



Lenalidomide induced secondary Acute Lymphoblastic Leukemia in a Multiple Myeloma patient: A case-report

Dr. Saqib Raza Khan^{a,*}, Dr. Muhammad Tariq^b, Dr. Sidra Malik Fayyaz^c,
Salman Muhammad Soomar^a, Dr. Munira Moosajee^a

^a Department of Oncology, Aga Khan University Hospital, Karachi, Pakistan

^b Lady Reading Hospital, Peshawar, Pakistan

^c Heartlands Hospital, Birmingham, England

ARTICLE INFO

Keywords:

Lenalidomide
Secondary acute lymphoblastic leukemia
Multiple myeloma
Case report

ABSTRACT

Lenalidomide mechanism of action has been shown to modulate the different components of the immune system. A 68-year-old lady presented to us with severe backache and was then diagnosed with MM. Lenalidomide started as per protocol along with dexamethasone. Later, she presented with complaints of generalized weakness and her workup showed significant blast cells with Pan-B-cell markers consistent with secondary B-ALL. The reported incidence of secondary Acute Lymphocytic Leukemia is 2.3%. The development of more aggressive neoplasm in a patient with prior malignancy dictates a poor outcome and hence such patients should be enrolled in a clinical trial whenever available.

Abbreviations

ALL: Acute Lymphoblastic Leukemia
BMB: Bone Marrow Biopsy
CR: Complete Remission
MM: Multiple Myeloma
OS: Overall Survival
PFS: Progression Free Survival
s-ALL: Secondary Acute Lymphoblastic Leukemia
SPM: Second Primary Malignancies
vGPR: Very Good Partial Response

1. Introduction

Lenalidomide is a very active agent in hematologic malignancies. Its' mechanism of action has been shown to modulate different components of the immune system by altering cytokine production, regulating T cell co-stimulation, and augmenting the Natural Killer (NK) cell cytotoxicity [1]. Lenalidomide binds cereblon to form a complex that then targets B-cell transcription factors, Ikaros family zinc finger proteins (IKZF) 1 and 3, for proteasome degradation and loss of which is thought to play an important role in lenalidomide's therapeutic effect [2]. It was first approved for the treatment of MM and now is the standard of care in the

first line in combination with proteasome inhibitors and steroids. Lenalidomide is also the preferred agent for maintenance therapy in standard-risk MM. In a randomized trial, lenalidomide maintenance until progression was associated with better progression-free survival compared to no maintenance in patients with MM [3]. Therapy-related malignancies are a sub-group of secondary malignancies during which exposure to prior chemotherapy or radiotherapy is a key factor in the pathogenesis of secondary cancer. The reported incidence of secondary Acute Lymphocytic Leukemia (s-ALL) who previously had primary malignancy is 2.3% with a high prevalence of pre-B-cell immunophenotype, however, a study on s-ALL, multiple myeloma was not observed to be primary malignancy [4]. Secondary malignancies are a known albeit rare complication of long-term lenalidomide therapy. However, the incidence of s-ALL because of lenalidomide is very low. We report a case of a patient with IgG Kappa multiple myeloma who developed pre-B cell ALL during maintenance therapy with lenalidomide.

2. Case presentaion

A 68-Year-old woman, known case of hypertension, chemistry professor by profession, widowed, mother of three children, resident of Karachi, Pakistan, presented to our institution in the fall of 2009 with a one-month history of generalized weakness and severe backache. She

* Corresponding author.

E-mail address: saqib.raza31@yahoo.com (Dr.S.R. Khan).

<https://doi.org/10.1016/j.lrr.2022.100315>

Received 20 December 2021; Received in revised form 9 March 2022; Accepted 11 April 2022

Available online 13 April 2022

2213-0489/© 2022 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

had no other symptoms. Complementary examinations and laboratory investigations were performed. Her physical examination was completely normal. An x-ray lumbosacral spine showed compression collapse of the L2 vertebral body. A routine complete blood count at the time of presentation showed hemoglobin of 10.4 g/dL, normal white blood cell count, and platelets of 159,000/ μ L. The erythrocyte sedimentation rate (ESR) was elevated to 62 mm/h (normal <20 mm/h). The blood urea increased to 8.1 mmol/L (normal <7.1 mmol/L) and creatinine increased to 140 μ mol/L (normal <133 μ mol/L). The results of a random blood glucose test, liver function, electrolytes, and lipid profile were all normal. Serum protein electrophoresis revealed a raised serum kappa paraprotein band with IgG levels of 36.3 g/l (Normal 6.29-13.5 g/l). Bence-Jones proteins in the urine were negative. Her beta 2 microglobulin was raised (2516.00 ng/ml). A bone marrow biopsy (BMB) was performed which showed 41% pleomorphic plasma cells. These findings were consistent with the diagnosis of MM; ISS-III as per International staging system (ISS) of multiple myeloma. Her bone marrow cytogenetics was normal (46XX). Fish analysis for high-risk features was not sent. Her skeletal survey showed innumerable small punched-out lytic lesions with diffuse involvement of the skeleton. (Fig. 1)

She was started on lenalidomide at a dose of 25 mg daily for 21 days, followed by 7 days off, for a 28-day cycle with dexamethasone was given at a dose of 40 mg weekly and pamidronate 90 mg IV monthly. She also received aspirin for thromboembolic prophylaxis. The patient achieved a very good partial response (VGPR). She was then switched to maintenance lenalidomide 10 mg/day. She then achieved a complete hematologic response (CR) with complete disappearance of the monoclonal protein in the serum with 4% plasma cells in bone marrow aspirates in 17 months from diagnosis. Autologous stem cell transplant (ASCT) was offered but refused by the patient. She was kept on surveillance for 22 months and followed from time to time in the clinics via clinical examination and lab investigating with SPEP and IgG levels. She developed disease progression, evident when she presented with increased lethargy and fatigue. Furthermore, investigations revealed raised kappa protein band with an increased appearance of IgG levels and BMB confirmed the reappearance of a significant no of plasma cells. She was then re-started on lenalidomide with a dose of 10 mg daily for 21 days followed by 7 days off, for a 28-day total cycle along with dexamethasone 40 mg weekly. She again achieved a CR with less than 4% plasma cells in bone marrow aspirate in 12 months. She continued taking lenalidomide from 2014 till 2020.

She then presented in June 2020 with complaints of generalized weakness and loss of appetite for two months. General physical examination showed pallor skin and bilateral pedal edema. Her systemic examination was unremarkable. Her complete blood count showed

hemoglobin of 7.8 g/dl, white blood cell counts $34.5 \times 10^9/L$, platelets $30 \times 10^9/L$, and 79% blast cells (Fig. 2). Bone marrow biopsy was performed which showed hyper-cellular specimens exhibiting diffuse infiltration with blast cells that constitute around 85% of the total nucleated non-erythroid cell population (Fig. 3a,b). Immunophenotyping by flow cytometry showed blast cells reactivity with Pan-B-cell markers i.e., CD19 and cCD79a along with HLA-DR, CD45, CD34, and Tdt. (Fig. 4). Overall findings were consistent with secondary B-cell acute lymphoblastic leukemia (B-ALL). Limited cytogenetic panel was performed. Translocation of (8;14) (q24; q32), T-P53 as well as deletion of 11q23 was not detected. Philadelphia chromosome (Ph.) was checked which was also negative. Her serum protein electrophoresis and immunofixation showed no evidence of monoclonal gammopathy.

After negative COVID testing, she was admitted and commenced on modified Hyper-CVAD protocol with, Dexamethasone 40 mg per oral daily on days 1 through 4 and 11 through 14, Vincristine 1mg/m²-on day 4 and 11, Doxorubicin 25mg/m²-on day 4. On day 8 of chemotherapy, she developed worsening shortness of breath and fever. Chest X-Ray showed bilateral infiltrates. Extensive workup including all the viral markers, pan-cultures, fungal markers including BDG and Galactomannan were performed and they came out to be negative. COVID PCR was repeated, and which was driven out to be positive. The patient rapidly developed respiratory failure and eventually succumbed to the complications of coronavirus disease 5 days from diagnosis.

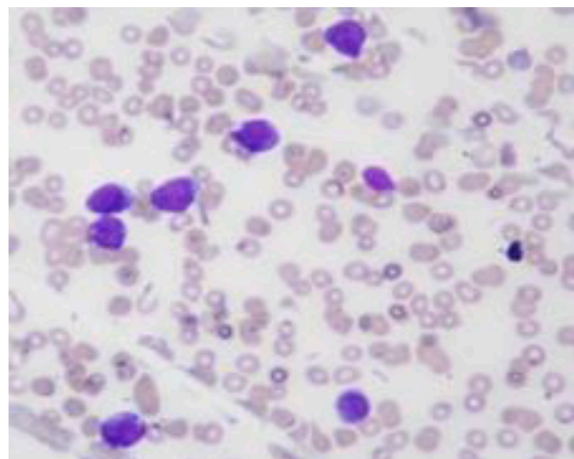


Fig. 2. Peripheral blood film showing presence of significant number of atypical lymphoid/blast cells.



Fig. 1. a,b: Skeletal survey shows innumerable small punched out lytic lesions involving skull pelvic bones diffusely, lumbosacral spine, mandible, distal left femur.

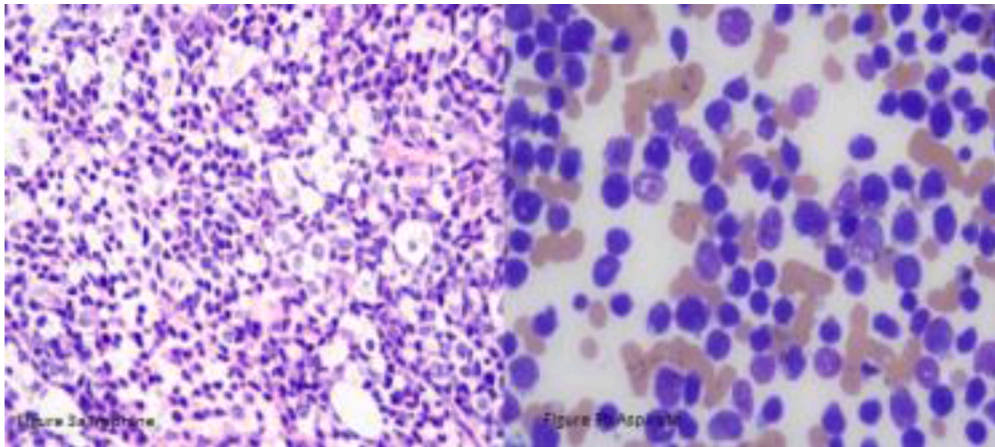


Fig. 3. a,b: Hyper-cellular specimen exhibiting diffuse infiltration with blast cells that constitute around 85% of the total nucleated non-erythroid cell population. These blast cells are small to medium in size having high nuclear to cytoplasmic ratio, scanty agranular cytoplasm with vacuolations, open chromatin and prominent nucleoli. Normal hematopoiesis is suppressed.

3. Discussion

There is a remarkable advancement in the development of treatment modalities and surveillance techniques of cancer which has resulted in marked improvement in cancer survival. Hence second primary malignancies are becoming an increasingly common problem for both clinicians and survivors. Multiple myeloma is a classic example. MM was thought to be a fatal disease with a short life expectancy. However, introduction of the various novel agents such as primary immunomodulatory agents as well as the proteasomal inhibitors and more recently monoclonal antibodies, the clinical course of MM can be altered to behave as a chronic disease with eventual remissions and relapses requiring multiple lines of treatment, therefore, increasing the risk for the development of secondary malignancies in MM survivors [5]. Triplet combinations with proteasome inhibitors, immunomodulators, and dexamethasone are currently the standard of care in MM. Long-term follow-up of len-Dex combination treatment with Bortezomib showed sustained survival benefits [6]. Maintenance therapy in MM has been considered to be a key component for at least a decade. Updated results of the Myeloma XI trial continued to show a highly statistically significant improvement in PFS with lenalidomide maintenance with a hazard ratio of 0.45 [7]. There are very rare documented cases of s-ALL after lenalidomide maintenance in MM. The impact of the long-term use of lenalidomide on the kinetics of minimal residual disease (MRD) has also been evaluated. A retrospective analysis of 139 patients who received lenalidomide maintenance and whose levels of MRD were measured during the treatment period by next-generation-sequencing (NGS) or flow cytometry maintenance lenalidomide correlated with an increased depth of the disease response. Maximum response was achieved in 38.1% of the patients during maintenance. In addition, 34% of patients who were MRD positive after induction therapy became MRD negative with lenalidomide maintenance therapy leading to their improvement in PFS [8]. The use of NGS in patients with secondary malignancies may highlight crucial steps in their management. We have not performed NGS study for our patient because of its unavailability in our institute. NGS study that can identify genomic markers such as IKZF1, TP53, CDKN2A, RB1, PAX5, DNMT3A, RUNX1, AXL1 may help to elaborate personalized therapy in certain patients with aggressive neoplasms [9].

The landmark trial of long-term maintenance lenalidomide after stem cell transplantation reported a statistically significant increase in the incidence of second primary malignancies (SPM) of 3.1 vs 1.2 per 100 patient-years [10]. In transplant-ineligible patients, the addition of lenalidomide to melphalan and prednisone (MP-R) demonstrated the incidence of SPM of 7% vs. 3% in the MP alone [11]. Palumbo et al reported in a meta-analysis of newly diagnosed MM patients that the

cumulative incidence of all second primary malignancies (SPM) at 5 years in patients treated with lenalidomide containing regimen was 6.9% compared with 3.8% in patients who were treated without lenalidomide [12]. Analysis of the Myeloma XI trial revealed that solid malignancies are the most common SPM diagnosed. Secondary hematological malignancies are rare with acute myeloid leukemia (AML) and myelodysplastic syndrome being the most common reported [13]. Therefore, it can be concluded the risk of SPM is a very small, albeit a well-described complication of long-term lenalidomide therapy. Literature does report this unique feature of lenalidomide associated with the development of s-ALL [14–16]. Germans Sharon Koorse et al., reported two cases of lenalidomide associated with s-ALL in patients who previously had multiple myeloma and underwent ASCT and later on developed s-ALL while on maintenance lenalidomide, however because of the rarity and unique features of lenalidomide induced s-ALL in MM patients, the clinicopathological features of this disease remains poorly understood [17].

The incidence of therapy-related to secondary acute lymphocytic leukemia (s-ALL) is very low. Studies have reported the incidence between 1.9%-9% of all patients with hematological SPM [18]. Clinically t-ALL appears to be more common in the older age group with a median latency to the diagnosis of approximately 6.8 years. When compared to de novo ALL, t-ALL is found to have a higher incidence of complex karyotype, MLL gene rearrangement, and monosomy of 5 and 7.

Studies have shown frequent detection of chromosome 11q23 abnormalities in therapy related-secondary ALL, which is the most common cytogenetic alteration found in s-ALL. Cases of s-ALL without chromosome 11q23 have rarely been described. Our patient developed s-ALL with no detection of chromosome 11q23 abnormality which is also unique to this case. A study on s-ALL showed that the median time from primary malignancy to the development of s-ALL was 67 months, however, our patient developed s-ALL approximately 11 years later after her primary malignancy hence, we still have limited data available to define the optimal duration for the development of s-ALL after primary malignancy [19]. Antecedent diagnosis of a hematological malignancy is seen in 1/3rd of the patients with myeloma present in 12% of these cases. Interestingly, there does not appear to be any difference in the frequency of B or T cell phenotype [20].

Several trials have evaluated different treatment protocols for ALL. Combination chemotherapy is the primary treatment modality for patients with ALL, to rapidly restore bone marrow function and attain a complete remission (CR). More than 80 % of newly diagnosed adults with ALL enter CR with such intensive chemotherapy regimens. In a retrospective analysis of over 1000 ALL, the CR rates of s-ALL were comparable to de novo ALL. In addition, patients who went on to receive

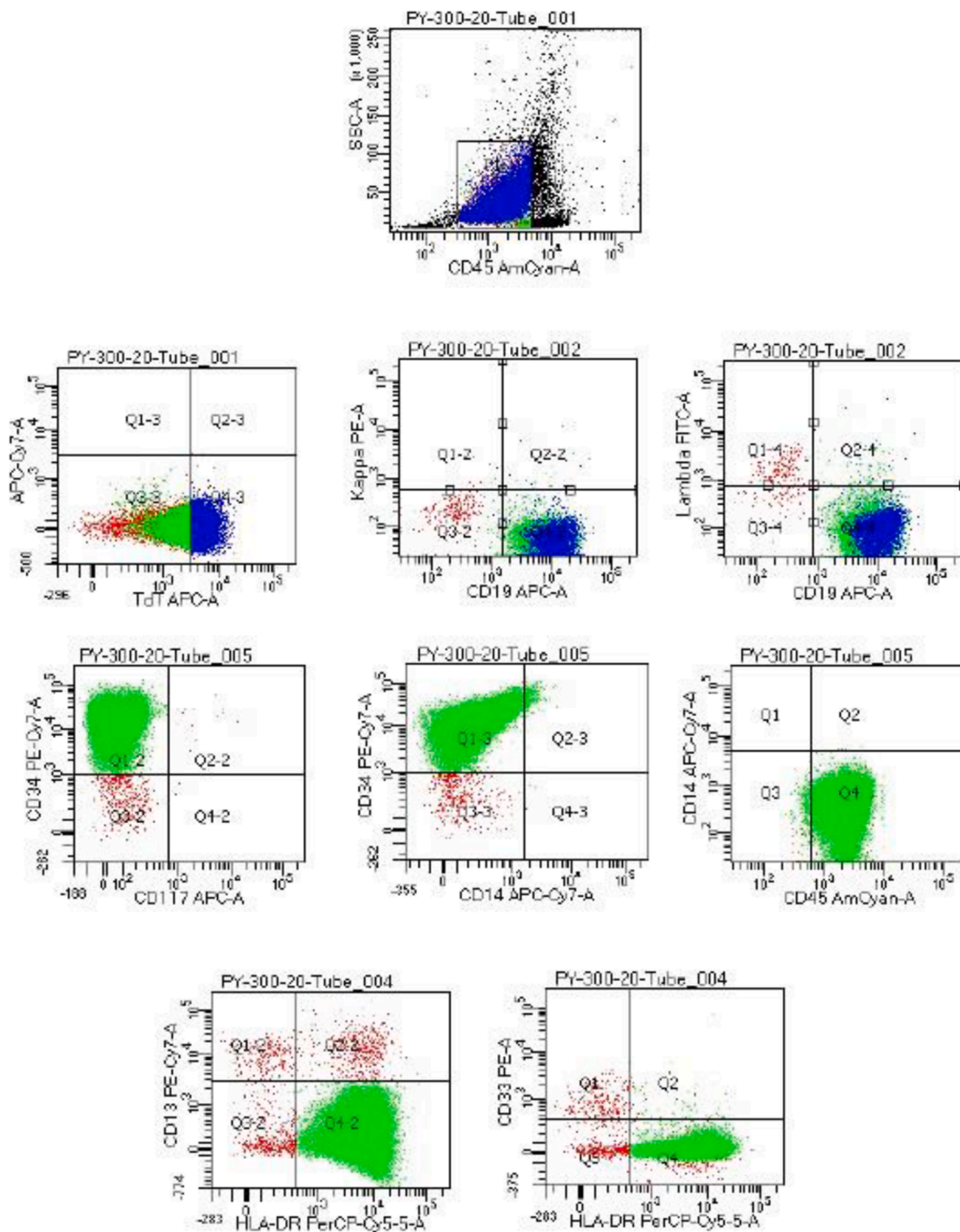


Fig. 4. Flow Cytometer, CD45 staining was performed and gating was done on dim CD45 positive blast (85%)cells population. This population shows reactivity with Pan-B-cell markers i.e. CD19 and cCD79a along with HLA-DR and CD45. This population also shows positivity to CD34 and Tdt

an allogeneic stem cell transplant in CR1 were found to have similar PFS and OS when compared to de novo ALL patients [21]. These results are in contrast to another retrospective analysis of 92 patients reporting a dismal outcome regardless of treatment modality especially in patients > 60 years [22]. Nonetheless, allogeneic stem cell transplantation appears to be the only curative option with a leukemia-free survival and overall survival of 47% and 51% [23].

Here we report a patient, who was on maintenance lenalidomide for a very long period for MM and then developed s-ALL 11 years after her diagnosis.

4. Conclusion

MM patients who are on maintenance treatment should be carefully followed with bone marrow examination, peripheral blood film review, flow cytology, and gene tests. The development of more aggressive neoplasm in a patient with prior malignancy dictates a poor outcome and required further assessment; hence such patients should be enrolled in clinical trials whenever available in order to understand them profoundly.

Declaration

Ethical Approval

Ethical Approval was taken from the Ethical Review Committee (ERC), Aga Khan University (AKU), Karachi Pakistan prior to the data collection [ERC Ref # 2020-3343-8894]. Informed written consent was taken from the participant prior to the data collection. Data collection process and methods followed ethical guidelines and participant's privacy, anonymity and confidentiality were maintained at every stage.

Availability of data and materials

Data and materials are available to the corresponding author, which can be shared at a reasonable request.

Funding

Not Applicable

Consent

Informed consent has been taken already when the patient was diagnosed with secondary malignancy (S-ALL). Can be shared on special requests.

CRedit authorship contribution statement

Dr. Saqib Raza Khan: Conceptualization, Writing – original draft. **Dr. Muhammad Tariq:** Data curation, Investigation. **Dr. Sidra Malik Fayyaz:** Data curation, Writing – review & editing. **Salman Muhammad Soomar:** Data curation, Writing – review & editing. **Dr. Munira Moosajee:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare no competing interest

Acknowledgements

We would like to acknowledge and thank Department. of Oncology, Aga Khan University Hospital for their logistic support and Department of Health Management and Information Systems (HIMS), Aga Khan University Hospital for their support in data processing.

References

- [1] V Kotla, S Goel, S Nischal, C Heuck, K Vivek, B Das, et al., Mechanism of action of lenalidomide in hematological malignancies, *Journal of hematology & oncology* 2 (1) (2009) 1–10.
- [2] G Lu, RE Middleton, H Sun, M Naniong, CJ Ott, CS Mitsiades, et al., The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins, *Science* 343 (6168) (2014) 305–309.
- [3] A Palumbo, R Hajek, M Delforge, M Kropff, MT Petrucci, J Catalano, et al., Continuous lenalidomide treatment for newly diagnosed multiple myeloma, *New England Journal of Medicine* 366 (19) (2012) 1759–1769.
- [4] L Pagano, A Pulsoni, ME Tosti, L Annino, A Mele, A Camera, et al., Acute lymphoblastic leukaemia occurring as second malignancy: report of the GIMEMA archive of adult acute leukaemia, *British journal of haematology* 106 (4) (1999) 1037–1040.
- [5] J Yang, HR Terebelo, JA. Zonder, Secondary primary malignancies in multiple myeloma: an old NEMESIS revisited, *Advances in hematology* 2012 (2012).
- [6] BG Durie, A Hoering, R Sexton, MH Abidi, J Epstein, SV Rajkumar, et al., Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT), *Blood cancer journal* 10 (5) (2020) 1–11.
- [7] GH Jackson, FE Davies, C Pawlyn, DA Cairns, A Striha, C Collett, et al., Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial, *The Lancet Oncology* 20 (1) (2019) 57–73.
- [8] R Alonso, M-T Cedena, S Wong, N Shah, R Ríos-Tamayo, JM Moraleda, et al., Prolonged lenalidomide maintenance therapy improves the depth of response in multiple myeloma, *Blood Advances* 4 (10) (2020) 2163–2171.
- [9] Raphael Szalat, Munshi Nikhil, Next-Generation Sequencing Informing Therapeutic Decisions and Personalized Approaches, *American Society of Clinical Oncology Educational Book* 36 (2016) e442–e448.
- [10] M Attal, V Lauwers-Cances, G Marit, D Caillot, P Moreau, T Facon, et al., Lenalidomide maintenance after stem-cell transplantation for multiple myeloma, *New England Journal of Medicine* 366 (19) (2012) 1782–1791.
- [11] A Palumbo, S Bringhen, SK Kumar, G Lupparelli, S Usmani, A Waage, et al., Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data, *The lancet oncology* 15 (3) (2014) 333–342.
- [12] MA Dimopoulos, PG Richardson, N Brandenburg, Z Yu, DM Weber, R Niesvizky, et al., A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide, *Blood, The Journal of the American Society of Hematology*. 119 (12) (2012) 2764–2767.
- [13] J Jones, D Cairns, W Gregory, C Collett, C Pawlyn, R Sigsworth, et al., Second malignancies in the context of lenalidomide treatment: an analysis of 2732 myeloma patients enrolled to the Myeloma XI trial, *Blood cancer journal* 6 (12) (2016) e506. -e.
- [14] M Tan, R Fong, M Lo, R. Young, Lenalidomide and secondary acute lymphoblastic leukemia: a case series, *Hematol Oncol* 35 (1) (2017) 130–134.
- [15] RB Sinit, DG Hwang, P Vishnu, JF Peterson, DM. Aboulafia, B-cell acute lymphoblastic leukemia in an elderly man with plasma cell myeloma and long-term exposure to thalidomide and lenalidomide: a case report and literature review, *BMC Cancer* 19 (1) (2019) 1147.
- [16] N Sharma, H Hassoun, J Hatem, P. Kouides, Cardiac ALL: most unusual occurrence of lenalidomide-associated acute lymphoblastic leukemia with subsequent cardiac involvement, *Cureus* 11 (10) (2019).
- [17] SK Germans, O Kulak, P Koduru, D Oliver, J Gagan, P Patel, et al., Lenalidomide-Associated Secondary B-Lymphoblastic Leukemia/Lymphoma—A Unique Entity: A Report of Two Cases With Low-Level Bone Marrow Involvement and Review of the Literature, *American Journal of Clinical Pathology* 154 (6) (2020) 816–827.
- [18] J-M. Ribera, Therapy-related acute lymphoblastic leukemia, *haematologica* 103 (10) (2018) 1581.
- [19] AS Rosenberg, A Brunson, JK Paulus, J Tuscano, T Wun, THM Keegan, et al., Secondary acute lymphoblastic leukemia is a distinct clinical entity with prognostic significance, *Blood Cancer Journal* 7 (9) (2017) e605. -e.
- [20] D. Kazandjian, Multiple myeloma epidemiology and survival: A unique malignancy, *Semin Oncol* 43 (6) (2016) 676–681.
- [21] I Aldoss, T Stiller, N-C Tsai, JY Song, T Cao, NA Bandara, et al., Therapy-related acute lymphoblastic leukemia has distinct clinical and cytogenetic features compared to de novo acute lymphoblastic leukemia, but outcomes are comparable in transplanted patients, *Haematologica* 103 (10) (2018) 1662.
- [22] R Shivakumar, W Tan, G Wilding, E Wang, M. Wetzler, Biologic features and treatment outcome of secondary acute lymphoblastic leukemia—a review of 101 cases, *Annals of oncology* 19 (9) (2008) 1634–1638.
- [23] C Saygin, A Kishtagari, RD Cassaday, N Reizine, I Yurkiewicz, M Liedtke, et al., Therapy-related acute lymphoblastic leukemia is a distinct entity with adverse genetic features and clinical outcomes, *Blood advances* 3 (24) (2019) 4228–4237.