Factores pronósticos en SMD *de novo*, neoplasia mieloide secundaria y leucemia mielomonocítica crónica: experiencia de América Latina

Prognostic factors in MDS *de novo*, secondary myeloid neoplasm and chronic myelomonocytic leukemia: Latin American experience

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Introduction

Myelodysplastic Syndromes (MDS) are a group of clonal bone marrow (BM) neoplasms characterized by ineffective hematopoiesis, morphologic dysplasia affecting hematopoietic cells and peripheral cytopenia(s)[1]. Although first described by von Leube in 1900, it was best recognized after the first systematic classification published by the French-American-British (FAB) group in 1982[8]. Five subgroups were recognized with differences in overall survival and rate of leukemia transformation, manly based on morphologic features, the percentage of blast cells in BM and peripheral blood (PB). Chronic myelomonocytic leukemia (CMML) entity was considered as one of these five subgroups recognized by the presence of more than 1.000 monocytes/mm^3 in PB and BM blast counts till 20%. This entity shares some dysplastic (white blood cells <13.000/mm^3) and proliferative (WBC ≥13.000/mm^3) characteristics, and was moved to a new group of diseases in the World Health Organization (WHO) classification in 2001[9]. Among this and other changes, the WHO classification diminished the cut-off value from 30% to 20% for the diagnosis of acute myeloid leukemia (AML).

The assigning of prognosis and the selection of appropriate therapy require careful application of prognostic scoring systems. Prognostic factors can be divided into those related to the disease and to patients. Blast cell counts, severity of cytopenia(s) and cytogenetic abnormalities are the risk factors most included in several prognostic scoring systems, although individual (age, performance status and comorbidities), social factors (medical assessment) and other biological factors (genetic abnormalities, BM fibrosis) are also important. The International Prognostic Scoring System (IPSS), described in 1997[6], is the gold standard for prognosis assessment in *de novo* MDS and it was revised (IPSS-R) in 2012[7].

MDS *de novo*

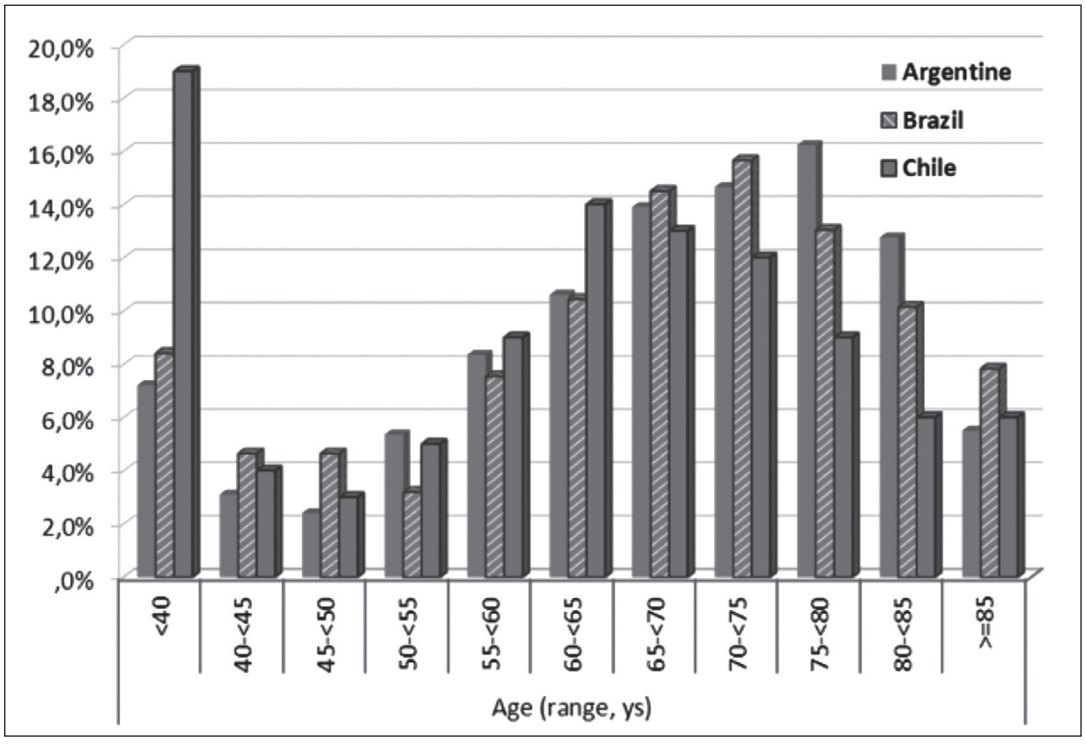
The experience of prognostic factors in MDS *de novo* was studied in a multinational study of South-American patients presented in the ASH meeting in 2014 and published in 2015. This was a retrospective analysis of 1080 patients from Argentina (Ar- 635, many centers including the Argentinean Registry, from 1981-2014), Brazil (Br- 345, 2 university centers, 1987-2012) and Chile (Ch- 100, 1 center, 1995-2012). Patients were classified following FAB and WHO criteria, including those with BM blasts less than 30% and CMML with leukocytes less than 12.000/mm^3, according to the IPSS original criteria. We compared differences in baseline characteristics and calculated the overall survival up to the introduction of disease modifying therapy (HSCT: 53 patients and hypomethylating agents: 137 patients).

Among baseline characteristics, the median age was 69 (15-99) years-old with a male/female rate of 1.2. Chilean patients were younger (P=0.001) with female preponderance (P=0.071) (**Figure 1**).

The distribution according to FAB classification was: RA (51.3%), RARS (10.9%), RAEB (21.4%). RAEBt (8.0%) and CMML-MDS (7.9%), and to WHO criteria was: 5q- (4.1%), RCUD (12.0%), RARS (5%), RCMD (42.0%) RCDM-RS (7.0%), RAEB-1 (13.2%), RAEB-2 (16.4%) and MDS-U (0.4%). Brazilian series showed a higher predominance of RARS subtype regarding FAB and WHO classifications (P<0.001).

Median hemoglobin level was 9.2 g/dL, median neutrophil counts were 1700/mm^3, platelet counts were 117.000/mm^3 and median BM blast cells were 2.0%. Hemoglobin levels were significantly lower in

Figure 1



Distribution of Argentinean, Brazilian and Chilean series according to the range of age

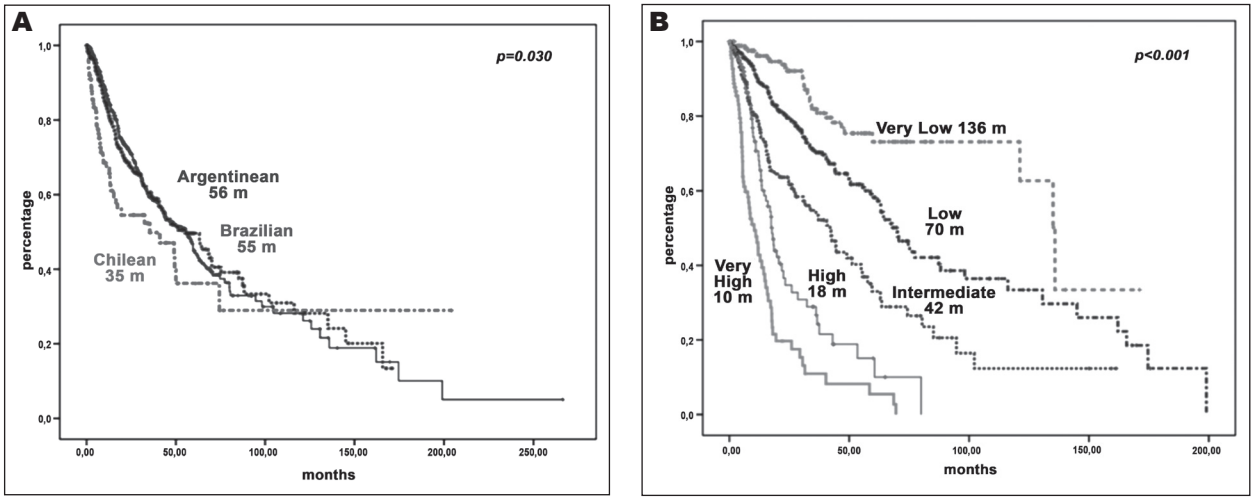
Brazilian and Chilean series (P<0.001), and Chilean series also showed a lower platelet count (P=0.028), with no differences concerning the neutrophil count and BM blast percentage.

Karyotypes were evaluated in 1040 patients and were abnormal in 40.5%. The most frequent cytogenetic aberrations were del5q (14.3%), +8 (11.4%), del7q/-7 (6.7%) and complex karyotypes were present in 19.5%. According to the original IPSS stratification, cytogenetic findings were distributed into: 69.4% good, 18.2% intermediate and 12.4% poor risk. Regarding the IPSS-R: 72% were very good/good, 16.7% intermediate, 5.4% poor and 5.9% very poor. Except for the high rate of complex karyotype in Chilean patients, there was no other difference in the distribution of cytogenetic risk groups (P>0.05). According to the global IPSS (n=1035), patients belong to low (32.6%), intermediate-1 (43.4%), intermediate-2 (14.5%) and high (14.5%) risk groups; and to IPSS-R (n=956): very low (18.3), low (38.1%), intermediate (17.9%), high (13.6%) and very high (12.1%), with more Chilean patients into the high risk group.

The follow-up for the whole series was 21 (1-26) months, with 497 deaths (187 AML). The median survival was 41 months, Chilean series depicted a lower overall survival (OS; 35 months vs. 56 months-Argentine; 55 months-Brazil, P=0.030, **Figure 2A**), which was consistent with a higher predominance of the high-risk group according both to the IPSS and IPSS-R (P=0.046 and P<0.001).

Parameters associated with survival were: gender, Hb, BM blast counts, cytogenetic group of risk, IPSS, and IPSS-R for all patients. The IPSS-R system and its variables showed a good reproducibility to predict clinical outcome for the whole population (**Figure 2B**).

Figure 2



Cumulative overall survival of South American patients.
A- Argentinean, Brazilian and Chilean series. B- IPSS-R for the FAB classified SA MDS population (N=956 patients).

Secondary myeloid neoplasms (s-MN)

Most of the cases with MDS or CMML arise as *de novo entities* with no recognized etiological agents. Therapy-related myeloid neoplasms (T-MN), including t-AML, t-MDS and myelodysplastic/myeloproliferative neoplasms (t-MDS/MPN), may occur as late complication of cytotoxic chemotherapy and/or radiation therapy, administered for a prior neoplastic or non-neoplastic disorder[12]. The secondary MN includes not only the T-NM but also myeloid diseases that appear after immunosuppression for aplastic anemia and solid transplants. The experience of prognostic factors in s-MN was published during the Brazilian Annual Hematological Meeting (HEMO) in November 2015, under the title: Karyotype is an independent prognostic factor in secondary myeloid neoplasms: study of 126 South-American cases.

The study was done in a cohort of 126 patients

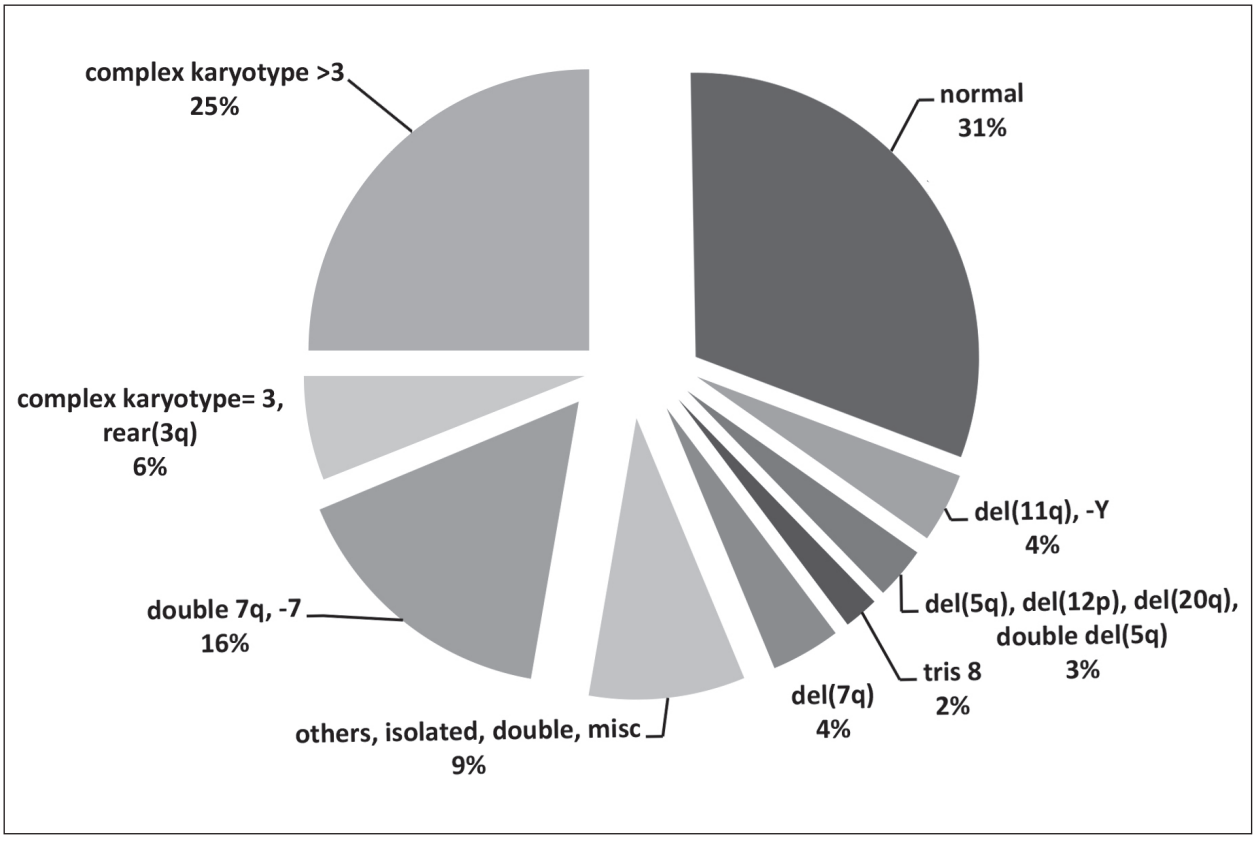
(Ar- 59 Argentinean MDS Registry, Br- unicentric HCFMUSP). Patients were evaluated according to the type of previous disease (hematological neoplasms, nonmalignant, solid tumor and aplastic anemia), therapeutic regimens for the treatment of those pre-existing diseases (QT, RT, autologous HSCT and immunosuppressive drugs), and latency period to s-MN. Laboratory findings studied were: hemoglobin, neutrophil and platelets counts, percentage of BM blast cells, ferritin and serum lactate dehydrogenase (LDH). The cytogenetic subtypes were classified according to the IPSS-R. The univariate analyses for survival were assessed by Kaplan-Meier and log-rank test, while multivariate analysis by Cox regression- Forward Stepwise method, up to last follow up or to allogeneic HSCT.

The median age was 61 years (4-88), 69 patients (54.8%) were male. The most common prior diseases were hematological neoplasms (39.7%), followed by solid tumors (35.7%), and the average latency was 68.5 months (1.4 to 763.2). Regarding therapy for s-MN, 19 patients underwent allogeneic HSCT and 35 used hypomethylating agents. The median follow-up was 18 months (1-118), during which 74 patients died, with a median overall survival of 34.8 months.

Cytogenetic findings are depicted in **Figure 3** showing that 69% of cases presented with abnormal karyotype (Figure 3), classified according to the IPSS-R into: 38% very good/good, 15% intermediate and 47% poor/very poor.

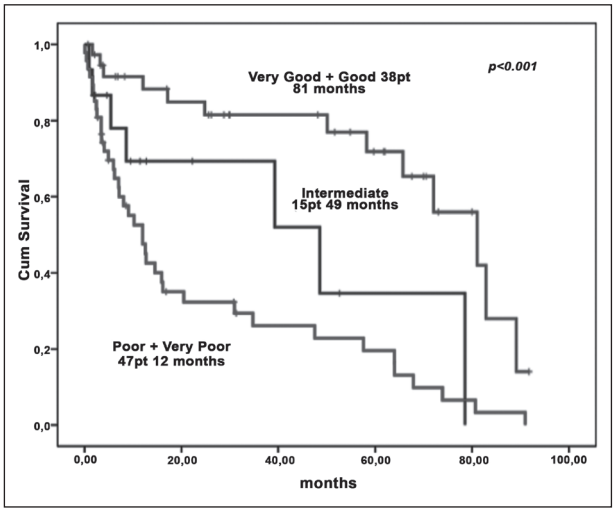
In univariated analysis, the parameters associated with survival were: age limit of 60 years (p=0.024), previous disease (p=0.002), type of treatment of pre-existing disease (p=0.027), hemoglobin level stratified by gender (p=0.041), platelets (p=0.003) and neutrophils (p=0.020), ferritin level of 700 ng/ml (p=0.002) and karyotypic abnormalities defined by IPSS-R (p<0.001, **Figure 4**). Multivariate analyses confirmed cytogenetic findings as independent factor for prognosis (p<0.001), with a marginal tendency for the type of the treatment for the previous disease (better outcome for previous radiotherapy, p=0.046). We concluded that in s-MN, like in MDS *de novo*, cytogenetics plays a key role in the stratification of prognosis.

Figure 3



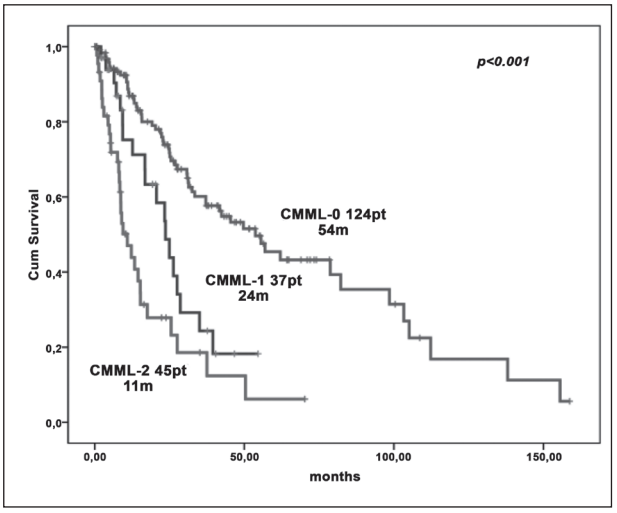
Distribution of cytogenetic findings in T-MN

Figure 4



Survival curves according to cytogenetic findings (groups were merged for statistical purpose)

Figure 5



Survival curves for CMML patients according to German purpose adopted afterward by the WHO 2016 proposal

Chronic Myelomonocytic Leukemia (CMML)

As previously introduced, CMML is a clonal hematologic disorder with a highly variable natural course. The diagnosis requires the presence of persistent PB monocytosis ≥1000/mm^3, monocytes accounting for ≥10% of the white blood cell differential count, exclusion of *BCR-ABL1* rearrangement in all cases and *PDGFRA, PDGFRB, FGFR1* rearrangements or *PCM1-JAK2* fusions if eosinophilia is present[1]. Two variants could be distinguished according to the FAB 1994 classification: a MDS (CMML-MD) and a myeloproliferative disorder (CMML-MP), according to the absolute WBC count (< or ≥13000/mm^3)[4]. The WHO 2001 and 2008 classifications divide this disorder in 2 subtypes, CMML-1 and CMML-2, depending on the percentage of blasts in bone marrow (BM) and peripheral blood (PB) [9]. Recently, there was a modification in the WHO 2016 classification and now three categories were recognized: CMML-0 (<2% blasts in PB and <5% blasts in BM), CMML-1 (2-4% blasts in PB and/or 5-9% blasts in BM) and CMML-2 (>5% PB blasts and >10% BM blasts)[1], originally proposed by the German Group in 2014.

The most used prognostic scoring system for MDS (IPSS and IPSS-R) exclude CMML-MP, therefore a specific Prognostic Scoring System for CMML was designed (CPSS) in 2013. It was based in a cohort of 558 patients and included FAB classification (CMML–MD vs. CMML–MP), WHO classification (CMML-1 vs. CMML-2), red blood cell (RBC) transfusion dependency at diagnosis (or hemoglobin level in the alternative CPSS) and the Spanish cytogenetic risk classification (low: normal and isolated –Y; intermediate: other abnormalities; and high: trisomy 8, complex karyotype and abnormalities of chromosome 7)[11].

Within the aims of a work published as abstract in the last EHA 2016 meeting, was to study the prognostic value of CPSS and the blast cell counts redefined CMML according to German Group in our population. This was a multicenter analysis of 234 patients with *de novo* CMML from Argentina (152) and Brazil (82) diagnosed between March 1985 and December 2015. Clinical and hematologic data of patients was retrospectively collected and diagnosis of *de novo* CMML was performed according to WHO 2008 criteria.

The median age was 71 (range 15-95) years, 83% older than 60 years old, with a sex ratio M/F 2:1. With a median overall survival of 31 months, 56 (24%) evolved to AML and 122 (52%) died.

Hb was above 10 g/dl in 56% and above 9 in males and above 8 in females in 75%; platelets above 100.000/mm^3 in 45%. LDH was elevated in 46% of patients. Most of the karyotypes belonged to good or intermediate subgroup as defined by CPSS. There were 54% of patients in CMML-0, 18% in CMML-1 and 23% in CMML-2 (**Figure 5**).

The distribution of patients according to the original CPSS (transfusion dependence), and to the alterna-

tive CPSS (Hb limit to 10 g/dl and Hb according to gender) were calculated, and the distribution was near 30% for low, intermediate-1 and intermediate-2 subgroup in the last alternative CPSS, because transfusion dependency was not available for Br series.
Most of the prognostic parameters and all CPSS proposals were useful to predict outcome in our population ($p<0.05$). Also LDH level and WHO 2016 criteria proposal, not included in the original CPSS system, were analyzed in a multivariate model. This last cut-off for BM blast cell showed an additive value to predict survival and evolution to AML [$p=0.053$ and $p=0.003$, exp(B) 1.335 and 2.057] when compared with the CPSS-Hb variant [$p<0.001$ and $p=0.052$, exp(B) 1.654 and 1.537]. The results showed that the new proposed classification for CMML dividing them into CMML-0, -1 and -2 may add prognostic value to the CPSS

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Declaración de conflictos de interés:
La autora declara que no posee conflictos de interés

References

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. Blood. 2016 Apr 11. pii: blood-2016-03-643544. [Epub ahead of print].
2. Belli CB; Feitosa Pinheiro R, Flores MG, et al. Clinical Characteristics and Prognosis in South-American Patients with Myelodysplastic Syndrome: A Multicenter Study. 56th American Society of Hematology Annual Meeting and Exposition. Blood 2014; 124 (21); Abstract 4651.
3. Belli C, Pinheiro RF, Bestach Y, et al. Myelodysplastic syndromes in South America: a multinational study of 1080 patients. Am J Hematol. 2015 Oct;90(10):851-8.
4. Bennett JM, Catovsky D, Daniel MT, et al. The chronic myeloid leukaemias: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid, and chronic myelomonocytic leukaemia. Proposals by the French-American-British cooperative leukaemia group. Br J Haematol. 1994 Aug;87(4):746-54.
5. Gonzalez J, Arbelbide J, Bestach Y, et al. Prognostic factors in chronic myelomonocytic leukemia from South America. 21th Congress of the European Hematology Association 2016, Abstract 2469.
6. Greenberg P, Cox C, Le Beau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997 Mar 15;89(6):2079-88.
7. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012 Sep 20;120(12):2454-65.
8. Hellström-Lindberg E. Myelodysplastic syndromes: an historical perspective. Hematology Am Soc Hematol Educ Program. 2008:42.
9. Orazi A, Bennett JM, Germing U, Brunning RD, Bain BJ, Thiele J. Chronic myelomonocytic leukaemia WHO Classif. Tumours Haematop. Lymphoid Tissues, France: IARC Press, Lyon (2008), pp. 76–79.
10. Such E, Germing U, Malcovati L, et al. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. Blood. 2013 Apr 11;121(15):3005-15.

11. Schuler E, Schroeder M, Neukirchen J, et al. Refined medullary blast and white blood cell count based classification of chronic myelomonocytic leukemias. Leuk Res. 2014 Dec;38(12):1413-9.

12. Vardiman JW, Matutes E, Arber DA, Baumann I, Brunning RD, Thiele J, Larson RA. Therapy-related myeloid neoplasms. WHO Classif. Tumours Haematop. Lymphoid Tissues, France: IARC Press, Lyon (2008), pp. 127–129.

13. Velloso ED, Tanizawa RS, Leal AM, et al. O cariótipo é variável definidora de prognóstico nas neoplasias mieloides secundárias: estudo de 126 casos sul-americanos. Hematologia 2015, 476.