Leukemia Research 71 (2018) 43–46

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

Management of melanoma in patients with chronic lymphocytic leukemia

William J. Archibald[a], Philip J. Meacham[b], AnnaLynn M. Williams[b], Andrea M. Baran[b], Adrienne I. Victor[b], Paul M. Barr[b], Deepak M. Sahasrahbudhe[b], Clive S. Zent[b,*]

[a] School of Medicine and Dentistry, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY, 14642, USA
[b] Wilmot Cancer Institute, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY, 14642, USA

ARTICLE INFO

Keywords:
Chronic lymphocytic leukemia
Small lymphocytic lymphoma
CLL
Melanoma
Immune checkpoint inhibitors
Pembrolizumab
PD-1 inhibitor

ABSTRACT

Melanoma is significantly more common and is associated with a poorer prognosis in patients with an underlying B-cell malignancy. This study reports on the management of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) and a subsequent diagnosis of melanoma. In the Wilmot Cancer Institute CLL cohort, which includes 470 patients followed for 2849 person-years, 18 patients (3.8%) developed 22 melanomas. Fourteen melanomas were invasive, a significantly higher rate as compared with the age and sex matched general population (standardized incidence ratio [SIR] 6.32 (95% CI 3.45; 10.60). Melanomas were most often detected (n = 15; 68.2%) through active surveillance in a dermatology clinic. Most melanomas (n = 17; 77.3%) were detected at a non-advanced stage (pathological stage grouping < III). The most common management was wide local excision without sentinel lymph node biopsy (n = 13, 59.1%). Management for the 4 (18.2%) patients with metastatic disease included the immune checkpoint inhibitor (ICI) pembrolizumab (n = 1), systemic chemotherapy with dacarbazine (n = 1), and palliative care (n = 2). The patient treated with ICI is in sustained remission of her melanoma after 23 cycles of therapy while her *TP53* disrupted CLL continues to respond to ibrutinib therapy. We conclude that patients with CLL may benefit from active surveillance for melanoma leading to early excision of locally-manageable disease. In patients with metastatic melanoma, combined treatment with targeted kinase inhibitors and ICIs can be successful and tolerable. Larger prospective studies should be considered to further evaluate these approaches.

1. Introduction

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) is the most prevalent lymphoid malignancy in the United States, with approximately 140,000 people living with the disease [1]. Immune dysfunction is an early and clinically important complication of CLL [2]. Patients with CLL are at significantly increased risk of skin cancer including melanoma, and have a ~2-fold increased risk of mortality from these second malignancies compared to patients without a preceding diagnosis of CLL [3–7]. As a result, patients with a diagnosis of CLL are often recommended to undergo routine skin cancer examinations because melanomas detected by health care providers or by a routine surveillance program have better outcomes than those who present due to symptomatic lesions [8]. In addition, for patients with metastatic melanoma, the introduction of immune checkpoint inhibitor (ICI) therapy has significantly improved outcomes. However, patients with a second malignancy were excluded from these clinical trials [9] so there is limited data on the efficacy of these treatments for metastatic melanoma in the CLL patient population. In this observational study, we investigated how melanomas were detected and managed in a single regional CLL patient population to provide data on the utility of active monitoring for melanoma and report that ICI could have a role in management of advanced disease in this population.

2. Methods

2.1. Study subjects

The Wilmot Cancer Institute (WCI) CLL cohort includes all consenting CLL and clinically detected CLL immunophenotype monoclonal B cell lymphocytosis (MBL) patients diagnosed using standard criteria [10] managed at the University of Rochester Medical Center (URMC). This is an open cohort, where participants may enter and leave at any point, and information is collected while they are managed at WCI. All 470 CLL cohort patients seen in the WCI Lymphoma/CLL clinic between 1 May 2000 and 1 September 2017 were included in this study. The

* Corresponding author.
E-mail address: clive_zent@urmc.rochester.edu (C.S. Zent).

https://doi.org/10.1016/j.leukres.2018.07.003
Received 25 May 2018; Received in revised form 5 July 2018; Accepted 5 July 2018
Available online 06 July 2018

Table 1
Demographic and clinical characteristics.

	Entire CLL cohort	No melanoma	Non-advanced melanoma[a]	Advanced melanoma[b]
Demographics				
N (%)	470	452	14 (3.0%)	4 (0.9%)
Follow up of CLL - years	4.3	4.3	2.6	7.4
(median, min, max)	(0.04, 39.1)	(0.04, 39.1)	(0.3, 22.9)	(2.0, 11.9)
Total person-years	2849.3	2732.6	89.7	27.0
Median age at CLL diagnosis (years, range, IQR)	62	61	63	68
	31–97, 15.8	31–97, 16.0	51–84, 11.0	62-76, 10.3
Median time to 1st melanoma (years, range, IQR)	NA	NA	1.8	7.4
			0.3–22.9, 8.4	2.0–11.9, 6.1
Male (n, %)	299 (63.6%)	282 (62.4%)	14 (100%)	3 (75%)
White (n, %)	451 (96.0%)	439 (97.1%)	14 (100%)	4 (100%)
FISH				
Only 13q14 deletion	153 (37.4%)	149 (37.8%)	4 (30.8%)	0 (0.0%)
No defect or trisomy 12	159 (38.9%)	152 (38.6%)	6 (46.2%)	1 (50.0%)
11q22.3 deletion	51 (12.5%)	49 (12.4%)	2 (15.4%)	0 (0.0%)
17p13 deletion	46 (11.2%)	44 (11.1%)	1 (7.7%)	1 (50.0%)
Unknown	61	58	1	2
TP53				
Mutated	17 (10.5%)	17 (10.9%)	0 (0.0%)	0 (0.0%)
Unmutated	145 (89.5%)	139 (89.1%)	6 (100.0%)	0 (0.0%)
Unknown	308	296	8	4
CD38				
Positive	124 (30.0%)	120 (30.1%)	8 (66.7%)	0 (0.0%)
Negative	289 (70.0%)	279 (69.9%)	4 (33.3%)	2 (100.0%)
Unknown	57	53	2	2
ZAP70				
Positive	177 (48.5%)	171 (48.6%)	4 (36.4%)	2 (100.0%)
Negative	188 (51.5%)	181 (51.4%)	7 (63.6%)	0 (0.0%)
Unknown	105	100	3	2
IGHV Somatic Hypermutation				
Yes	116 (55.2%)	112 (55.2%)	4 (57.1%)	0
No	94 (44.8%)	91 (44.8%)	3 (42.9%)	0
Unknown	260	249	7	4
CLL Treatment				
Never treated	212 (45.1%)	204 (45.1%)	6 (42.9%)	2 (50.0%)
1 treatment regimen	104 (22.1%)	102 (22.6%)	2 (14.3%)	0 (0.0%)
> 1 treatment regimen	154 (32.8%)	146 (32.3%)	6 (42.9%)	2 (50.0%)

NA – not applicable, IQR – interquartile range.
[a] Defined as pathological stage < III.
[b] Defined as pathological stage ≥ III.

period of observation for the detection of melanoma started on the date a diagnosis of CLL was documented at the WCI Lymphoma/CLL clinic and continued until the last documentation of medical intervention available (within the URMC medical records or records from other sites) as of 1 April 2018. This project was conducted with approval by the URMC Research Subjects Review Board with data captured using REDCap [11]. Sociodemographic and clinical data extracted from the medical record included age, race, gender, CLL characteristics, stage, previous treatments, and melanomas. Chromosomal aberrations detected by interphase fluorescent *in situ* hybridization (FISH) were classified according to the Dohner hierarchical model using the first assay done on each patient [12]. For patients on clinical trials, data were retrieved only from their medical records without using clinical trial specific information. CLL treatment data was classified as treatment-naïve or treated with one or > 1 treatment regimens.

2.2. Melanomas

We included melanomas diagnosed at URMC and at other medical centers as documented in the URMC medical records. For each incident melanoma, information was extracted on the anatomical site, date of diagnosis, staging, treatments, and response to treatment. The reason for the evaluation leading to the diagnosis of each melanoma was determined from the medical record and classified as: 1) Dermatology clinic follow up because of prior skin cancers; 2) Dermatology clinic follow up because of CLL diagnosis (irrespective of history of prior skin cancer); 3) Lymphoma/CLL clinic visit; or 4) Identification of a concerning lesion by the patient or a family member. Our institution's standard of care established in 2014 for patients with CLL is to recommend skin cancer screening at least annually by a dermatologist and to offer the opportunity to all patients with a diagnosis of CLL to be seen the same day as their CLL follow-up visits by a dermatologist embedded in the Lymphoma/CLL clinic. The clinical stage of CLL (modified Rai classification) [10] was collected at the time of diagnosis of a patient's first melanoma. Staging of melanoma used the American Joint Committee on Cancer 8th edition TNM prognostic stage groups [13]. Patients were considered to have recurrent melanoma if the disease occurred at the same anatomical site. Melanomas that did not invade beyond the epidermis were considered to be in situ (pathologic stage group 0). All melanomas with pathologic stage IA or greater were considered to be invasive. The subset with pathological stage III or greater were considered to be advanced-stage melanoma [13].

2.3. Statistical methods

We conducted an analysis to determine if the risk of detecting melanoma in our CLL-diagnosed study population was higher than the risk of detecting melanoma in an age and sex matched general