Absence of prognostic impact of CD13 and/or CD33 antigen expression in adult acute lymphoblastic leukemia. Results of the GIMEMA ALL 0496 trial

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ABSTRACT

Background and Objectives

The prognostic value of myeloid antigen (MyAg) expression in adult acute lymphoblastic leukemia (ALL) is still controversial. The aim of this study was to correlate the expression of MyAg with clinical, hematologic and biological parameters, and to analyze the impact on response to treatment and prognosis in a large series of adult ALL uniformly characterized and treated.

Design and Methods

We analyzed the expression of the MyAg CD13 and/or CD33 in a cohort of 377 adult patients with *de novo* ALL enrolled and treated in the GIMEMA ALL 0496 protocol.

Results

MyAg expression was documented in 35% of the 377 adult ALL cases analyzed. MyAg were significantly more frequently associated with B-lineage ALL (38%) than with T-ALL (24%) (p=0.02). No difference was found with regard to clinical features at presentation; a difference was found only for white cell count (p=0.03), percentage of peripheral blasts (p=0.004) and platelet count (p=0.004). No difference was observed in the expression of MyAg between patients with normal or abnormal cytogenetics or between those with high-risk (*BCR-ABL+, ALL1-AF4+, E2A-PBX1+*) or low-risk B-lineage ALL. We failed to observe any difference between MyAg-positive and MyAg-negative cases in terms of achievement of complete remission, disease-free survival and overall survival at 5 years.

Interpretation and Conclusions

Our data indicate that ALL MyAg expression in adults with ALL is not associated with adverse presenting clinical and biological features, and that response to treatment and prognosis is comparable in MyAg-positive and MyAg-negative ALL patients with regards to both complete remission rate and overall survival. We suppose that these result are due to more intensive treatment modalities adopted in the GIMEMA ALL 0496 protocol.

Key words: myeloid antigen, adult ALL, prognosis

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Aberrant myeloid antigen (MyAg) expression occurs in 10-40% of adult patients with acute lymphoblastic leukemia (ALL).[1-3] The prognostic value of MyAg expression in adult ALL is still controversial; while early studies suggested an inferior outcome for MyAg+ ALL patients,[2,4-6] other published series with protocols based on high-dose chemotherapies have failed to confirm a prognostic correlation.[3,7,8] Within the multicenter *Gruppo Italiano Malattie EMatologiche dell'Adulto* (GIMEMA) ALL 0496 protocol, a central handling of biological material at presentation was required for all registered cases. Taking advantage of this overall framework, we examined the expression of aberrant MyAg in a large cohort of adult ALL patients uniformly characterized and treated. The aims of our analysis were to determine the incidence of MyAg expression in a group of adult ALL evaluated homogeneously at diagnosis, to investigate the relationships of MyAg expression with other clinical, hematologic and biological characteristics, and to establish the prognostic importance of MyAg expression in terms of response to induction treatment and long-term survival.

Design and Methods

Between October 1996 and July 2000, 377 adults with *de novo* ALL were registered in the GIMEMA ALL 0496 protocol (Figure 1), which was derived from the ALLVR589 regimen[9] and included patients aged 14-60 years with a diagnosis of ALL, with the exclusion of L3 B-ALL. The study was approved by the Institutional Review Board of the Department of Cellular Biotechnologies and Hematology, "La Sapienza" University of Rome. Informed consent was provided according to the Declaration of Helsinki and signed by all included patients. All cases were analyzed through central handling of the samples at presentation at our center and all were uniformly investigated for morphology, immunophenotype, cytogenetics, molecular biology and multidrug resistance (MDR).

Morphology and immunophenotype

The referring centers evaluated morphology according to the French-American-British (FAB) classification[10] and immunophenotype according to a pre-defined diagnostic panel of reagents: CD34, HLA-DR, CD19, CD10, CD20, CD2, CD5, CD7, CD3, CD13, CD33, CD14, CD1a on the surface of leukemic cells and intracytoplasmic Igμ chain, CD3, CD79a and myeloperoxidase antigens, as well as nuclear TdT (Dako Cytomation, Copenhagen, Denmark) were evaluated using fluorescence conjugated monoclonal antibodies (Becton Dickinson, San Josè, CA, USA/Beckman Coulter, Fullerton, CA, USA). Marked cells were analyzed by flow cytometry according to standard operating protocols [FACScan flow-cytometer (Becton Dickinson) and FACScalibur flow cytometer (Becton Dickinson)]. The percentage of positive cells was calculated from the *gated* region of leukemic cells and surface markers were considered positive when 20% or more of the blasts expressed the antigen; intracytoplasmic positivity required 10% or more reactive blasts. The GIMEMA biological committee reviewed the results according to the European Group for the Immunological Characterization of Acute Leukemias (EGIL) classification system.[11]

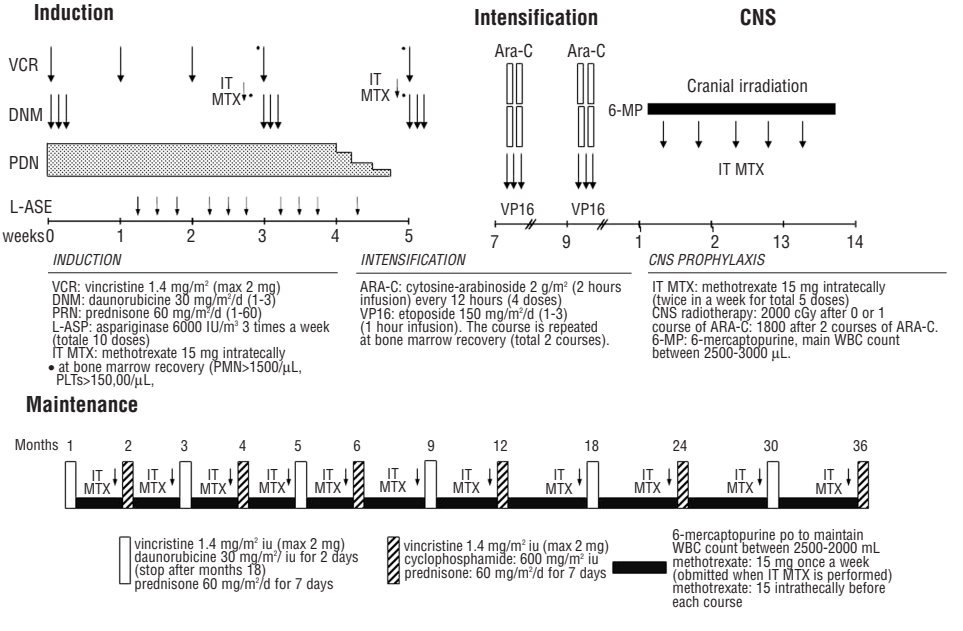

Figure 1. GIMEMA ALL 0496 protocol.

Cytogenetic and molecular investigations

Metaphases from short-term bone marrow cultures were prepared in a single laboratory (Department of Hematology: "La Sapienza", University Rome) according to standard methods and GTG banded chromosomes were classified following the International System for Human Cytogenetic Nomenclature[12] A minimum of ten GTG banded metaphases were required to consider the case evaluable. Three referral laboratories (Departments of Hematology: "La Sapienza", University Rome; University of Ferrara; and University of Perugia) performed the cytogenetic analyses at diagnosis. The GIMEMA cytogenetic committee reviewed all cases. The presence of different fusion transcripts (*E2A-PBX1, BCR-ABL, ALL1-AF4, TEL-AML1*) was detected by reverse transcriptase polymerase chain reaction (RT-PCR) as previously described.[13] All these analyses were carried out in three referral laboratories (Department of Cellular Biotechnology and Hematology, "La Sapienza" University, Rome; Department of Clinical and Biological Sciences, Orbassano, University of Turin; Department of Biochemistry and Medical Biotechnologies, Federico II University, Naples).

Multidrug resistance

MDR1 expression and function were assessed in the same laboratory (Department of Cellular Biotechnology and Hematology, "La Sapienza" University, Rome) by two cytometric tests, as described elsewhere.[14] MDR1 expression was measured by flow cytometric detection of P-gp expression, which was considered positive when the D value was ≥0.05; MDR1 function was investigated using the rhodamine-123 efflux test, which was considered positive when values were 1.10 or greater.

Statistical analysis

A statistical analysis was performed taking into account gender, age, white blood cell count, hemoglobin level, platelet count, presence or absence of CD13, CD33 and CD34 antigens, cytogenetics, molecular biology and MDR. The cut-off levels for age, leukocytosis, anemia and thrombocytopenia used for statistical comparisons were derived from median values of our data and earlier studies that established significant correlations between these values and patients' survival.[15-17] Differences in the distributions of variables between groups of patients were analyzed by the Kruskal-Wallis, χ^2 or Fisher's exact test. Overall survival (OS) from diagnosis and disease-free survival (DFS) from complete remission were estimated using the Kaplan-Meier method. The cumulative incidence of relapse was estimated using the appropriate non-parametric method. The log-rank test was applied to compare treatment effect and risk factor categories, using the Simon and Lee method 95% confidence intervals (95% CI) for these probabilities. Logistic regression and Cox proportional hazard regression models were performed to evaluate treatment results and risk factors affecting complete remission (CR) rate and time to event. The SAS software (SAS Institute, Cary, NC, USA) was used for the analyses.

Results

The clinical and biological characteristics of the 377 patients at presentation are shown in Table 1. There were 153 females and 224 males, with a median age of 30.3 years and a median white blood cell count of 15.6×10^9/L. Anemia (hemoglobin <10.0 g/dL) was present in 61.5% of patients and thrombocytopenia (platelet count $<100\times10^9$/L) in 73.0%. Physical examination revealed hepatomegaly (≥2 cm) in 38.4%, splenomegaly (≥2 cm) in 46.8% and lymphadenopathy in 55.6% of patients. The central nervous system was involved in 2.8% of patients. A mediastinal mass was present in 16.8% of patients; of these, 63% had T-lineage ALL and 37% B-lineage ALL. Eighty percent of patients was classified as having B-lineage ALL (pro-B ALL 20%, common-B ALL 64%, pre-B ALL 16%) and 20% as having T-lineage ALL (pro-T ALL 5%, pre-T ALL 46%, cortical-T ALL 38%, mature-T ALL 11%). CD13 and CD33 antigens were expressed in 25% and 23% of the 377 cases analyzed, respectively; thus aberrant MyAg (CD13 and/or CD33) expression was observed in 35% of all ALL cases. We also assessed whether the concomitant presence of the CD13 and CD33 antigens had a prognostic implication compared with individual positivity for CD13 or CD33. Since we found no differences, the results are reported according to the presence of CD13 and/or CD33.

The CD34 antigen was expressed in 270 of the 374 cases analyzed (72%). CD34 positivity was much higher in B-lineage ALL (82%) than in T-ALL (35%), ($p<0.0001$); moreover, in B-lineage ALL, CD34 positivity was significantly associated with the presence of the *BCR/ABL* rearrangement ($p<0.0001$). In 259/377 ALL patients, the karyotype was successfully evaluated and 60% of those examined had an abnormal karyotype. In 292 B-lineage ALL cases in which molecular analysis was evaluable, 32% of the cases were positive for the *BCR/ABL* rearrangement; in addition, 210 patients were studied for the *ALL1/AF4* rearrangement, which was found in 10.5% of cases; 119 patients were studied for the *E2A/PBX1* rearrangement, and 5% were found to be positive. MDR was evaluated through its expression in 273 patients and proved to be positive in 23%; it was also evaluated as a function in 198 and was found to be positive in 14% of cases.

On the basis of the positivity for at least one of the two myeloid markers (CD13 and/or CD33), we stratified the patients into two groups: $MyAg^+$ and $MyAg^-$ (Table 1).

Table 1. Distribution of CD13 and / or CD33 expression according to clinical and biological features in 377 cases of adult ALL.

Factors	*MyAg+*	*MyAg-*	*p value*
Gender (Female/male)	68/64	85/160	0.001
Age (median, range)	30.9 yrs (15.4-59.4)	30.0 yrs (14.0-59.8)	NS
WBC count (median, range)	$10.3x10^9$/L (0.6-353)	$18.5x10^9$/L (0.5-848)	0.03
Peripheral blasts (median, range)	54 (0-100)	71 (0-100)	0.004
Hemoglobin level (median, range)	9.0xg/dL (4.5-15.7)	9.4xg/dL (3.4-16.8)	NS
Platelet count (median, range)	$67x10^9$/L (2.0-390)	$47.5x10^9$/L (1.0-407)	0.004
FAB (L1/L2)	40/84	80/145	NS
Bone marrow blasts (median, range)	90 (30-100)	90 (39-100)	NS
Mediastinal involvement (+/-)	16/106	43/186	NS
Lymphadenomegaly (+/-)	65/62	137/99	NS
Hepatomegaly (+/-)	44/74	84/131	NS
Splenomegaly (+/-)	48/68	159/181	NS
B-lineage ALL/T-lineage ALL	114/18	187/58	0.02
CD34 (+/-)	116/16	154/88	<0.0001
Cytogenetics (normal/abnormal)	42/49	62/106	NS
Molecular biology B-ALL: (high risk)			
BCR/ABL +/-	42/68	51/131	0.07
ALL1/AF4 +/-	0/75	22/113	<0.0001
E2A/PBX1 +/-	0/44	5/70	0.08
MDR expression (≥ 0.05) (+/-)	20/69	43/141	NS
MDR function (≥ 1.10) (+/-)	12/53	16/117	NS

Table 2. Clinical course of MyAg$^+$ and MyAg$^-$ cases.

Variable	*MyAg$^+$*	*MyAg$^-$*	*p value*
Remission rate	88/115 (76.5%)	186/229 (81.2%)	
Resistant disease	18/115 (15.6%)	21/229 (9.1%)	p=0.1902
Induction death	9/115 (7.8%)	22/229 (9.6%)	
Cumulative incidence of relapse (5 years)	60% (CI 95%: 47-72)	61% (CI 95%: 52-69)	p=0.7692
Overall survival (5 years)	33% (CI 95%: 25-42)	32% (CI 95%: 25-38)	p=0.7592
Disease-free survival (5 years)	34% (CI 95%: 23-44)	32% (CI 95%: 25-39)	p=0.6858

The presence of MyAg$^+$ was significantly more frequent in females than in males (44.4% vs 28.6%; p=0.001). A difference was found with regard to the median white cell count (p=0.03) and the number of peripheral blasts (p=0.004), which were both lower in the MyAg$^+$ group; a difference was also recorded in the median platelet count, which was higher in the MyAg$^+$ group (p=0.004). No differences were found between the MyAg$^+$ and MyAg$^-$ groups with regard to median age, median hemoglobin level, bone marrow findings (FAB and percentage of bone marrow blasts) and clinical features at presentation. MyAg were significantly more frequently associated with B-lineage ALL (38%) than with T-ALL (24%) (p=0.02) and, when considered according to immunophenotypic subtype were significantly more frequently associated with common ALL (52%; p=0.05) and pre-T ALL (50%; p=0.07). CD34 expression was found in 43% of MyAg$^+$ and in 15% of MyAg$^-$ cases (p<0.0001).

No difference was observed in the expression of MyAg between the groups of patients with normal or abnormal cytogenetics. In high risk B-lineage ALL (*BCR-ABL$^+$, ALL1-AF4$^+$, E2A-PBX1$^+$*), no difference was observed in the expression of MyAg and the presence of the *BCR/ABL* rearrangement or of the *E2A/PBX1* rearrangement; however, in the same group, the absence of MyAg was strongly associated with the *ALL1/AF4* rearrangement (p<0.0001). An equivalent expression of MyAg was recorded in all MDR$^+$ and MDR$^-$ ALL cases, both with respect to MDR expression (32% vs 33%) and MDR function (43% vs 31%). Furthermore, no differences were recorded when the expression of MyAg was analyzed in MDR$^+$ and MDR$^-$ patients subdivided according to B- or T-cell lineage affiliation.

The clinical course of MyAg$^+$ and MyAg$^-$ patients is summarized in Table 2. The presence of aberrant MyAg did not affect the achievement of CR or cumulative incidence of relapse; no differences were found between MyAg$^+$ and MyAg$^-$ cases in terms of DFS and OS at 5 years. In addition, we failed to observe any statistical difference between the two groups in the incidence of death either during induction or in CR. We also separately analyzed MyAg expression in T-ALL and B-lineage ALL cases according to the following subgroups: (i) MyAg$^+$ in high risk B-lineage ALL, (ii) MyAg$^-$ in high risk B-lineage ALL;

(iii) MyAg$^+$ in B-lineage ALL without known transcripts; (iv) MyAg$^-$ in B-lineage ALL without known transcripts; (v) and MyAg$^+$ in T-lineage ALL; and (vi) MyAg$^-$ in T-lineage ALL. No differences in CR achievement, OS and DFS were recorded between MyAg$^+$ and MyAg$^-$ cases in the different ALL subgroups (Figure 2). Furthermore, when cases with B-lineage ALL with *BCR/ABL* rearrangement were analyzed as a separate group, we found no differences in CR achievement, OS and DFS between MyAg$^+$ and MyAg$^-$ cases. In addition, in B-lineage ALL, we analyzed MyAg expression according to immunophenotypic subtypes (pro-B ALL MyAg$^+$ vs pro-B ALL MyAg$^-$; common-B ALL MyAg$^+$ vs common-B MyAg$^-$; pre-B ALL MyAg$^+$ vs pre-B MyAg$^-$) once again finding no differences between MyAg$^+$ and MyAg$^-$ groups in CR achievement, DFS and OS, even if a higher probability of OS was recorded in the pro-B MyAg$^-$ group (p=0.06). A multivariate analysis including clinical and biological data was performed to determine the prognostic value of MyAg and CD34 expression; no specific effect on CR, DFS or OS could be found (*data not shown*).

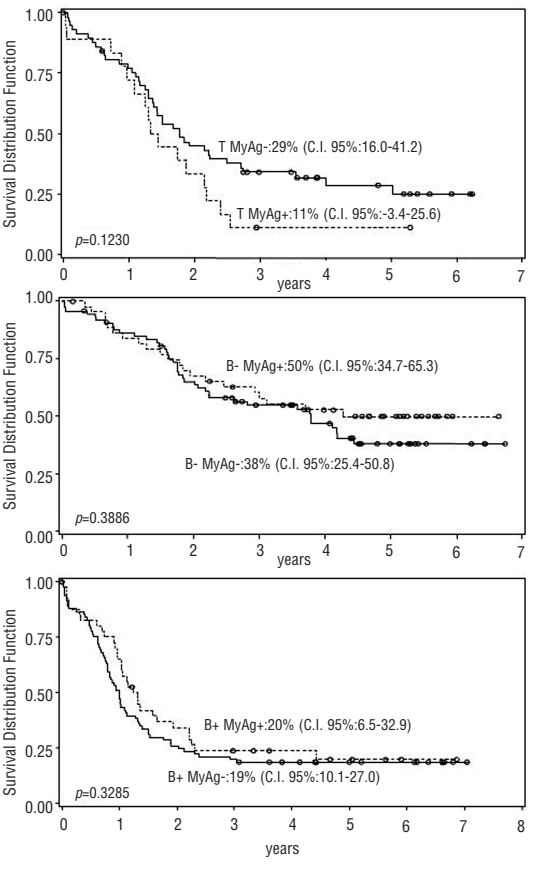

Figure 2. **Overall survival.**

Discusssion

The prognostic value of MyAg expression in adult ALL is still a controversial issue. The relatively small numbers of patients in adult ALL series and differences in the treatment protocols have led to divergent results. Sobol *et al.*[4] observed MyAg expression in 33% of 76 patients with adult ALL treated with the 8011, 8411 and 8513 CALGB protocols, and found significantly lower CR rates (35% vs 76%) in the MyAg$^+$ group. Urbano-Ispizua *et al.*[5] and Guyotat *et al.*[6] observed similar results analyzing 62 and 41 patients with adult ALL, respectively. Boldt *et al.*[2] studied 113 patients treated with the L10M regimen and reported that the mortality rate was higher among MyAg$^+$ patients than in MyAg$^-$ ones (p=0.013). Preti *et al.*[3] analyzed 164 adult ALL cases treated with the VAD protocol and did not observe statistical differences in remission duration or survival between MyAg$^+$ and MyAg$^-$ patients. Another study conducted by Larson *et al.*,[7] which included 197 adult ALL patients treated with the Hyper-C-VAD protocol, suggested that the co-expression of MyAg did not affect CR rate, nor CR duration if intensive treatment were utilized. Czuczman *et al.*[8] evaluated the prognostic value of immunophenotype in 259 adult patients with ALL in the CALGB 8364 study and concluded that the expression of MyAg had no significance on outcome.

In the present study we examined the impact of aberrant MyAg expression on prognosis in a cohort of 377 adult patients treated uniformly with the GIMEMA ALL 0496 protocol, the largest series so far investigated. The presence of MyAg was correlated with a number of clinical and biological data. Among the clinical data, a difference was found only for white cell count (p=0.03), percentage of peripheral blasts (p=0.004) and platelet count (p=0.004). Among the biological data, there was a statistical difference in the incidence of aberrant MyAg expression between B-lineage ALL and T-ALL subgroups (p=0.02), and a significant association with the expression of the CD34 antigen (p<0.0001). We have previously reported[18] that in T-ALL patients MyAg positivity and/or CD34 positivity and/or MDR positivity (as evaluated by function) shows a highly negative association with CR achievement. The same association in the subgroup with B-lineage ALL did not correlate with response to therapy. We separately analyzed the presence of MyAg in T and B-lineage ALL cases, and failed to find any difference in CR achievement, OS or DFS.

Even if the absence of MyAg expression was strictly associated with the *ALL1/AF4*$^+$ rearrangement (p<0.0001), the small number of patients prevents any firm conclusions from being reached. Besides, in univariate analysis, we found no significant differences in CR, DFS and OS between the MyAg$^+$ and MyAg$^-$ groups with *BCR/ABL* and *E2A/PBX1* rearrangements. In addition, we also analyzed the value of CD34 antigen as a separate parameter and found no prognostic significance in either univariate

or multivariate analysis.

The overall incidence of MyAg expression in our study (35%) is in line with the data reported in the literature. Our results suggest that there are no differences between MyAg+ and MyAg- groups in terms of CR, DFS and OS, in either B- or T-lineage ALL. These findings are likely to be due to the more intensive treatment modalities adopted in the GIMEMA ALL 0496 protocol which is characterized by high-dose daunorubicin during the induction phase and by high-dose aracytin in the post-remission phase. In conclusion, when analyzed homogeneously and prospectively in a large cohort of uniformly characterized and treated adult ALL cases, the expression of MyAg alone does not bear short and long-term prognostic significance. Nonetheless, the evaluation of the expression of these antigens and the level of antigenic expression remains valuable for a more precise characterization of the leukemic population in each individual patient. This has clinical implications in terms of therapeutic decisions (e.g. anti-CD33 treatment) and for monitoring minimal residual disease during the course of the disease.

Appendix

The following members of the GIMEMA group participated in this study: U.O.A. di Ematologia, Ospedale S.S. Antonio e Biagio, Alessandria, Alessandro Levis; Istituto di Ematologia, Nuovo Ospedale "Torrette", Ancona, Pietro Leoni; Servizio di Ematologia, Azienda Ospedaliera "S.G. Moscati", Avellino, Nicola Cantore; Centro di Riferimento Oncologico, Aviano, Umberto Tirelli; Istituto di Ematologia, Università di Bari, Bari, Vincenzo Liso; Istituto di Ematologia "L. e A. Seràgnoli", Bologna, Michele Baccarani; Divisione di Ematologia, Azienda Ospedaliera "A. Di Summa", Brindisi, Giovanni Quarta; Cattedra di Ematologia, Ospedale "Ferrarotto", Catania, Rosario Giustolisi; Divisione di Ematologia, Ospedale Regionale "A. Pugliese", Catanzaro, Antonio Peta; Divisione di Ematologia, Ospedale "S. Croce", Cuneo, Andrea Gallamini; Sezione di Ematologia, Arcispedale "S. Anna", Ferrara, Gianluigi Castoldi; Divisione di Ematologia, Policlinico di Careggi, Firenze, Alberto Bosi; Divisione di Medicina, Ospedale "S. Antonio Abate", Gallarate, Ruggero Mozzana; Dipartimento di Medicina Interna, Ospedale "S. Martino", Genova, Riccardo Ghio; Ematologia ed Autotrapianto di Midollo, Ospedale "S. Martino", Genova, Michele Carella; Divisione di Ematologia, Ospedale "S. Maria Goretti", Latina, Angelo De Blasio; Divisione Medica, Ospedale Maggiore, Lodi, Giulio Nalli; Divisione di Ematologia, Ospedale Niguarda "Ca Granda", Milano, Enrica Morra; Dipartimento di Scienze Mediche, Oncologiche e Radiologiche, Policlinico, Modena, Giuseppe Torelli; Ematologia, Ospedale, Montefiascone, Marco Montanaro; Ematologia, Università Federico II, Napoli, Bruno Rotoli; Divisione di Ematologia e Trapianto di Midollo, Ospedale "A. Cardarelli", Napoli, Felicetto Ferrara; Ospedale S. Giovanni Bosco, Napoli, Eustachio Miraglia; Divisione di Ematologia, Ospedale "A. Cardarelli", Napoli, Vincenzo Mettivier; Sezione di Ematologia Clinica, Ospedale "S. Francesco", Nuoro, Attilio Gabbas; Divisione di Ematologia, Ospedale "S. Luigi Gonzaga", Orbassano, Giuseppe Saglio; Divisione di Ematologia, Istituto di Clinica Medica, Palermo, Pietro Citarrella; Divisione di Ematologia, Ospedale "V. Cervello", Palermo, Salvatore Mirto; Divisione di Ematologia, Università degli Studi, Palermo, Vincenzo Abbadessa; Medicina Interna ed Oncologia Medica, IRCCS San Matteo, Pavia, Edoardo Ascari; Istituto di Ematologia, Policlinico Monteluce, Perugia, Massimo Martelli; Divisione di Ematologia, Ospedale San Salvatore, Pesaro, Giuseppe Visani; Divisione di Ematologia, Ospedale Civile "S. Salvatore", Pescara, Giuseppe Fioritoni; Divisione di Ematologia, Ospedale S. Carlo, Potenza, Michele Pizzuti; Servizio di Ematologia, Azienda Ospedaliera "Bianchi-Melacrino-Morelli", Reggio Calabria, Francesco Nobile; Servizio di Ematologia, Arcispedale "S. Maria Nuova", Reggio Emilia, Luigi Gugliotta; Divisione di Ematologia, Dipartimento di Biotecnologie Cellulari ed Ematologia, Università "La Sapienza", Roma, Robin Foà; Divisione di Ematologia, Università Cattolica del Sacro Cuore, Roma, Giuseppe Leone; Divisione di Ematologia, Università degli Studi di Tor Vergata; Roma, Sergio Amadori; Servizio di Ematologia, Università di Sassari, Sassari, Maurizio Longinotti; Divisione di Ematologia, Ospedale Casa Sollievo della Sofferenza, S. Giovanni Rotondo, Nicola Cascavilla; Cattedra e UO di Ematologia, Università degli Studi – Azienda Ospedaliera "A. Sclavo", Siena, Francesco Lauria; Divisione di Medicina Generale – Ematologia, Ospedale "E. Morelli", Sondalo, Alessandro Pastorini; Ematologia, Ospedale "S.S. Annunziata", Taranto, Patrizio Mazza; Ematologia, Azienda Ospedaliera "S. Giovanni Battista", Torino, Eugenio Gallo; Ematologia, Università degli Studi, Torino, Mario Boccadoro; Divisione di Ematologia, Ospedale Policlinico Borgo Roma, Verona, Giovanni Pizzolo.

Authors' Contributions

AV: wrote the manuscript, coo-rdinated central sample handling, analyzed immunologic data, revision of statistical data; AG: analyzed immunologic data, revised the manuscript; CA: central sample handling, revision of statistical data; GM: patient management, provided clinical samples and clinical information; OP: analyzed immunologic data; MP: patient management, provided clinical samples and clinical information; CFG: patient management, provided clinical samples and clinical information; VM: patient management, provided clinical samples and clinical information; AP: patient management, provided clinical samples and clinical information; GP: analyzed immunologic data, revised the manuscript; MV: writing and design of the protocol, collection and statistical analyses of the data; FM: GIMEMA chairman; RF: designed research and supervised the manuscript, biological study coordinator.

Conflict of Interest

The authors reported no potential conflicts of interest.

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