Authors' contributions

PD contributed to data acquisition and analysis and drafted the manuscript.

DZ contributed to data acquisition and analysis and critically revised the manuscript.

N-AV contributed to data acquisition and analysis and critically revised the manuscript.

AA contributed to data acquisition and analysis.

GK contributed to data acquisition and analysis.

KF contributed to data acquisition and analysis.

HG contributed to data acquisition and analysis and critically revised the manuscript.

Conflict of interest statement

PD reports personal fees from Roche and Novartis, outside the submitted work.

HG reports grants and personal fees from BMS, grants and personal fees from Roche, grants and personal fees from MSD, personal fees from Novartis, personal fees from Amgen, personal fees from Pierre Fabre, outside the submitted work.

The remaining authors report no conflict of interests.

Consent for publication

Written informed consent was given by all patients for the publication of the cases and figures. Interventions/treatments were implemented by the treating doctors; thus no additional informed consent was requested.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Panagiotis T. Diamantopoulos https://orcid.org/0000-0003-2692-5944

Dimitrios Ziogas https://orcid.org/0000-0003-2620-4004

References

1. Donin N, Filson C, Drakaki A, *et al.* Risk of second primary malignancies among cancer survivors in the United States, 1992 through 2008. *Cancer* 2016; 122: 3075–3086.
2. Riou JP, Ariyan S, Brandow KR, *et al.* The association between melanoma, lymphoma, and other primary neoplasms. *Arch Surg* 1995; 130: 1056–1061.
3. Wu YH, Kim GH, Wagner JD, *et al.* The association between malignant melanoma and noncutaneous malignancies. *Int J Dermatol* 2006; 45: 529–534.
4. Smith A, Howell D, Patmore R, *et al.* Incidence of haematological malignancy by sub-type: a report from the haematological malignancy research network. *Br J Cancer* 2011; 105: 1684–1692.
5. Kumar V, Ailawadhi S, Bojanini L, *et al.* Trends in the risk of second primary malignancies among survivors of chronic lymphocytic leukemia. *Blood Cancer J* 2019; 9: 75.
6. Spanogle JP, Clarke CA, Aroner S, *et al.* Risk of second primary malignancies following cutaneous melanoma diagnosis: a population-based study. *J Am Acad Dermatol* 2010; 62: 757–767.
7. Brewer JD, Shanafelt TD, Call TG, *et al.* Increased incidence of malignant melanoma and other rare cutaneous cancers in the setting of chronic lymphocytic leukemia. *Int J Dermatol* 2015; 54: e287–e293.
8. Tsimberidou AM, Wen S, McLaughlin P, *et al.* Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. *J Clin Oncol* 2009; 27: 904–910.
9. Famenini S, Martires KJ, Zhou H, *et al.* Melanoma in patients with chronic lymphocytic leukemia and non-Hodgkin lymphoma. *J Am Acad Dermatol* 2015; 72: 78–84.
10. Brewer JD, Shanafelt TD, Otley CC, *et al.* Chronic lymphocytic leukemia is associated with decreased survival of patients with malignant melanoma and Merkel cell carcinoma in a SEER population-based study. *J Clin Oncol* 2012; 30: 843–849.
11. Brewer JD, Christenson LJ, Weenig RH, *et al.* Effects of chronic lymphocytic leukemia on the development and progression of malignant melanoma. *Dermatol Surg* 2010; 36: 368–376.
12. Velez NF, Karia PS, Vartanov AR, *et al.* Association of advanced leukemic stage and skin cancer tumor stage with poor skin cancer outcomes in patients with chronic lymphocytic leukemia. *JAMA Dermatol* 2014; 150: 280–287.
13. Hisada M, Biggar RJ, Greene MH, *et al.* Solid tumors after chronic lymphocytic leukemia. *Blood* 2001; 98: 1979–1981.
14. McKenna DB, Doherty VR, McLaren KM, *et al.* Malignant melanoma and lymphoproliferative malignancy: is there a shared aetiology? *Br J Dermatol* 2000; 143: 171–173.
15. Loriot Y, Chaoui D, Dorval T, *et al.* Association between lymphoma and melanoma: report of a single-center series of eight patients and a review of the literature. *Leuk Lymphoma* 2006; 47: 1023–1028.
16. McKenna DB, Stockton D, Brewster DH, *et al.* Evidence for an association between cutaneous malignant melanoma and lymphoid malignancy: a population-based retrospective cohort study in Scotland. *Br J Cancer* 2003; 88: 74–78.
17. Lam CJ, Curtis RE, Dores GM, *et al.* Risk factors for melanoma among survivors of non-Hodgkin lymphoma. *J Clin Oncol* 2015; 33: 3096–3104.
18. Jurmeister P, Bockmayr M, Treese C, *et al.* Immunohistochemical analysis of Bcl-2, nuclear S100A4, MITF and Ki67 for risk stratification of early-stage melanoma - a combined IHC score for melanoma risk stratification. *J Dtsch Dermatol Ges* 2019; 17: 800–808.
19. Kim YJ, Tsang T, Anderson GR, *et al.* Inhibition of BCL2 family members increases the efficacy of copper chelation in $BRAF^{V600E}$-driven melanoma. *Cancer Res* 2020; 80: 1387–1400.
20. Lee EF, Harris TJ, Tran S, *et al.* BCL-XL and MCL-1 are the key BCL-2 family proteins in

melanoma cell survival. *Cell Death Dis* 2019; 10: 342.

21. Li G, Tang L, Zhou X, *et al.* Chemotherapy-induced apoptosis in melanoma cells is p53 dependent. *Melanoma Res* 1998; 8: 17–23.
22. Thiem A, Hesbacher S, Kneitz H, *et al.* IFN-gamma-induced PD-L1 expression in melanoma depends on p53 expression. *J Exp Clin Cancer Res* 2019; 38: 397.
23. DeLeon TT, Almquist DR, Kipp BR, *et al.* Assessment of clinical outcomes with immune checkpoint inhibitor therapy in melanoma patients with CDKN2A and TP53 pathogenic mutations. *PLoS One* 2020; 15: e0230306.
24. Bentham G. Association between incidence of non-Hodgkin's lymphoma and solar ultraviolet radiation in England and Wales. *BMJ* 1996; 312: 1128–1131.
25. Hall P, Rosendahl I, Mattsson A, *et al.* Non-Hodgkin's lymphoma and skin malignancies–shared etiology? *Int J Cancer* 1995; 62: 519–522.
26. Adami J, Frisch M, Yuen J, *et al.* Evidence of an association between non-Hodgkin's lymphoma and skin cancer. *Br Med J* 1995; 310: 1491–1495.
27. Adami J, Grindley G, Nyren O, *et al.* Sunlight and non-Hodgkin's lymphoma: a population-based cohort study in Sweden. *Int J Cancer* 1999; 80: 641–645.
28. Farma JM, Zager JS, Barnica-Elvir V, *et al.* A collision of diseases: chronic lymphocytic leukemia discovered during lymph node biopsy for melanoma. *Ann Surg Oncol* 2013; 20: 1360–1364.
29. Velter C, Pagès C, Schneider P, *et al.* Four cases of rituximab-associated melanoma. *Melanoma Res* 2014; 24: 401–403.
30. Peuvrel L, Chiffoleau A, Quéreux G, *et al.* Melanoma and rituximab: an incidental association? *Dermatology* 2013; 226: 274–278.
31. Mercer LK, Askling J, Raaschou P, *et al.* Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers. *Ann Rheum Dis* 2017; 76: 386–391.
32. Fang D, Nguyen TK, Leishear K, *et al.* A tumorigenic subpopulation with stem cell properties in melanomas. *Cancer Res* 2005; 65: 9328–9337.
33. Bittner M, Meltzer P, Chen Y, *et al.* Molecular classification of cutaneous malignant melanoma by gene expression profiling. *Nature* 2000; 406: 536–540.
34. Pinc A, Somasundaram R, Wagner C, *et al.* Targeting CD20 in melanoma patients at high risk of disease recurrence. *Mol Ther* 2012; 20: 1056–1062.
35. Winkler JK, Schiller M, Bender C, *et al.* Rituximab as a therapeutic option for patients with advanced melanoma. *Cancer Immunol Immunother* 2018; 67: 917–924.
36. Archibald WJ, Meacham PJ, Williams AM, *et al.* Management of melanoma in patients with chronic lymphocytic leukemia. *Leuk Res* 2018; 71: 43–46.
37. ClinicalTrials.gov. Ibrutinib in treating patients with refractory metastatic cutaneous melanoma, https://www.clinicaltrials.gov/ct2/show/NCT02581930?id=NCT02581930&draw=2&rank=1&load=cart (2020, accessed 15 March 2020).
38. ClinicalTrials.gov. Pembrolizumab and ibrutinib in treating patients with stage III-IV melanoma that cannot be removed by surgery, https://www.clinicaltrials.gov/ct2/show/NCT03021460?term=ibrutinib%2C+pembrolizumab&draw=2&rank=1 (2020, accessed 8 August 2020).
39. Tiacci E, Trifonov V, Schiavoni G, *et al.* BRAF mutations in hairy-cell leukemia. *N Engl J Med* 2011; 364: 2305–2315.
40. Langabeer SE, Quinn F, O'Brien D, *et al.* Incidence of the BRAF V600E mutation in chronic lymphocytic leukaemia and prolymphocytic leukaemia. *Leuk Res* 2012; 36: 483–484.
41. Jebaraj BM, Kienle D, Bühler A, *et al.* BRAF mutations in chronic lymphocytic leukemia. *Leuk Lymphoma* 2013; 54: 1177–1182.
42. Yaktapour N, Meiss F, Mastroianni J, *et al.* BRAF inhibitor-associated ERK activation drives development of chronic lymphocytic leukemia. *J Clin Invest* 2014; 124: 5074–5084.
43. Johnstone KJ and Strutton GM. A rare pitfall in the molecular interpretation of BRAF V600E status in melanoma in the setting of BRAF V600E-mutated chronic lymphocytic leukemia/small lymphocytic lymphoma. *J Cutan Pathol* 2019; 46: 455–456.
44. El Demellawy D, Ross C, Sur M, *et al.* Synchronously diagnosed lymph nodal collision tumor of malignant melanoma and chronic lymphocytic leukemia/small lymphocytic lymphoma: case report. *Diagn Pathol* 2007; 2: 34.
45. Dueber JC and Coffin CM. Collision of chronic lymphocytic leukemia/small lymphocytic lymphoma and melanoma. *Blood* 2013; 121: 4819.

46. McClanahan F, Hanna B, Miller S, *et al*. PD-L1 checkpoint blockade prevents immune dysfunction and leukemia development in a mouse model of chronic lymphocytic leukemia. *Blood* 2015; 126: 203–211.
47. Rusak M, Eljaszewicz A, Bołkun Ł, *et al*. Prognostic significance of PD-1 expression on peripheral blood CD4+ T cells in patients with newly diagnosed chronic lymphocytic leukemia. *Pol Arch Med Wewn* 2015; 125: 553–559.
48. Ramsay AG, Clear AJ, Fatah R, *et al*. Multiple inhibitory ligands induce impaired T-cell immunologic synapse function in chronic lymphocytic leukemia that can be blocked with lenalidomide: establishing a reversible immune evasion mechanism in human cancer. *Blood* 2012; 120: 1412–1421.
49. Xerri L, Chetaille B, Serriari N, *et al*. Programmed death 1 is a marker of angioimmunoblastic T-cell lymphoma and B-cell small lymphocytic lymphoma/chronic lymphocytic leukemia. *Hum Pathol* 2008; 39: 1050–1058.
50. Brusa D, Serra S, Coscia M, *et al*. The PD-1/PD-L1 axis contributes to T-cell dysfunction in chronic lymphocytic leukemia. *Haematologica* 2013; 98: 953–963.
51. Ding W, LaPlant BR, Call TG, *et al*. Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. *Blood* 2017; 129: 3419–3427.
52. Jain N, Basu S, Thompson PA, *et al*. Nivolumab combined with ibrutinib for CLL and Richter transformation: a phase II trial. *Blood* 2016; 128: abstract 59.
53. Xu-Monette ZY, Zhou J and Young KH. PD-1 expression and clinical PD-1 blockade in B-cell lymphomas. *Blood* 2018; 131: 68–83.
54. Clinicaltrials.gov. Ibrutinib and PD-1 blockade in high risk lymphocytic leukemia, https://www.clinicaltrials.gov/ct2/show/NCT03514017?term=pd1cond=Chronic+Lymphocytic+Leukemiarank=1 2019, Accessed 20 March 2020.
55. Clinicaltrials.gov. Copanlisib and nivolumab in treating participants with Richter's transformation or transformed indolent non-hodgkin's lymphoma, https://www.clinicaltrials.gov/ct2/show/NCT03884998?term=pd1&cond=Chronic+Lymphocytic+Leukemia&rank=3 (2019, accessed 20 March 2020).
56. Motta M, Rassenti L, Shelvin BJ, *et al*. Increased expression of CD152 (CTLA-4) by normal T lymphocytes in untreated patients with B-cell chronic lymphocytic leukemia. *Leukemia* 2005; 19: 1788–1793.
57. Joshi AD, Hegde GV, Dickinson JD, *et al*. ATM, CTLA4, MNDA, and HEM1 in high versus low CD38 expressing B-cell chronic lymphocytic leukemia. *Clin Cancer Res* 2007; 13: 5295–5304.
58. Mittal AK, Chaturvedi NK, Rohlfsen RA, *et al*. Role of CTLA4 in the proliferation and survival of chronic lymphocytic leukemia. *PLoS One* 2013; 8: e70352.
59. Shanafelt TD and Call TG. Current approach to diagnosis and management of chronic lymphocytic leukemia. *Mayo Clin Proc* 2004; 79: 388–398.
60. Parikh SA. Chronic lymphocytic leukemia treatment algorithm 2018. *Blood Cancer J* 2018; 8: 93.
61. Solomon BM, Chaffee KG, Moreira J, *et al*. Risk of non-hematologic cancer in individuals with high-count monoclonal B-cell lymphocytosis. *Leukemia* 2016; 30: 331–336.
62. Mulcahy A, Mulligan SP and Shumack SP. Recommendations for skin cancer monitoring for patients with chronic lymphocytic leukemia. *Leuk Lymphoma* 2018; 59: 578–582.
63. Conte MJ, Bowen DA, Wiseman GA, *et al*. Use of positron emission tomography-computed tomography in the management of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. *Leuk Lymphoma* 2014; 55: 2079–2084.