Therapy-related B-lymphoblastic leukemia after multiple myeloma

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ABSTRACT

New therapies for multiple myeloma have improved outcomes, but are associated with therapy-related hematologic malignancies. We report eight patients with therapy-related B-lymphoblastic leukemias (t-B-ALL) in the setting of therapy for multiple myeloma, which included lenalidomide maintenance. A subset of patients had pancytopenia and low-level marrow involvement by acute leukemia, an unusual finding in de novo B-ALL. One patient died of chemotherapy complications; the other seven responded. No patient died of B-ALL (median follow up of 1.0 years). Our series suggests that t-B-ALL is clonally unrelated to myeloma, presents with diverse cytogenetic abnormalities, and responds well to B-ALL therapy.

1. Introduction

Multiple myeloma (MM) is a clonal proliferation of plasma cells, usually based in the bone marrow, and spanning a clinical spectrum from asymptomatic to highly aggressive [1]. While smoldering MM is not always treated, symptomatic MM requires therapy, and therapeutic options have expanded in recent years, with improved outcomes. Recommended front-line therapy in transplant-eligible newly diagnosed symptomatic MM patients includes induction therapy with corticosteroids, proteasome inhibitors and immunomodulatory drugs (IMiDs) [2], followed by high-dose melphalan, autologous hematopoietic stem cell transplantation, and lenalidomide maintenance therapy, though this approach is non-curative in the majority of patients [2].

The immunomodulatory drug lenalidomide is a synthetic analog of thalidomide with a more favorable toxicity profile and with activity against a variety of hematologic neoplasms, including MM and multiple lymphoma subtypes [3]. Lenalidomide maintenance therapy prolongs remission in MM, but is also associated with an increased risk of second primary malignancies (SPMs), including both solid and hematologic neoplasms. Clinical trials in myeloma have demonstrated a 7–8% rate of SPMs with lenalidomide, compared to 3–4% in placebo groups [4–6], and a retrospective pooled review of phase 3 clinical trials showed a 4% rate of SPM development with lenalidomide versus 1.4% with placebo [7]. While the majority of SPMs in MM patients treated with maintenance lenalidomide are therapy-related myeloid neoplasms or solid tumors, therapy-related lymphoblastic leukemias are increasingly recognized.

SPMs have also been associated with conventional MM therapy such as high dose melphalan followed by ASCT [8]; a report using Surveillance, Epidemiology, and End Results (SEER) data of over 4500 MM patients demonstrated a 10-fold increase in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) when compared to non-conventional therapies [9]. The study describes a cumulative incidence of MDS or AML in MM patients, occurring in 0% of patients at 1 year post-transplant, 0–1% of patients at 3 years post-transplant, 1–2% of patients at 5 years post-transplant, and 2–3% of patients at 10 years post-transplant. The latency of therapy-realted lymphoblastic leukemias post MM is less well studied, though a larger recent series of 14 patients describes a median time to development of 6 years (range 2–14 years) [10].

Therapy-related B-ALL post MM has also been reported following melphalan, in the absence of lenalidomide exposure [11,12]. IMiD-based treatment regimens followed by maintenance therapy represents a new treatment paradigm in MM, and offers improvements such as lower toxicity and mitigated risk of SPMs than conventional chemotherapy [8], though the risks of SPMs still merit consideration.

We report eight cases of therapy-related B-lymphoblastic leukemia (t-B-ALL) in the setting of MM, including a description of clinicopathologic features and a summary of our clinical experience. t-B-ALL is a rare neoplasm, representing a small fraction of both SPMs and B-ALL in

general, but has the potential to complicate the management of myeloma patients. Increasing awareness of this emerging entity and larger studies will be needed to establish optimal treatment.

2. Methods

After IRB approval was obtained, a retrospective search was performed through the pathology case materials at the University of Maryland School of Medicine. Patients with the diagnosis of multiple myeloma and subsequent B-lymphoblastic leukemia/lymphoma were collected, and clinical information was retrieved from the electronic medical record.

Plasma cell and blast percentages were obtained by 500 cell manual differential counts. Histologic sections were routinely made of bone marrow trephine core material, and immunohistochemical stains (CD34, TdT, PAX5, CD20, and CD138) were performed, using standard techniques. *In situ* hybridization studies were similarly performed by standard techniques to assess kappa and lambda light chain expression. Flow cytometry studies were performed on peripheral blood and/or bone marrow aspirates using a 4-color assay.

Cytogenetic studies were performed on bone marrow or peripheral blood samples using standard procedures. Karyotype analysis was performed, as well as fluorescence in situ hybridization (FISH) on enriched CD138+ cells using column-based magnetic cell isolation using magnetic CD138 anibodies on nano-sized beads (Miltenyi Biotec). FISH probes targeted *CDKN2C* (1p32)/*CKS1B* (1q21), *MYC* (8q24), 13q14/13q34, *TP53 and IGH* (14q32) rearrangement, with reflex to *FGFR3* (4p16.3)/*IGH, CCND1* (11q13.3)/*IGH, IGH/MAF* (16q23.2), and *IGH/MAFB* (20q12). Next generation sequencing studies were not able to be performed in the majority of cases.

3. Results

Presentations and clinical courses of the eight patients with B-ALL following MM are summarized in Table 1. Patients were 53 – 76 (median 68) years old at diagnosis of ALL. They included four men and four women. One patient (Patient 8) had been diagnosed with breast cancer and received chemotherapy and radiation therapy 3 years prior to her myeloma diagnosis.

MM was κ-restricted in six and λ-restricted in two patients. Four patients had an abnormal karyotype and/or MM FISH study, without consistent abnormalities; three had high-risk cytogenetic abnormalities, including gain of 1q, del(17p) and t(14;20). Induction regimens included lenalidomide (len; Revlimid)/bortezomib (bor; Velcade)/dexamethasone (dex) (RVD), thalidomide (thal)/dex, lenalidomide (len)/dex, cyclophosphamide /bor/dex (CyBorD), and carfilzomib (Kyprolis)/len/dex (KRD). Six patients underwent autologous hematopoietic stem cell transplantation. Stem cells were mobilized with cyclophosphamide in all six patients and the conditioning regimen was high-dose melphalan in five patients for whom transplant details are known. All patients received lenalidomide maintenance therapy, with durations of 17 – 60 (median 41) months.

Time from MM diagnosis to B-ALL diagnosis ranged from 2.5 to 7.3 (median 4.25) years. B-ALL presented with pancytopenia in 5 patients, leukocytosis (WBC 17.9 K/uL) in one patient, and normal blood counts in two patients (unknown in 1 patient). Six patients had a leukemic presentation with >20% blasts in peripheral blood and/or bone marrow, but two patients demonstrated an unusual presentation with <20% marrow blasts and a later evolution to overt B-ALL. The B-ALL immunophenotypes were in keeping with those classically described, including CD34 expression in 7 cases, CD10 in 7 cases, and B-cell markers including CD19, cytoplasmic CD79a, and CD22, as well as markers of immaturity including cytoplasmic TdT, and aberrant markers including CD33 (3 cases), CD15 (2 cases), and CD56 (1 case); there was no κ or λ light chain expression. Cytogenetic abnormalities included t(9;22) in two patients, hyperdiploidy in two, hypodiploidy in one and i

(9)(q10) in one other. Patient 8 had del(7)(p13p21) and t(11;14)(q23; q32); she had also received docetaxel, cyclophosphamide, and radiation therapy for breast cancer antedating her MM.

B-ALL induction regimens included rituximab, cyclophosphamide, vincristine, doxorubicin (adriamycin), and dexamethasone (R-hyper-CVAD), dasatinib, doxorubicin (dox), dexamethasone (dex), vincristine (vcr), PEG-asparaginase (peg-asp), blinatumomab, and 6-mercaptopurine, vincristine, methotrexate, prednisone (POMP). One patient received allogeneic stem cell transplantation (alloSCT). One patient developed relapsed B-ALL and was treated with inotuzumab x 5 cycles. Of the 8 patients, one died of MM 11.9 years after initial MM diagnosis (without B-ALL relapse), one died during induction chemotherapy for B-ALL, one died after B-ALL relapse and treatment cessation for dementia (0.8 years after B-ALL diagnosis), and one achieved remission from B-ALL but died shortly thereafter of unknown causes. Of the two patients with indolent/evolving B-ALL presentations, one (Patient 3) died 1.9 years post B-ALL diagnosis (without MM or B-ALL relapse), and the other (Patient 7) is alive and has low level residual B-ALL (6%) at 0.7 years post diagnosis. The remaining two patients are in remission (1.1 and 1.2 years after B-ALL diagnosis, respectively), including a patient who received alloSCT (Patient 6). The follow-up time from diagnosis of B-ALL ranges from 0 to 4.6 (median 1.0) years.

4. Discussion

We report our institution's experience with eight patients diagnosed with t-B-ALL or incipient t-B-ALL in the setting of therapy for MM, including lenalidomide maintenance therapy. While therapy-related malignancies in this setting are far more commonly myeloid neoplasms [13], recent reports of t-B-ALL in the literature reflect increasing recognition of this entity [10,14–29]. t-B-ALL is rare or under-recognized, with <50 reported cases to our knowledge individually or in small series, and additional cases described within larger analyses [30,31] Table 2. A recent review describes a wide age range at diagnosis (range 33–82 years), with a median age of 61.5 years [15]; our patients had a narrower age range of 51–76 years, and a similar median age of 64 years. The published time to development of t-B-ALL is also highly variable, with a range of 2–84 months, median 32.5 months [15]; similarly, t-B-ALL developed after 23 – 88 months in our patients, with a median of 51.5 months. As in prior reports, most of our t-B-ALL cases were diagnosed following new onset of cytopenias, though a small subset of cases were incidentally detected during routine follow-up bone marrow examination in patients with normal blood counts.

An interesting phenomenon to emerge in t-B-ALL is that we were able to observe the slow development of the lymphoblastic leukemia, as seen in Patients 3 and 7 in our series, with a small increase in B-cell precursors detected, with or without an atypical immunophenotype. The distinction between hematogone hyperplasia of reactive etiology versus early detection of an evolving acute leukemia can be diagnostically challenging, and relies heavily on the presence or absence of immunophenotypic patterns of aberrancy and dysmaturation in the B-cell precursors, and/or cytogenetic abnormalities associated with B-ALL. The putative and potentially subtle hematogone hyperplasia is sometimes caught incidentally, and by WHO criteria cannot be called B-ALL with low level involvement at an early timepoint. Low-level marrow involvement and early detection is a fairly unusual occurrence in de novo B-ALL, but may be a recurrent feature seen in t-B-ALL, including in several recent reports [14,15,17,18]. The etiology of this phenomenon is uncertain, but its possibility supports considering early B-ALL, as well as MDS, in cytopenic patients with a history of lenalidomide exposure. Cytogenetic studies for ALL are also useful in this situation, and helped detect incipient disease in Patient 7 in this series. Another question raised by this phenomenon is whether early detection would change the course of the disease, i.e., could melphalan / lenalidomide discontinuation result in spontaneous remission?

The cytogenetic findings in our series are reflective of the small

Table 1
Patient characteristics.

| Multiple Myeloma (MM) | | | | | B - Lymphoblastic Leukemia (B-ALL) | | | | |
Patient	Age Sex	Year of diagnosis, presentation, isotype, phenotype	Karyotype / molecular	Treatment	Duration of lenaliomide maintenance prior to B-ALL (months)	Time fromMM to ALL (yrs)	Year of diagnosis, presentation, phenotype	Karyotype / molecular	Treatment	Outcome
1	68F	2008: Plasmacytoma then MM, κ-restricted	46,XX MM FISH negative	RVD x 6; CTX, ASCT-R	22	7.3	2014: Thrombocytopenia, WBC 17.9 K/uL, HgB 10.3 g/dL, PLT 13 K/uL 69% PB blasts: CD34, CD19, CD10, CD22, CD20 partial, cCD79a, cTdT, HLA-DR	t(9;22)(q34;q11.2)	R-hyperCVAD, dasatinib, IT MTX	MM relapse 9.3 yrs post MM diagnosis; died of MM 11.9 yrs after MM diagnosis, without ALL relapse
2	76M	2007: MM IgGκ	Unknown	thal, dex; len, dex; len	~60	7	2013: Pancytopenia, WBC 1.7 K/uL, HgB 10.8 g/dL, PLT 330 K/uL 68% BM blasts: CD34, CD19, CD10 variable	84–87,XXYY, t(1;2)(p13;p23)x2, −7,−7[cp4]	dox, dex, VCR, peg-asp	Died during induction chemotherapy course
3	68M	2014: MM IgGκ	−13, t(11;14)	CyBorD; CTX, ASCT-R	~60	5.4	2019: 1 year of thrombocytopenia evolving into pancytopenia, WBC 0.4 K/uL, HgB 8.5 g/dL, PLT 7 K/uL 95% BM blasts: CD19, CD20, CD22, cTdT, cCD79a partial, CD10, CD38 Preceded by hypocellular marrow with del(20q)	i(9)(q10) NRAS (47.1%) IDH2 (49.9%)	Blinatumomab x 5, IT MTX, POMP	Died 1.9 yrs post ALL diagnosis without MM or ALL relapse, but with del(20q) in marrow with megakaryocytic hypoplasia
4	72F	2015: MM IgGκ 10% CD5+λ+ small B cells	46,XX MM FISH negative	CyBorD; KRD; len	39	3.7	2020: Thrombocytopenia evolving to pancytopenia, WBC 2.1 K/uL, HgB 12.3 g/dL, PLT 104 K/uL 30% PB blasts: 80% BM blasts, CD34, CD19 dim, CD22, CD10, cCD79a, cTdT	46,XX at diagnosis; 46,XX,t(3;19)(p21;p13.3) at relapse	Blinatumomabx3; IT MTX; inotuzumab ozogamicin x 5 for relapse	Treatment stopped due worsening dementia. Died 4.5 yrs after MM diagnosis and 0.8 yrs after ALL diagnosis.
5	54M	2016: MM κ-restricted	46,XY FISH results not available	RVD; ASCT-R *	43	3.7	2020: Pancytopenia, WBC 1.0 K/uL, HgB 8.0 g/dL, PLT 8 K/uL 88% BM blasts: CD19, CD20, CD22, CD10, HLA-DR, CD34, CD79a, TdT, CD56, CD11c partial dim, CD64 partial dim, CD33 partial dim	33, XY,−2,−3,−4,−5,−7,−8,−9,−12,−13,−16,−17,−20,−22	dox, dex, VCR, peg-asp	Achieved remission Transferred care Died 0.2 yrs later, cause unknown.
	56M				35	3				

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Table 1 (*continued*)

| Multiple Myeloma (MM) | | | | | | B - Lymphoblastic Leukemia (B-ALL) | | | | |
Patient	Age Sex	Year of diagnosis, presentation, isotype, phenotype	Karyotype / molecular	Treatment	Duration of lenaliomide maintenance prior to B-ALL (months)	Time fromMM to ALL (yrs)	Year of diagnosis, presentation, phenotype	Karyotype / molecular	Treatment	Outcome
6		2017: Pancytopenia MM IgGλ	46,XY FISH +1p32,+1q21, +9,+11,+15	RVD x 5; CTX, ASCT; RVD x 2; len			2020: Pancytopenia, WBC 1.1 K/uL, HgB 8.5 g/dL, PLT 18 K/uL 45% BM blasts: CD34, CD19, CD20, CD10, CD22, CD15, cCD79a, cTdT	61,XXYY,+del (6)(q21)x2,+8,+8,+10,+10,+11,+12,+14,+21,+21,+22 [cp5]	Dox, dex, VCR, peg-asp, IT MTX; AraC, CTX, VCR, 6MP, peg-asp; AlloSCT	In remission 1.2 yrs after ALL diagnosis, 0.6 yrs after alloSCT
7	53F	2019: MM IgGκ	del(17)(p13), additional copies of 3,5,9,11,15	RVD x 5; KRD; CTX, ASCT-R	17	2.5	2021: Normal blood counts, WBC 6.2 g/dL, HgB 12.4 g/dL, PLT 190 K/uL 10% BM blasts: CD34 subset, CD20 subset, CD10, CD19, CD33 dim, partial, CD22, cTdT partial, cCD79a	t(9;22)(q34; q11.2)	Dasatinib, prednisone	Minute residual involvement by B-ALL (6% *BCR-ABL1*+) at 0.7 yrs after ALL diagnosis, 3.2 yrs after MM
8**	69F	2016: MM λ-restricted	t(8;16)(q24; p11.2),add (13)(q12),t (14;20)(q32; q11.2),add(15) (p11.2) FISH Gain of *CKS1B*	RVD; CTX, ASCT-R	50	4.8	2021: Bicytopenia, WBC 11.6 K/uL, HgB 8.4 g/dL, PLT 30 K/uL 50% BM blasts: CD19, HLA DR, CD34, CD33, CD38, CD22, TdT, cCD79a,CD15dim	del(7)(p13p21),t(11;14) (q23;q32)	HyperCVAD; Blinatumomab x2	In remission 1.1 yrs after B-ALL diagnosis, 5.9 yrs after MM

Abbreviations: M, F, male, female; FISH, Fluorescence in situ hybridization; RVD, Revlimid (lenalidomide), Velcade (bortezomib), dexamethasone; ASCT, autologous hematopoietic stem cell transplantation (conditioned with melphalan); R, Lenalidomide; alloSCT, allogeneic hematopoietic stem cell transplant; len, lenalidomide; thal, thalidomide; dex, dexamethasone; CyBorD, cyclophosphamide, bortezomib, dexamethasone; KRD, carfilzomib, lenalidomide, dexamethasone; yrs, years; BM, bone marrow; PB, peripheral blood; R-hyperCVAD, rituximab, cyclophosphamide, vincristine, doxorubicin (adriamycin), and dexamethasone; IT MTX, intrathecal methotrexate; Dox, doxorubicin; Dex, dexamethasone; VCR, vincristine; peg-asp, PEG-asparaginase; POMP, 6-mercaptopurine, vincristine, methotrexate, prednisone; AraC, cytarabine; CTX, cyclophosphamide (Cytoxan); 6MP, 6-mercaptopurine.
* Details unknown.
** Additional history of breast cancer diagnosed 3 yrs before MM, treated with docetaxel, cyclophosphamide, and radiation therapy.

Table 2
Characteristics of patients with B-ALL post MM from selected references.

Reference	Number of patients in study	Age, sex	Multiple myeloma (MM) genetic features	Duration of lenalidomide maintenance prior to B-ALL (months)	Time from MM to B-ALL	B-ALL presentation	Karyotype / molecular	Treatment	Outcome
Parrondo RD et al. - 10	14	Mean 63.9 yrs, 29% male		In 12 patients, median duration 53 months (range 17–121)	In 12 patients, median time to develop B-ALL 61 months (range 17–123 months)		Hypodiploidy/near triploidy 43%, hyperdiploidy 14%, normal karyotype 7%, complex karyotype 14%	HyperCVAD 71%, transplant in CR1 71%	MRD+ 4/12 pts, death after ALL diagnosis 4/14 pts, death after transplant 2/11 pts, relapse 1/14 pts, non-relapse mortality after transplant 2/11 pts
Khan A et al. – 14	2	Pt 1 – 53F, pt 2 – 69F		Pt 1 - 6 yrs, pt 2 - 15 months			Pt 1 - trisomies 8,10,21, monosomy 20; pt 2 – t (7;19) in one cell	Pt 1 -CALGB study 8811, pt 2 - HyperCVAD	Pt 1 - In remission at 12 months; Pt 2 – in remission at 36 months but 6% abnormal plasma cells
Germans SK et al. – 15	2	Pt 1 – 64 M, Pt 2 – 43M	Pt 1 - Biclonal myeloma with high risk features (del13q and del *TP53*); Pt 2 – t(4;14), aneuploidy 9 and 15	Pt 1 - 21 months; Pt 2 – 75 months	Pt 1 - 25 months; Pt 2 – 83 months	Pt 1 - 5% B-lymphoblasts first classified as hematogones	Pt 1 - Shared abnormalities with MM clone (del13q14, del *TP53*), additional abnormalities associated with MM including loss of *FGFR, MAF;* Pt 2 – *TP53* mutation, loss of function *CREBBP* variant	Pt 1 – HyperCVAD; Pt 2 – HyperCVAD x 4 cycles, inotuzumab after relapse	Pt 1 - remission at 17 months, residual *TP53* mutation; Pt 2 – death from ALL 23 months after diagnosis
Garcia-Munoz R et al. - 16	1	62F		20 months			Normal karyotype	Induction therapy	Died during induction from septicemia
Li J et al. - 17	1	66M		31 months (thalidomide)	38 months		add(4)(P16)	CHOP	Died of ALL
Tan M et al. – 18	3	Pt 1 - 59 M, Pt 2 – 34 M, Pt 3 – 53M		Pt 1 – 2.5 yrs, Pt 2 – 3 yrs, Pt 3 – 7 yrs			Pt 1 - del20q, Pt 2 – abnormality of chromosome 14, Pt 3 – small population of tetraploid cells	Pt 1 - Modified Linker regimen, alloSCT, Pt 2 – CALGB 8811, Pt 3 – modified Linker regimen followed by SCT	Pt 1 – in remission 1 year post transplant; Pt 2 – deceased 1 month post ALL; Pt 3 – remission 1 year post alloSCT
Gonzalez MM et al. - 21	1	72M	46XY[20]/+55XY,+9mar[1]		8 years	Concomitant acute myelofibrosis		HyperCVAD	Relapsed B-ALL at 28 months
Tashakori M et al. – 22	1	65F		5 years			Trisomy 8, 2 *TP53* missense mutations		
Mei J et al. – 24	2	Pt 1 - 68 M, Pt 2 – 65F		Pt 1 – 2 yrs, Pt 2 – 5 yrs			Pt 2 – hypodiploid and complex karyotype	Pt 1 – declined therapy, Pt 2 –	Pt 1 – died 4 months after ALL diagnosis, Pt 2 -

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Table 2 (*continued*)

Reference	Number of patients in study	Age, sex	Multiple myeloma (MM) genetic features	Duration of lenalidomide maintenance prior to B-ALL (months)	Time from MM to B-ALL	B-ALL presentation	Karyotype / molecular	Treatment	Outcome
Sinit RB et al. – 25	1	67M		15 yrs		Bone marrow biopsy with 20% MM, 60% B-ALL	Trisomies 8 and 21, near tetraploidy; plasma cells with *TP53* deletion, trisomies 3,7,11, trisomies/tetrasomies 9,15	low dose chemotherapy Inotuzumab at B-ALL relapse	died 1 month after ALL diagnosis Stable M-protein and no circulating blasts 15 months post diagnosis
Lee HY et al. – 26	2	Pt 1 - 54 M, Pt 2 – 54F	Pt 1 – normal karyotype; Pt 2 - 52,XX,+add(3) (q12),+5,−6,−8,+9,−10,+11,+15,−17,+18,+19,+20,−22,+3mar [2]/46, XY[7]		Pt 1 - 8 yrs, Pt 2 – 8 yrs		Pt 1 −45,XY,−7,1dmin [14]/46, XY,−7,+21,1dmin[5]/ 46,XY[1], Pt 2 – normal karyotype	Pt 2 – HyperCVAD x 6	Pt 1 - Remission after induction and 2 cycles of consolidation; Pt 2 - remission
Aldoss I et al. – 27	13	60 yrs (range 43–67), 62% male			5.4 yrs (range 3.3–10)		Normal karyotype – 5 pts, *TP53* mutation / deletion – 3 pts, monosomy 7 / del7q – 2 pts	HyperCVAD (12/ 13 pts)	85% complete remission, 8/13 pts went to alloSCT, one year event free survival and overall survival were 77%
Konishi Y et al. – 28	1	54M			8 yrs		t(X;9;1)(q12:q34:p34)	hyperCVAD, alloSCT	Remission from ALL at 3 years, detectable serum M-protein
Piszcz J et al. – 29	1	56F			9 yrs		Normal karyotype	Conservative management due to comorbidities	Died after 10 days of conservative management

Abbreviations: M, F, male, female; Pt, patient; FISH, Fluorescence in situ hybridization; alloSCT, allogeneic hematopoietic stem cell transplant; yrs, years; HyperCVAD, cyclophosphamide, vincristine, doxorubicin (adriamycin), and dexamethasone; MRD, minimal residual disease; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone.

number of cases reported by others to date, in that no specific recurrent features are apparent. The initial MM demonstrated high-risk abnormalities in two patients (deletion 17p in Patient 7, translocation 14;20 in Patient 8) and intermediate-risk abnormalities in Patient 3. The International Myeloma Working Group lists emergent risk factors for development of t-B-ALL including high risk myeloma cytogenetic features [32], though larger studies will be needed to fully elucidate their specific impact. The t-B-ALL patients in our series show a similar diversity of cytogenetic aberrancies, including *BCR-ABL1* (Patients 1 and 7), *KMT2A*/11q23.3 rearrangement (Patient 8), complex hyperdiploid karyotypes (Patients 2 and 6), a low hypodiploid karyotype (Patient 5), an uncommon isochromosome 9q (Patient 3), and an unusual t(3;19) (p21;p13.3) in Patient 4; the latter abnormality has been reported rarely in AML [33], but not in ALL. Next generation sequencing data was unable to be obtained.

Our series did not detect persistence and evolution of any clonal plasma cell population into a t-B-ALL by cytogenetic methods, though next-generation sequencing data are unavailable. Of interest, however, are the findings of dysmegakaryopoiesis, del(20q), and mutations in *NRAS* and *IDH2* in Patient 3, all seen prior to development of t-B-ALL; these findings are indicative of myeloid clonal hematopoiesis and raise the possibility of concomitant therapy-related myeloid neoplasia, though their relationship to the antecedent MM (in remission) and incidental B-cell precursor hyperplasia (incipient t-B-ALL) are uncertain. The role of melphalan and other alkylating agents (such as cyclophosphamide used in chemomobilization of stem cells) in causation of t-B-ALL is similarly not established, although recent data suggest a "melphalan signature," referring to a specific mutational burden solely attributable to this alkylator [34].

Although outcome data are limited, our series is in keeping with emerging reports that t-B-ALL following MM responds to treatment. Notably, none of our patients died directly of B-ALL within the short time-frame of the study. Our data are in contrast to several larger series of t-B-ALL, in which outcomes were worse than in *de novo* B-ALL [10,30, 35–37]; these series also noted that t-B-ALL patients were more often older and female, and had a distinct genetic profile including propensity for *MLL* rearrangements, *TP53* mutations, hypodiploidy, and/or abnormalities similar to therapy-related myeloid neoplasms. A key difference between these series and ours may reflect their definition of t-B-ALL as restricted to patients whose B-ALL was preceded by cytotoxic chemotherapy and/or radiation; this describes 6 of our 8 cases, but may in part explain the adverse clinical outcomes. Greater numbers of cases are needed to rigorously compare outcomes versus de novo B-ALL, and to establish optimal therapy. Additionally, the emergence of targeted therapies presents treatment options for refractory B-ALL [38], and could be deployed in therapy-related cases.

5. Conclusion

New therapies represent a paradigm shift in the treatment of multiple myeloma, but are also associated with therapy-related hematologic malignancies. Whle the majority of these are therapy-related myeloid neoplasms, B-lymphoblastic leukemias are increasingly recognized in this clinical context, and are thought to be clonally unrelated to the preceding MM. Our series of 8 such patientsis one of the larger series reported to date, though is limited by lack of next generation sequencing data. The unusual finding of incipient or low-level B-ALL in this setting is highly uncommon in de novo B-ALL cases, and merits a high index of suspicion in cytopenic patients post MM therapy. The notably better prognosis seen in our series, in which none of our patients died directly of acute leukemia, albeit with limited follow-up data, is in contrast to other reports of therapy-related B-ALL, and may broaden the spectrum of clinical behavior. Greater numbers of cases are needed for rigorous clinical comparison with *de novo* B-ALL cases and establishment of optimal therapy. The emergence of targeted therapies for refractory B-ALL presents treatment options that could be deployed in t-B-ALL.

References

[1] Swerdlow S.H.C.E., Harris N.L., Jaffe E.S., Pileri S.A., Stein H., Thiele J., Arber D. A., Hasserjian R.P., Le Beau M.M., Orazi A., Siebert R. WHO classification of tumours of hematopoietic and lymphoid tissues. Revised 4th edition ed. Lyon: IARC; 2017.
[2] P.M. Voorhees, J.L. Kaufman, J. Laubach, D.W. Sborov, B. Reeves, C. Rodriguez, et al., Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial, Blood 136 (8) (2020) 936–945.
[3] J.G. Gribben, N. Fowler, F. Morschhauser, Mechanisms of action of lenalidomide in B-cell non-hodgkin lymphoma, J. Clin. Oncol. 33 (25) (2015) 2803–2811.
[4] P.L. McCarthy, K. Owzar, C.C. Hofmeister, D.D. Hurd, H. Hassoun, P.G. Richardson, et al., Lenalidomide after stem-cell transplantation for multiple myeloma, N. Engl. J. Med. 366 (19) (2012) 1770–1781.
[5] M. Attal, V. Lauwers-Cances, G. Marit, D. Caillot, P. Moreau, T. Facon, et al., Lenalidomide maintenance after stem-cell transplantation for multiple myeloma, N. Engl. J. Med. 366 (19) (2012) 1782–1791.
[6] A. Palumbo, R. Hajek, M. Delforge, M. Kropff, M.T. Petrucci, J. Catalano, et al., Continuous lenalidomide treatment for newly diagnosed multiple myeloma, N. Engl. J. Med. 366 (19) (2012) 1759–1769.
[7] M.A. Dimopoulos, P.G. Richardson, N. Brandenburg, Z. Yu, D.M. Weber, R. Niesvizky, et al., A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide, Blood 119 (12) (2012) 2764–2767.
[8] D. Kazandjian, C.C. Mo, O. Landgren, P.G. Richardson, The role of high-dose melphalan with autologous stem-cell transplant in multiple myeloma: is it time for a paradigm shift? Br. J. Haematol. 191 (5) (2020) 692–703.
[9] T. Radivoyevitch, R.M. Dean, B.E. Shaw, R. Brazauskas, H.R. Tecca, R.J. Molenaar, et al., Risk of acute myeloid leukemia and myelodysplastic syndrome after autotransplants for lymphomas and plasma cell myeloma, Leuk. Res. 74 (2018) 130–136.
[10] R.D. Parrondo, Z.A. Rahman, M.G. Heckman, M. Wieczorek, L. Jiang, H. B. Alkhateeb, et al., Unique characteristics and outcomes of therapy-related acute lymphoblastic leukemia following treatment for multiple myeloma, Blood Cancer J. 12 (6) (2022) 87.
[11] K. Ueda, G. Yamamoto, A. Shinohara, A. Hangaishi, M. Kurokawa, Early onset of acute lymphoblastic leukemia with MLL rearrangement after autologous stem cell transplantation for multiple myeloma, Ann. Hematol. 88 (8) (2009) 813–814.
[12] L.G. Lau, L.K. Tan, E.S. Koay, T.C. Liu, Acute lymphoblastic leukemia after tandem autologous stem cell transplantations for multiple myeloma, Leukemia 19 (2) (2005) 299–301.
[13] M.A. Gertz, E. Terpos, A. Dispenzieri, S. Kumar, R.A. Shah, R. Orlowski, et al., Therapy-related myelodysplastic syndrome/acute leukemia after multiple myeloma in the era of novel agents, Leuk. Lymphoma 56 (6) (2015) 1723–1726.
[14] A.M. Khan, J. Muzaffar, H. Murthy, J.R. Wingard, J.S. Moreb, Acute lymphoblastic leukemia following lenalidomide maintenance for multiple myeloma: two cases with unexpected presentation and good prognostic features, Case Rep. Hematol. 2018 (2018) 9052314.
[15] S.K. Germans, O. Kulak, P. Koduru, D. Oliver, J. Gagan, P. Patel, et al., Lenalidomide-associated secondary B-lymphoblastic leukemia/lymphoma-A unique entity, Am. J. Clin. Pathol. 154 (6) (2020) 816–827.
[16] R. García-Muñoz, D. Robles-de-Castro, A. Muñoz-Rodríguez, P. Rabasa, Acute lymphoblastic leukemia developing during maintenance therapy with lenalidomide in a patient with multiple myeloma, Leuk. Lymphoma 54 (12) (2013) 2753–2755.
[17] J. Li, J. Zhan, F. Zhang, Z. Ye, J. Ouyang, Secondary lymphoblastic leukemia occurring 38 months after the primary diagnosis of multiple myeloma: a case report, Oncol. Lett. 12 (2) (2016) 847–856.
[18] M. Tan, R. Fong, M. Lo, R. Young, Lenalidomide and secondary acute lymphoblastic leukemia: a case series, Hematol. Oncol. 35 (1) (2017) 130–134.

[19] Y. Tsukada, Y. Hattori, H. Nakajima, K. Yokoyama, M. Murata, N. Shimizu, et al., [B-cell acute lymphoblastic leukemia developed 5 years after autologous stem cell transplantation for multiple myeloma], Rinsho Ketsueki 53 (2) (2012) 219–223.

[20] L. Junxun, L. Junru, C. Meilan, L. Chujia, C. Shaoqian, Z. Jieyu, et al., Three patients with multiple myeloma developing secondary lymphoblastic leukemia: case reports and review of the literature, Tumori 102 (Suppl. 2) (2016).

[21] M.M. Gonzalez, L. Kidd, J. Quesada, N. Nguyen, L. Chen, Acute myelofibrosis and acute lymphoblastic leukemia in an elderly patient with previously treated multiple myeloma, Ann. Clin. Lab. Sci. 43 (2) (2013) 176–180.

[22] M. Tashakori, J.D. Khoury, B acute lymphoblastic leukemia arising during maintenance therapy for multiple myeloma, Blood 136 (23) (2020) 2720.

[23] A. Alhuraiji, K. Naqvi, Y.O. Huh, C. Ho, S. Verstovsek, P. Bose, Acute lymphoblastic leukemia secondary to myeloproliferative neoplasms or after lenalidomide exposure, Clin. Case Rep. 6 (1) (2018) 155–161.

[24] J. Mei, L. Na, J. Dexiang, L. Fei, Z. Zhanglin, Acute B lymphoblastic leukemia developing in patients with multiple myeloma: presentation of two cases, Turk. J. Haematol. 36 (4) (2019) 287–289.

[25] R.B. Sinit, D.G. Hwang, P. Vishnu, J.F. Peterson, D.M. 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.

[26] H.Y. Lee, C.J. Park, A. Ahn, M.Y. Lee, Y.U. Cho, S. Jang, et al., Two rare cases of therapy-related acute lymphoblastic leukemia in patients with plasma cell myeloma, Ann. Lab. Med. 39 (5) (2019) 496–498.

[27] I. Aldoss, M. Capelletti, J. Park, R.S. Pistofidis, R. Pillai, T. Stiller, et al., Acute lymphoblastic leukemia as a clonally unrelated second primary malignancy after multiple myeloma, Leukemia 33 (1) (2019) 266–270.

[28] Y. Konishi, K. Tada, K. Nishi, K. Imada, Allogeneic bone marrow transplantation for therapy-related acute lymphocytic leukemia after autologous hematopoietic stem cell transplantation for multiple myeloma, Ann. Hematol. 95 (10) (2016) 1739–1740.

[29] J. Piszcz, L. Bolkun, E. Cichocka, J. Kloczko, Secondary acute lymphoblastic leukaemia in a multiple myeloma patient, Contemp. Oncol. (Pozn) 16 (6) (2012) 593–595.

[30] Z.H. Abdel Rahman, R.D. Parrondo, M.G. Heckman, M. Wieczorek, K.C. Miller, H. Alkhateeb, et al., Comparative study of therapy-related and de novo adult b-cell acute lymphoblastic leukaemia, Br. J. Haematol. 196 (4) (2022) 963–968.

[31] I. Aldoss, T. Stiller, J. Song, M. Al Malki, H. Ali, A. Salhotra, et al., Philadelphia chromosome as a recurrent event among therapy-related acute leukemia, Am. J. Hematol. 92 (2) (2017) E18–Ee9.

[32] P. Musto, K.C. Anderson, M. Attal, P.G. Richardson, A. Badros, J. Hou, et al., Second primary malignancies in multiple myeloma: an overview and IMWG consensus, Ann. Oncol. 28 (2) (2017) 228–245.

[33] W. Zhu, Z. Sun, Z. Zhai, K. Ding, G. Wu, A novel t(3;19)(p21;p13) in a patient with acute myelocytic leukemia, Cancer Genet. Cytogenet. 179 (2) (2007) 165–166.

[34] F. Maura, N. Weinhold, B. Diamond, D. Kazandjian, L. Rasche, G. Morgan, et al., The mutagenic impact of melphalan in multiple myeloma, Leukemia 35 (8) (2021) 2145–2150.

[35] I. Aldoss, T. Stiller, N.C. Tsai, J.Y. Song, T. Cao, N.A. 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) 1662–1668.

[36] C. Saygin, A. Kishtagari, R.D. 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 Adv. 3 (24) (2019) 4228–4237.

[37] L. Barnea Slonim, J. Gao, M. Burkart, O.E. Odetola, M. Kocherginsky, S.N. Dinner, et al., Therapy-related B-cell acute lymphoblastic leukemia in adults has unique genetic profile with frequent loss of TP53 and inferior outcome, Leukemia 35 (7) (2021) 2097–2101.

[38] Z. Shi, Y. Zhu, J. Zhang, B. Chen, Monoclonal antibodies: new chance in the management of B-cell acute lymphoblastic leukemia, Hematology 27 (1) (2022) 642–652.