Original Study

Elderly Patients (Age 70 Years or Older) With Secondary Acute Myeloid Leukemia or Acute Myeloid Leukemia Developed Concurrently to Another Malignant Disease

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Abstract

This study gives a detailed description of acute myeloid leukemia (AML) following another malignancy in a single-center cohort of patients with AML aged 70 and older. The most important finding is the lack of independent prognostic impact of secondary AML in elderly patients.
Introduction: Secondary acute myeloid leukemia (sAML) remains a therapeutic challenge. In elderly patients with AML, it is unclear whether sAML displays an inferior outcome compared with de novo AML. **Patients and Methods:** We studied AML with an antecedent of hematologic disease, treatment-related AML, or AML occurring concurrently to another malignancy in a single-center cohort of patients aged 70 and older with AML. The study included 169 patients who were compared with a cohort of patients with de novo AML, without any prior history of malignant disorders, seen during the same period of time. **Results:** Hematologic antecedents or presence of prior/concurrent solid malignancy did not impact complete remission rates and overall survival. In multivariate analysis, sAML appeared without independent prognostic value in the elderly. **Conclusion:** Our results support that sAML and de novo AML in elderly patients are not prognostically distinct entities. They should therefore not be considered separately when investigating outcomes and new treatment strategies.

Introduction

The median age at diagnosis of acute myeloid leukemia (AML) ranges between 68 and 72 years. Incidence increases with age and is about 12 cases per 100,000 for those at and above 70 years of age.[1] AML in the elderly is a clinical entity distinct from AML in younger adults or children. Poor outcome is the result of treatment-related

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toxicity in elderly patients, owing to comorbidities, biologically poor risk prognosis, and a higher possibility of other hematopoietic disorders.[2]

Secondary AML (sAML) represent a heterogeneous and poorly defined category of disease entities. They are well-recognized subtypes of AML, which increase in frequency with age,[3] and have previously been associated with inferior outcomes compared with de novo AML.[4] They refer to AML developing after an antecedent of hematologic disorder (AHD-AML) (myelodysplastic syndrome [MDS], chronic myelomonocytic leukemia [CMML], myeloproliferative neoplasia [MPN] [excluding chronic myeloid leukemia]) regardless of prior cytotoxic therapy for these disorders. They also include therapy-related AML secondary to a proven leukemogenic chemotherapeutic and/or radiotherapy exposure (t-AML).[5] Besides these 2 AML categories, we can individualize another group of older patients with AML presenting with a prior or concurrent history of

solid tumor, but not treated by chemo/radiotherapy (pc-AML) and therefore not entering into the definition of sAML.

As these 3 subgroups represent separate entities, they were analyzed mainly separately. In this study, our objectives were to estimate and compare incidences and latency times in AHD-AML, t-AML, and pc-AML in patients age 70 years or older, and to compare these entities with de novo AML not associated with another malignant disease in order to describe their differences in terms of characteristics, treatment, and outcome.

Patients and Methods

Patients and Study Groups

A retrospective chart review was performed to evaluate older patients (≥ 70 years old) with newly diagnosed AML (including acute promyelocytic leukemia [APL]) who were treated in the Department of Hematology at Lyon University Hospital from July 1986 to June 2014.[6] AML was defined by the presence of at least 20% myeloblasts in the bone marrow.[7] The presence of primary malignant disease was captured at baseline on case report forms. The patients with prior or concurrent history of malignant disease were grouped into 4 study cohorts: (1) AHD-AML, comprised of MDS-sAML and non-MDS-sAML. MDS-sAML was defined as a diagnosis of MDS recorded at least 3 months before the AML diagnosis.[3] Non-MDS-sAML was defined as a previous diagnosis of CMML, MPN, or other hematologic disorder of nonlymphoid origin recorded more than 3 months before the AML diagnosis.[3] (2) t-AML was defined as sAML caused by exposure to any cytotoxic agent or radiotherapy, regardless of dose or the time of exposure.(3) AML discovered concurrently to another malignant disease or after another malignant disorder not exposed to chemo/radiotherapy (pc-AML) were also registered.(4) A fourth group was represented by patients with AML patients with a prior history of malignant disease, but with unknown or incomplete data regarding potential prior treatment conditions (u-AML). A fifth group, represented by patients with de novo AML not associated with another malignant disease, was used as a control cohort. All baseline characteristics were measured at time of diagnosis. Patients developing MDS between the chemotherapy or radiation treatment for their primary disease and the diagnosis of AML were classified as t-AML. Patients treated with chemotherapy or novel molecules for their MPN or MDS were classified as AHD-AML.

Treatments

Treatment varied according to treatment period and patient's physical condition evaluated by the referent physician. The patients were grouped into several cohorts according to their treatment regimen:(1) The first group included patients who were treated on front-line by anthracycline- (or anthracenedione) and cytarabine-based intensive chemotherapy regimens.[8] Patients who achieved complete remission after 1 or 2 courses of induction were given consolidation chemotherapy according to the protocol design in which they were included. Among this group, patients with APL also received all-trans retinoic acid during induction therapy.[2] The second study group was comprised of patients who were treated on front-line by lower-intensity treatments: low-dose cytarabine (LD-AraC)[9] or hypomethylating agents (HMAs) (azacitidine or decitabine).[10,11] Patients received LD-AraC at 20 mg once or twice

daily (according to physician's choice) by subcutaneous injection for 10 consecutive days. Azacitidine was given at the dose of 75 mg/m^2/day for 7 consecutive days by subcutaneous injection. Decitabine was administered by intravenous route once daily at 20 mg/m^2 for 5 consecutive days. Subsequent courses of low-intensity treatment were administered after intervals of 4 to 6 weeks until disease progression. (3) A third group included few patients treated in investigational trials using novel agents: tipi-farnib,[12] or lenalidomide.[13] (4) The last group was comprised of patients only treated by best supportive care. Policies with regard to blood product support, antibiotics and anti-fungal prophylaxis, and treatment of febrile neutropenia were determined by established local practice.[6] Best supportive care consisted only in the application of these policies plus eventually the administration of hydroxyurea or 6-mercaptopurine in order to control white blood cell (WBC) count in case of proliferative disease. All clinical trials received approval from the institutional review board and were conducted in accordance with the Declaration of Helsinki. All participants gave their written informed consent.

Cytogenetic Risk Classification

Cytogenetic risk was classified as 'favorable,' 'intermediate,' 'unfavorable,' or 'indeterminate' according to the following definitions.[14] The favorable risk category included patients with t(15;17), inv(16)/t(16;16)/del(16q), or t(8;21) with or without additional abnormalities. The intermediate risk category included patients characterized by +8; −Y; +6; del(9q); del(12p) or normal karyotype. The unfavorable risk category was defined by the presence of one or more of −5/del(5q); −7/del(7q); inv(3q)/t(3;3); abnormal 20q or 21q; translocation involving 11q23, t(6;9); t(9;22); abnormal 17p or complex karyotype, defined as 3 or more chromosomal abnormalities. We did not include the mutational status in our study analysis because we did not have molecular information for a large proportion of our patients, most of which were treated in the pre-mutation profiling era of AML.[15]

Statistical Analyses

Descriptive statistics were used to characterize patients and their disease. Descriptive data were stratified by type of AML and treatment. Latency time was defined as time from first hospital contact for the preceding disease of interest to date of AML diagnosis. Differences among variables were compared by the χ^2 tests and Wilcoxon rank sum tests for categorical and continuous variables. Study endpoints included the complete response (CR)/CR with low platelets (CRp) according to the international criteria,[16] the overall survival (OS), and the 2-month mortality rate. CR was defined according to standard criteria as less than 5% blasts in bone marrow aspirates with evidence of maturation of cell lines and restoration of peripheral blood counts.[14] Hematologic relapse was considered when more than 5% blasts were seen in 2 bone marrow aspirates obtained at a 15-day interval. OS was calculated from the time of AML diagnosis to the date of death or was censored at the time of the last follow-up if the patient was alive.

Estimated probabilities of survival were calculated using the Kaplan-Meier method, and the log-rank test evaluated differences between survival distributions. Variables showing significant differences by univariate analyses were included in the multivariate