Fulminant onset of acute leukemia from normal hematopoiesis within 3 months of follow up for multiple myeloma treated with total therapy protocols

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Key Clinical Message
Assiduous surveillance for genetic aberrations is necessary in patients on cytotoxic therapies to detect therapy-related myeloid neoplasms (t-MN). Current modalities include metaphase cytogenetics and FISH. Since t-MN may develop abruptly in cytogenetically normal patients, a discussion exploring additional methods such as SNP-array and targeted-deep-sequencing to detect subchromosomal abnormalities is needed.

Keywords
Acute leukemia, cytogenetic abnormalities, myeloma, therapy-related myeloid neoplasm.

Introduction
The development of secondary malignancies following high-dose chemo-radiotherapy (HDT) in multiple myeloma (MM) is well established [1–3]; recent reports have described an association with IMiD therapy as well [4, 5]. Based on a large population-based study [6] therapy-related myeloid neoplasms (t-MN) are the most common second malignancy in MM patients on therapy, with a standardized incidence ratio of 11.51 (CI 8.19–15.74). We and others, have previously shown that clonal, myelodysplasia-associated cytogenetic abnormalities (MDS-CA) may be transiently observed during the course of chemotherapy, and do not always correlate with presence of morphological dysplasia, or require specific therapeutic intervention. [5, 7, 8] However, most...
patients who have persistent or progressive cytopenia, and eventually develop t-MN, harbor persistent cytogenetic abnormalities [1–3]. In a recent paper, [5] we described a number of pretreatment host-, and treatment-related variables that could be linked to development of MDS-CA, such as advanced age, longer duration of pretreatment chemotherapy, low CD34 yield, and more leukapheresis sessions to obtain the desired quantity of hematopoietic progenitor cells. In this study, we draw attention to fulminant onset of acute leukemia (FOAL) in patients who did not have any previously identified significant morphological dysplasia or MDS-CA, and had a morphologically and karyotypically normal staging bone marrow (BM) within the previous 3 months. We searched for FOAL-defining features in the context of the more common therapy-related acute leukemia (t-AL) arising with prodromal clinical features or MDS-CA.

Patients and Methods

Patient cohort

Our MM database was scrutinized for all patients who had received hematopoietic progenitor cell-supported HDT at our institution since 1989. Only patients who had received at least one HDT regimen and an autologous hematopoietic stem-cell transplantation (auto-HSCT), and had informative cytogenetic data, defined as at least one evaluable karyotype before, and one at a minimum of 28 days after HDT, are included in the study. All participating patients had signed an initial informed consent in keeping with institutional, federal, and international guidelines. A subset of the patients in this cohort (patients on TT2, TT3a, and TT3b protocols) was included in a recent publication on risk factors for myelodysplasia [5]. This study includes all qualifying MM patients who received any of the following: Total therapy protocols (TT-P) for newly diagnosed MM [9–12] non-TT protocol, or off-protocol therapies. BM examinations and cytogenetic studies were performed for all patients at diagnosis, at 3-month intervals during the first year of maintenance, every 6 months for 3 years, and annually thereafter.

Definitions

CA commonly observed in myelodysplasia or acute leukemia [13] are referred to as MDS-CA in this study. We define MDS-CA as “persistent” when the same clonal chromosomal abnormality was observed in three successive metaphase cytogenetic analyses, and as “transient” when the clonal abnormalities were observed in less than three successive analyses, or when the abnormalities observed in the successive evaluations were dissimilar [8]. Since chemotherapy per se can result in morphological dyspoiesis, to avoid confounding bias, we identify a patient as having developed t-MN only when associated with persistent MDS-CA. Patients who required management of cytopenias with disease-modifying therapies such as hypomethylating agents including decitabine and 5-azacytidine, or cytotoxic chemotherapy, which is typically a combination of doxorubicin, Ara-C, and melphalan (DAM), or HSCT with BEAM conditioning, are designated as clinical MDS (C-MDS). Patients who received transfusion support, erythropoiesis-stimulating agents, or myeloid growth factors are excluded from the C-MDS because these management modalities are frequently used to facilitate recovery from cytopenia following HDT or HSCT. The FOAL group has already been defined. Acute leukemia developing following HDT is referred to as t-AL (AML/ALL). Patients with t-MN who had less than 20% blasts in the BM or peripheral blood are termed as t-MDS in this study. Complete remission is defined by the international myeloma working group (IMWG) criteria. [14].

Morphology, flow cytometry, and cytogenetics

A diagnosis of FOAL pertained to eight patients who, within 3 months of their last thorough evaluation at our institution, qualified as having no clinical, morphological, or genetic evidence indicative of MDS. All BM specimens within the one-year period prior to FOAL were reevaluated. Morphological evaluation of myelodysplasia was based on previously described parameters [15, 16] and performed by three experienced hematopathologists (Z. S., G. P., D. A.). Flow cytometry was performed on BM samples for quantitation and immunophenotypic characterization of the blasts. Metaphase cytogenetic analysis by GTG banding was performed on unstimulated BM specimens using standard techniques. At least 20 metaphases were examined from each specimen. The cytogenetic nomenclature followed standard ISCN criteria [17]. Interphase FISH was performed using probes to detect abnormalities commonly observed in MDS and AML such as −5/del(5q), −7/del (7q), del(20)(q11.2), +8, and −13. Additional probes were used in some patients at the onset of FOAL to detect translocations involving 11q23/MLL gene, t(8;21), t(15;17), inv (16) or t(16;16), t(9;22), and t(8;14).

Results

Of the 3941 patients undergoing mainly melphalan-based HDT, 391 patients developed MDS-CA (Fig. 1). Since the emphasis of this work is on t-MN, the 56 patients who
exhibited MDS-CA prior to first transplant were excluded from further analysis. Of the 335 remaining patients, 213 showed transient MDS-CA and 122 had persistent MDS-CA. Fifty patients with t-MN requiring disease-modifying therapies qualified as C-MDS. Of these 50 patients, 11 presented with t-AL (t-AML (10); t-ALL(1)) and 39 with t-MDS. Fifteen of the t-MDS patients subsequently progressed to t-AL. Of the 3550 patients who did not have MDS-CA, nine developed t-AL: eight of them qualified for a diagnosis of FOAL as previously defined; one patient who had persistent, clinically significant cytopenia prior to onset of leukemia, was not included in the FOAL group.

Characteristics and treatment of FOAL patients

The baseline MM parameters of FOAL patients are outlined in Table 1. Their age ranged from 41 years to 66 years, six were males and two females. The immunoglobulin distribution of the MM was representative of our referral population. The time from MM diagnosis ranged from 4 to 12 years. Myeloma-associated CA (MM-CA) were present in three of the eight patients at diagnosis of MM. Gene expression profiling (GEP)-defined molecular subgroups [18] were representative of newly diagnosed patients. Both GEP-70 and GEP-80 risk scores [19] were low in seven patients, while one had high-risk features in both models. Treatment regimes included TT2 without thalidomide in 1, TT2 with thalidomide [9] in 2, TT3a (maintenance with bortezomib, thalidomide, and dexamethasone) [10] in 3, TT3b (maintenance with bortezomib, lenalidomide, and dexamethasone) [11] in 1, and TT4 (similar to TT3b for GEP-defined low-risk MM) [12] in one patient. Table 2 summarizes the clinical, cytogenetic, morphological, and immunophenotypic features of patients with FOAL at onset of t-AL. The complete blood count (CBC) values over the last 12–18 months (at 3- to 6-month intervals) were as follows: hemoglobin 12.8 g/dL (range 7.8–13.6 g/dL; mean 12.0 g/dL), WBC 3.52 K/μL (range 1.17–9.7 K/μL; mean 4.38 K/μL), and platelet count 147 K/μL (range 60–280 K/μL; mean 157 K/μL). Latency periods to FOAL diagnosis from treatment initiation, and from first HDT, ranged from 11 to 134 months and 6–118 months, respectively (Table 2). The MM status at onset of FOAL was stringent complete response (sCR) in seven patients and complete response (CR) in one patient. Seven of the eight FOAL patients were classified as t-AML and 1 as t-precursor B-ALL. The morphology and immunophenotype from representative t-AML and t-ALL cases are illustrated in Figures 2A–C and 3A–C, respectively.
Table 1. Baseline myeloma parameters in FOAL patients.

| Patient no. | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   |
|-------------|-----|-----|-----|-----|-----|-----|-----|-----|
| Parameters  |     |     |     |     |     |     |     |     |
| Age/Sex     | 41/M| 44/M| 59/M| 54/M| 61/M| 66/F| 48/F| 66/M|
| Race        | AA  | W   | W   | W   | AA  | W   | W   | W   |
| MM Ig subtype | IgG K | IgG L | K light chain | Nonsecretory | K light chain | IgA K | IgG K | IgG K |
| Date of diagnosis | 09/2005 | 08/2009 | 01/2001 | 05/2005 | 03/2001 | 09/2005 | 12/2001 | 09/2006 |
| Risk-score at Diagnosis | 70-gene: Low | 70-gene: Low | 70-gene: Low | 70-gene: High | 70-gene: Low | 70-gene: Low | 70-gene: NA | 70-gene: NA |
| Molecular subtype | CD2 LB Hyperdiploidy | Proliferation subset with LB | 38–40,X, –Y,+1, add(1)(p11), der(1;16)(q10;p10), –4,–6, t(8;14), (q24.1;q32),–8,–12, –13,–16 [c4p4] | 46,XY[20] | 42–44,X,–X, add(6)(q22), der(1;2)t(1;12), (q11–12;q24.3), -13 [cp9/46, XX[cp11] |
| Karyotype at diagnosis of MM | 46,XY[20] | 46,XY[20] | 46,XY[20] | 46,XY[20] | 46,XY[20] | 46,XY[20] | 46,XY[20] | 46,XY[20] |
| Treatment protocol | 2003-33 (TT3) randomized to VTD arm | 2008-01 (TT4) randomized to lite arm | 98-026 (TT2) randomized to T-arm | 2003-33 (TT3) randomized to VTD arm | 98-026 (TT2) randomized to T-arm | 2003-33 (TT3) randomized to T-arm | 98-026 (TT2) randomized to non-T-arm | 2006-66 (TT3) randomized to non-T-arm |
| Lenalidomide: Yes/No, duration | Yes, 7 months | No | Yes, 30 months | No | Yes, 4 months | No | Yes, 6 months |
| No. of HSCT | 2   | 2   | 2   | 2   | 2   | 2   | 3   | 3   |
| Preparatory regimen | Mel 200 | Mel 200 | Mel 200 | Mel 200 | Mel 200 | Mel 200 | Mel 200 | Mel 200 |
| Stem cells collected >3 x 10^6 | No | No | Yes | No | No | No | No | No |
| >2 apheresis | No | No | Yes | No | No | No | No | No |
| Patient no. | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  |
|------------|----|----|----|----|----|----|----|----|
| Parameters |    |    |    |    |    |    |    |    |
| Latency period from start of chemotherapy to FOAL | 66 months | 11 months | 134 months | 75 months | 127 months | 77 months | 68 months | 65 months |
| Latency period from last transplant to FOAL | 52 months | 6 months | 118 months | 71 months | 116 months | 68 months | 25 months | 60 months |
| MM status at FOAL | sCR | sCR | CR | sCR | sCR | sCR | sCR | sCR |
| Karyotype within 3 months prior to FOAL | 46,XY[20] | 46,XY[20] | 46,XY[20] | 46,XY[20] | 46,XX[20] | 46,XX[20] | 46,XX[20] | 46,XX/XY[19]/46,XY,del(20)(q11.2)/1 |
| FISH within 3 months prior to FOAL | ND | Normal | Normal | ND | ND | ND | Normal | Normal |
| BM within 3 months prior to FOAL | Normocellular, No dysplasia, no residual MM | Normocellular, No dysplasia, no residual MM | Normocellular, No dysplasia, no residual MM | Normocellular, No dysplasia, no residual MM | Normocellular, No dysplasia, no residual MM | Normocellular, Hematogones 10%, no residual MM | Normocellular, No dysplasia, no residual MM | Mildly hypocellular with rare hypolobate megakaryocytes |
| Karyotype at time of FOAL | 46,XY[20] | 46,XY[20] | 46,XY[20] | 46,XY[20] | 46,XX,del(9)(p12),del(20)(q11.2;q13.1) | 46,XX,del(9)(p12),del(20)(q11.2;q13.1) | 46,XX,del(9)(p12),del(20)(q11.2;q13.1) | 46,XX,del(9)(p12),del(20)(q11.2;q13.1) |
| FISH | ND | Normal | de(5q31), del(7q) | de(5q31), del(7q) | de(5q31), del(7q) | de(20q) | Normal | –7, del(7q) |

(Continued)
Table 2. Continued.

| Patient no. | 1     | 2     | 3     | 4     | 5     | 6     | 7     | 8     |
|-------------|-------|-------|-------|-------|-------|-------|-------|-------|
| Other molecular tests | ND    | ND    | ND    | Negative for JAK2 V617F | ND    | ND    | ND    | ND    |
| FOAL subtype | AML   | AML   | AML   | AML   | AML   | AML   | Precursor B-ALL | AML   |
| BM at FOAL | Hypercellular, blasts 75%; Decreased megakaryopoiesis and erythropoiesis | Hypercellular (35%), blasts 20%, No significant dyspoiesis | Hypercellular, blasts 32%, marked trilineage dysplasia | Hypercellular, blasts 85-90%, markedly decreased Erythropoiesis and megakaryopoiesis, marked dysgranulopoiesis on peripheral blood | Hypercellular, blasts 35%; trilineage dysplasia | Hypercellular, blasts 40%; erythroid and Megakaryocytic dysplasia, mild granulocytic dysplasia | Hypercellular, blasts 65%; dysmegakaryopoiesis |
| Immunophenotype | Details not available | Positive: CD33, CD15, CD13, (variable), HLA-DR, CD14, CD11b, CD56 (subset), and CD4(dim) | Positive: CD34, CD117, CD13, CD33, CD7, CD5, and MPO, and CD4 (partially, weak) | Negative: HLA-DR, TdT, CD14, CD56, CD15, glycoporphin-A, and all lymphoid antigens. Decitabine, followed by Decitabine + Azacitidine + Melphalan | Negative: CD3, CD19, MPO, TdT, and other tested myeloid, and lymphoid antigens. Decitabine, Allogenic HSCT | Negative: CD3, CD19, CD15, CD11b, all other myeloid antigens, and lymphoid antigens. 7 + 3 induction with idarubicin, ara-C, Decitabine + Azacitidine + Melphalan | Negative: CD3, CD19, CD15, CD11b, all other myeloid antigens, and lymphoid antigens. Hyper-CVAD with Rituxumab and inotuzumab | Negative: CD34, and all myeloid and lymphoid antigens |
| Acute leukemia therapy | Clofarabine, Idarubicin, ara-C, etoposide, and fludarabine | Positive: CD34, CD117, CD13, CD33, CD7, and CD4(dim), and HLA DR | Negative: CD34, CD117, cMPO | Positive: CD45 (dim), CD34, CD33, CD13, CD56, and HLA DR | Positive: CD45 (dim), CD34, CD117, CD33, CD13, CD56 (dim), and HLA DR | Positive: CD45 (dim), CD34, CD117, CD33, CD120, CD20, CD99, CD44 | Positive: CD34, CD117, CD13, CD33, CD56, CD5, and CD7 |
| Response | Refractory AML | In CR for t-AML and MM for 3 months | In CR for t-AML and MM for 2 months | CR t-AML and MM | In CR for 5 months, then relapsed | In CR for t-ALL and MM for 3 months | In CR for t-ALL and MM for 2 months |
| Survival in months after FOAL | 11 | 17 | 6 | 11 | 5 | 9 | 38 | 2 |
| Outcome | Death | Death | Alive | Death | Alive | Alive | Death | Alive |

The bold text highlights the cytogenetic abnormalities commonly associated with myelodysplasia.
None of the patients had MM-related karyotypic abnormalities in the year preceding the onset of FOAL, or any MDS-CA by conventional metaphase cytogenetic study or FISH, at any time prior to the development of FOAL. FISH data available in four patients during the 3-month-period prior to FOAL, did not identify MDS-CA with the employed probes. In one patient, del(20)(q21) was identified transiently in 1 of 20 metaphases, which does not qualify as clonal. At onset of FOAL, the karyotype in this patient did not show the del(20)(q21) abnormality (Table 2). At the onset of FOAL, clonal MDS-CA were present in six of eight patients, in five of whom the karyotype was highly complex. Complete or partial deletions of chromosomes 5 or 7 were
observed in three and three patients, respectively, and abnormalities of both 5 and 7 were present in two patients. The MDS-CA identified by FISH in four of the seven cases examined matched those observed by metaphase karyotyping.

Treatment of FOAL was individualized and was based on the patients’ comorbidities and performance status (Table 2). Seven of the eight patients achieved CR, which was short-lived, ranging from 2 to 17 months.

Discussion

The development of secondary malignancies following HDT in multiple myeloma (MM) is well established [1–3]; recent reports have described an association with IMiD therapy as well [4, 5]. In our population of 3941 patients who received HDT, 8.5% developed MDS-CA, which were transient in the majority (two-thirds) of the patients. A subset of patients with MDS-CA required therapy (C-MDS); of those patients, 39 fulfilled diagnostic criteria for t-MDS and 11 were classified as t-AL (group C). Of those patients with t-MDS, 15 transformed to t-AML (group B-indicate). In contrast, FOAL was observed in eight patients without antecedent MDS-CA, significant morphologic dysplasia or clinically significant cytopenias (group A). The classic form of t-MN that develops following heavy prior treatment with alkylating agents, is usually associated with a prior myelodysplastic phase marked by cytopenia, and significant morphological dysplasia in the BM, often involving all three cell lines [1–3]. In this respect the FOAL patients, all of whom were heavily pretreated with melphalen, an alkylating agent, had an unusual presentation.

We attempted to identify predictive features for FOAL vis-à-vis patients with MDS-CA who presented as t-AL (11 patients; group C) or developed t-AL from antecedent t-MDS (15 patients; group B). There were no differences among the three groups with respect to age, sex number of transplants received or latency phase to t-AL. In our previous study on a large cohort of patients [5], and also from a recent paper by Pemmaraju et al. from M.D. Anderson cancer center [20], data highlights advanced age, longer duration of pretransplantation chemotherapy, low CD34 yield, and more leukapheresis sessions to obtain the desired quantity of hematopoietic progenitor cells as predictive of t-MN. Interestingly, 3 (6.4%) patients described by Pemmarju and others developed therapy-related chronic myelomonocytic leukemia, not a commonly described t-MN. Forty-three of the 46 patients (93%) who developed t-MN in their study had cytogenetic abnormalities, with high-risk abnormalities in 78% patients, but no patients are described to have an abrupt onset of acute leukemia without prior t-MDS or CA as observed by us. In fact, in our review of literature no specific mention of such a catastrophic development of t-AL has been previously made. This is especially remarkable because although the FOAL patients did not have any prior MDS-CA, interestingly, the proportion of patients with high-risk MDS-CA including −7, del(17)(p13)/TP53 and complex karyotypes (>3 abnormalities), were higher in this group (FOAL) of patients at the onset of t-AL compared with the two other groups in our study. There was no difference in survival from onset of t-AL among the patients groups (medians of 14, 9, and 10 months, respectively), nor did the latency duration affect survival in any of the groups of t-AL (data not shown). Notably, all FOAL patients had received TT protocols compared with five of 11 of group B (non-TT-P-1; off-P, 5), and seven of 15 of group C patients (non-TT-P, 4; off-P, 4). Of all the parameters evaluated, we noted that patients with prior exposure to lenalidomide had a higher incidence of developing FOAL; four of eight patients in the FOAL group had prior lenalidomide exposure, which is higher in incidence than the two of 15 of group B, and 0 of 11 of group C patients (P = 0.018). This observation is interesting with respect to recent reports linking lenalidomide to secondary malignancies in MM [4, 5]. The sample size in our analysis is small to derive definite conclusions.

Cytotoxic therapies cause BM damage by formation of highly mutagenic methylated-base-lesions, inter- and intrastand crosslinks in DNA, DNA double strand-breaks, and impaired DNA repair [21–23]. Progressive accumulation of DNA-damaging mutations results in emergence of abnormal clones with a proliferative and survival advantage [21–23]. Li et al. [24] found differences in expression levels of genes related to mitochondrial function, metabolism, DNA repair, and cell cycle regulation in CD34+ hematopoietic stem and progenitor cells between patients with Hodgkin or non-Hodgkin lymphoma, who developed t-MDS/AML following autologous HSCT, and those (matched controls) who did not have such an outcome. Barletta et al. [25] reported detection of RAS mutations in the peripheral blood of patients with chemotherapy exposure, prior to onset of hematological abnormalities (cytopenia). These studies provide evidence that cytotoxic exposure makes the cells genetically unstable and vulnerable to subsequent insults. The exact host factors, or the type of, or dosage of chemo- or radiotherapy that can tip the balance and trigger development of t-MN are poorly understood, and may also involve the BM microenvironment [25]. Prior studies by Bejar et al. [26] and Thol et al. [27] demonstrated that point mutations in TP53, EZH2, ETV6, RUNX1, ASXL1, [26] and in genes involved in the splicing machinery [27] are significantly associated with progression from MDS to AML. By sequencing of
MDS genomes, scientists have hypothesized that early driver mutations, typically involving RNA splicing, direct evolution of the disease, and also influence the clinical phenotype including BM morphological features, blast count, hemoglobin level, and clinical presentation [26–29]. Although mutational analysis for these genes was not performed in this study, it is very likely that one or more such genetic events, not detected at the resolution level of metaphase cytogenetics or FISH were the trigger for leukemic transformation in these patients.

**Conclusion**

The FOAL in the index group of heavily pretreated patients suggests that hematopoietic dysregulation leading to this clinical event may be the result of genetic alterations at the DNA level that cannot be detected by conventional cytogenetics or FISH. Studies in our institution are in progress to determine whether MM- and stroma-related genetic features can be identified as contributors to clinical t-AL development. Our group is also working on a GEP-based model, which will help in identifying patients at increased risk of developing t-MDS after chemotherapy. We, and others [25, 30] envision that data from studies based on GEP and massively parallel, whole-genome sequence analysis will help to select specific, frequently occurring genomic aberrations that can reliably predict a t-MN event, and be used to develop targeted genetic tests for surveillance of patients receiving cytotoxic therapy. A collaborative approach to develop cost-effective clinical tests for submicroscopic genomic aberrations in this target population is clearly warranted.

**Conflict of Interest**

None declared.

**Ethics**

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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