Sustained MRD negative remission in del17p and TP53 mutated B cell prolymphocytic leukemia with ibrutinib and venetoclax

Maria Tariq Siddiqui *, Allyson Price, Alessandra Ferrajoli, Gautam Borthakur

The Department of Leukemia, MD Anderson Cancer Center, Houston, TX, United States

ARTICLE INFO

Keywords:
B cell prolymphocytic leukemia
Ibrutinib
Venetoclax
Deletion 17p
TP53

ABSTRACT

B cell prolymphocytic leukemia is a rare and aggressive disorder often with high risk features including TP53 mutation, deletion 17p and complex karyotype. There is scarcity of data regarding treatment and existing therapies induce short lived remissions. Ibrutinib, a Bruton tyrosine kinase inhibitor, has had success in some patients with high risk features. Venetoclax, a BCL-2 inhibitor, has primarily been used in the relapsed setting. We present a case of B PLL with deletion 17p and mutated TP53 treated with ibrutinib and venetoclax in the frontline setting which resulted in measurable/minimal residual disease negative remission for approximately three years.

1. Introduction

B cell prolymphocytic leukemia (B PLL) represents < 1% of all B cell leukemias and is characterized with an aggressive clinical course [1]. TP53 status remains critical in therapy consideration as a mutation and/or deletion 17p (del17p) is expected to confer resistance to chemotherapy necessitating search for alternate options. There is scarce published evidence, mostly from case reports and series, and no formal treatment guidelines exist. Alemtuzumab [2], idelalisib/rituximab [3] have been employed with varying success. Rationale for Bruton Tyrosine Kinase inhibitor (BTKi) use was extrapolated from outcomes in TP53 mutated chronic lymphocytic leukemia (CLL). Venetoclax, a BCL-2 protein inhibitor, use has been suggested in relapsed/refractory setting [1,4]. We share our experience of treatment with ibrutinib in combination with BCL-2 inhibitor venetoclax in the frontline setting in del17p and TP53 mutated B PLL leading to minimal residual disease negative durable complete remission.

2. Case report

A 68-year-old female presented to an outside hospital with left upper quadrant pain of 3 months’ duration and imaging confirmed splenomegaly. Peripheral blood leukocytosis prompted a bone marrow aspiration/biopsy, and a diagnosis of CLL/SLL was made at which point she presented to our institution. She reported decreased appetite, low-grade fevers, night sweats and unintentional weight loss of 15 – 20 pounds. Physical exam revealed massive splenomegaly (25 cm) but no palpable lymphadenopathy. Labs showed an elevated white blood cell (WBC) count of 116.3 K/uL with 60% prolymphocytes, hemoglobin of 8.7 gm/dL, MCV 86fL and platelet count of 101 K/uL. Peripheral blood smear showed absolute lymphocytosis with predominantly intermediate to large cells with round nucleus, moderately condensed chromatin, prominent central nucleolus representing prolymphocytes. A bone marrow biopsy (BM) showed B cell prolymphocytic leukemia representing 75% of the marrow cells. By flow cytometry cells were positive for CD5, CD11c partial, CD19, CD20, CD22, CD79b, CD200 partial, FMC-7 and monoclonal lambda light chain restricted B cell population. The cells stained negative for cyclin D1 and ZAP 70. Cyto-genetics revealed complex karyotype, with Florescence in situ Hybridization (FISH) showing 17p deletion and gain of MYC gene. Molecular studies unmutated IGHV and later a TP53 mutation. Positron Emission Tomography (PET) scan done showed splenomegaly (19.2 × 8.9 × 27.3 cm) and small bilateral mildly hypermetabolic axillary, retroperitoneal and inguinal lymph nodes. A diagnosis of B PLL was made and ibrutinib 420 mg daily was started. At two months follow up, her WBC count and spleen size decreased dramatically. At six and ten months of treatment, her counts continued to improve; BM performed showed persistent disease (80% and 60% of marrow cellularity) and marked resolution of splenomegaly and lymphadenopathy by PET scan. At thirteen months follow up patient was noted to have an increased WBC count of 20.8 K/uL (absolute lymphocyte count 16.02 K/uL) on routine labs. BM showed persistent disease (50% of marrow cellularity) and monthly rituximab was added to her regimen for 3 months with resolution of leukocytosis. After

* Corresponding author.

https://doi.org/10.1016/j.lrr.2021.100266

Received 10 April 2021; Received in revised form 10 August 2021; Accepted 27 August 2021
Available online 30 August 2021

2213-0489/© 2021 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/).
rituximab completion, venetoclax was then added and the dose ramped up to 400 mg without any tumor lysis.

At twenty months follow up, she was in complete remission (CR) with minimal residual disease (MRD) negativity by flow cytometry, clearance of TP53 mutation with absence of del17p on FISH. Her dose of ibrutinib was decreased to 280 mg daily as the patient reported myalgias and arthralgias. At 38 months follow up treatment her venetoclax dose was decreased to 200 mg day because of thrombocytopenia. Four and a half years after beginning treatment with ibrutinib and three years after venetoclax initiation, patient continues to be in MRD negative CR (Table I).

### Table 1
Treatment course.

| Time point, months | WBC count, (4.0–11.0 × 10^9/L), | Absolute lymphocyte count, (1.00–4.80 × 10^9/L) | FISH | Bone Marrow mutation | Treatment | Flow cytometric (FC) immunophenotyping bone marrow | Measurable residual disease (MRD) by FC in bone marrow |
|-------------------|-------------------------------|-----------------------------------------------|------|-----------------------|-----------|-----------------------------------------------|-----------------------------------------------|
| Baseline          | 116                           | 104.63                                        | Increased copy of the MYC gene, Del TP53, unmutated IGHV |                  | Ibrutinib 420 mg started | 74% aberrant B-cells | – |
| 6                 | 23.8                          | 21.42                                         | Del TP53 | TP53 | Ibrutinib 420 mg started | 64.75% aberrant cells | – |
| 10                | 12.2                          | 9.04                                          | Del TP53 | TP53 | Ibrutinib 420 mg started | 52.3% aberrant cells | – |
| 13                | 20.8                          | 16.02                                         | Del TP53 | TP53 | Ibrutinib 420 mg started | 45.1% aberrant cells | – |
| 20                | 2.7                           | 1.16                                          | Negative | No mutation | Venetoclax 400mg | – | MRD negative |
| 30                | 4.7                           | –                                             | Negative | No mutation | Ibrutinib 280 mg started | – | MRD negative |
| 42                | 3.5                           | –                                             | Negative | No mutation | Venetoclax 200mg | – | MRD negative |
| 55                | 4.1                           | –                                             | Negative | No mutation | Ibrutinib 280 mg started | – | MRD negative |

3. Discussion

B cell prolymphocytic leukemia, formerly considered as a variant of CLL, was recognized as a distinct entity by the World Health Organization in 2008 [5]. The average age at diagnosis is 69 years with the highest incidence in Caucasians with an equal male to female ratio [5]. Patients usually present with splenomegaly, B symptoms like fever, night sweats and weight loss and elevated lymphocyte count with concurrent cytopenias [6]. A small proportion of patients can have an indolent disease course lasting for several months to years [7].

B PLL diagnosis requires careful integration of morphological, immunophenotypic, cytogenetic and molecular data since significant overlap exists with CLL with B-PLL, mantle cell lymphoma in leukemic phase, splenic marginal zone lymphoma and hairy cell leukemia. Diagnosis is made with > 55% prolymphocytes in peripheral blood. Morphologically cells are medium sized (roughly twice the size of CLL cells) with no projections or villi, have prominent central nucleoli surrounded by condensed chromatin. By immunophenotyping B PLL cells express surface IgM and/or IgD (bright) together with other B cell antigens (CD11c, CD19, CD22, CD24, CD79a, CD 79b and FMC7). Bright expression of surface immunoglobulins and CD 20 differentiates it from CLL. CD 5 and CD 23 presence may indicate mantle cell lymphoma in leukemic phase and t(11;14) and cyclin D1 testing should be undertaken. CD 25, CD103, CD125 present in hairy cell leukemia are absent in B PLL [1,8].

B PLL lacks a distinct cytogenetic signature likely due to scarcity of data. Markers such as ZAP 70, CD38 and IGHV gene rearrangement that are prognostic in CLL do not appear to be of significance in B PLL, though this remains to be determined in larger studies [7,9,10]. MYC aberrations and complex karyotype have been associated with aggressive disease course [11,12]. In a recent study by Chapleo et al. characterizing genomic makeup in thirty-four B-PLL patients, MYC abnormalities (76%) [translocation (62%) or gain (15%)] were the most common aberration (these abnormalities interestingly were mutually exclusive), followed by 17p deletion (38%). Complex karyotype was seen in 75% patients and a highly complex karyotype in 45% patients. Other chromosomal abnormalities included trisomies 3, 12 and 18, del 13q and del 8p. High frequency mutations included TP53, BCL2 and MYD88 [pre-exist exclusively in patient with t(MYC)], MYD88 and MYC genes. Further analysis showed having both MYC aberrations and del17p conferred the worst prognosis with an overall median survival of < 1 year. This data offers insight into leukemogenesis, signifies prognostic implications and potential therapeutic considerations in a disease with limited options [13].

CLL treatment algorithms are used for B PLL treatment given sporadic data. To date, the largest clinical trial of B PLL contained 14 patients who were treated with pentostatin [14]. As mentioned earlier, historically TP53 abnormalities have determined treatment (this might change given the recent evidence of MYC aberrations). In patients lacking TP53 abnormalities chemo-immunotherapy is used [15,16]. In patients with mutated and/or deletion of TP53 alemtuzumab and ide-cel/rituximab had short responses or significant toxicities [2,3,7]. Data for BTKi use has been gathered from case. Coelho et al. reported in which ibrutinib was used after idecilisib-rituximab with success and the patient underwent allo-HSCT [18]. Gordon et al. reported two cases of patients treated with ibrutinib after rituximab with both achieving CR for more than 12 months [19]. Bindra et al. and Oka et al. used ibrutinib as frontline therapy in del17p B PLL for a CR for 10 months [20] and 12 months [21]. It should be noted that in the latter, low dose ibrutinib was used.

Our patient was treated with ibrutinib monotherapy with persistent disease course and subsequent addition of venetoclax that led to molecular, flow cytometric and cytogenetic remission. She did not experience leukocytosis after administration of ibrutinib therapy as commonly observed in CLL. With both MYC and TP53 abnormalities she fell in the highest risk group according to Chapleo et al. but treatment with ibrutinib and venetoclax has led to a sustained response of almost 3 years, allowing deferment of HSCT considered as the only curative option. As reported by Jain et al. in a phase II trial this regimen showed sustained responses in high risk and older patients with CLL [22]. This deserves further investigation as this regimen may lead to a deeper remission in a disease with historically poor outcomes and provide a chemotherapy-free option. With high frequency of MYC abnormalities, menin inhibitors could also provide another option in future as MENIN interacts with TAD domain of MYC and enhances MYC mediated transcription.
3

4. Conclusion

Optimal treatment for B PLL requires large prospective clinical trials but the rarity of the disease precludes this. The use of ibrutinib as monotherapy with sequential addition of venetoclax deserves to be considered in patients other than in relapsed/refractory setting in B PLL and TP53 abnormalities as it can lead to a deeper remission than with conventional strategies.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Maria Tariq Siddiqui: Writing - original draft, Writing - review & editing. Allyson Price: Writing - original draft, Writing - review & editing. Alessandra Ferrajoli: Writing - original draft, Writing - review & editing. Gautam Borthakur: Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors have no conflict of interest

Acknowledgements

None

References

[1] M. Cross, C. Dearden, B and T cell prolymphocytic leukaemia, Best Pract. Res. Clin. Haematol. 32 (2019) 217–228, https://doi.org/10.1016/j.beha.2019.06.001.

[2] B.T. Chaz, P.J. Petrasku, Complete response to alemtuzumab in a patient with B prolymphocytic leukaemia [7], Am. J. Hematol. 82 (2007) 417, https://doi.org/10.1002/ajh.20843.

[3] T.A. Eyre, C.P. Fox, A. Boden, A. Bloor, M. Durgavatessa, P. Shankara, R. Weng, A.H. Schub, Ibrutinib-rituximab induces durable remissions in TP53 disrupted B-PLL, but results in significant toxicity: updated results of the UK-wide compassionate use programme, Br. J. Haematol. 184 (2019) 667–671, https://doi.org/10.1111/bjh.15802.

[4] T.A. Eyre, A.A. Kirkwood, S. Gohill, G. Follows, R. Walewska, H. Walter, M. Cross, T.A. Eyre, A.A. Kirkwood, S. Gohill, G. Follows, R. Walewska, H. Walter, M. Cross, J. Swerdlow, S.H.; Campo, E.; Harris, N.L.; Jaffe, E.S.; Pileri, S.A.; Stein, H.; Thiele, J.; Vardiman, WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th ed., 2008.

[5] M. Cross, C. Dearden, B and T cell prolymphocytic leukaemia, Best Pract. Res. Clin. Haematol. 32 (2019) 217–228, https://doi.org/10.1016/j.beha.2019.06.001.

[6] S.L. McCune, J.P. Gockerman, J.O. Moore, C.M. DeCastro, A.J. Bass, N.J. Chao, G. DiNardo, P. Bose, M. Ohanian, N. Pemmaraju, E. Jabbour, K. Sasaki, R. Kanagal-Sha, H. Coelho, M. Badior, T. Melo, Sequential kinase inhibition (idelalisib/ibrutinib) for a patient with B cell prolymphocytic leukemia [7], Am. J. Hematol. 82 (2007) 417, https://doi.org/10.1016/j.ajh.2019.02.01597.

[7] L. Shvidel, M. Shtalrid, L. Bassous, A. Klefish, E. Vorst, A. Berrebiz, B-Cell prolymphocytic leukemia: a survey of 35 patients emphasizing heterogeneity, prognostic factors and evidence for a group with an indolent course, Leuk. Lymphoma. 33 (1999) 169–179, https://doi.org/10.3109/104281999090013739.

[8] C. Dearden, How I treat prolymphocytic leukemia, Blood 120 (2012) 538–551, https://doi.org/10.1182/blood-2012-01-380139.