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To the editor:

Statin and aspirin use is associated with improved outcome of FCR therapy in relapsed/refractory chronic lymphocytic leukemia

Statins and aspirin are widely prescribed medications that have long been associated with improved survival outcome in patients with various types of cancers.1,2 Both statins and aspirin were found to induce apoptosis of chronic lymphocytic leukemia (CLL) cells.3,4 The intake of statins and aspirin was associated with reduced incidence of CLL.5,6 However, statin intake did not affect treatment-free survival in patients with early CLL.7,8 Whether statin or aspirin use will benefit patients with advanced CLL is unknown.

Therefore, we retrospectively investigated the clinical outcome of patients with relapsed/refractory CLL treated with salvage fludarabine, cyclophosphamide, and rituximab (FCR)9 with or without concomitant statins, aspirin, or both. We analyzed 280 patients who received salvage FCR between 1999 and 2012. The patients’ median age was 59 years (range: 31-84). The median progression-free survival (PFS) of all patients was 1.7 years, and the median overall survival (OS) was 4.0 years. Of the 280 patients, 58 patients received statins, aspirin, or both; 21 (8%) were taking aspirin only; 17 (6%) statins only; and 20 (7%) used both for at least 1 month prior to, during, and 1 month after salvage therapy. Among statin users, 15 patients (41%) were using atorvastatin, 12 patients (32%) were using simvastatin, 7 patients (19%) were using pravastatin, 2 patients (5%) were using rosuvastatin, and 1 patient (3%) was using lovastatin. Clinical characteristics of statin and/or aspirin users were similar to those of nonusers except for age. Patients on both statin and aspirin were 6 years older than nonusers ($P < .01$).

The overall response rate of patients receiving statins and aspirin concomitantly was superior (100%; 40% complete response, 60% partial response) to that of other patients (81% for aspirin-only users, 82% for statin-only users, and 72% for those who took neither drug; $P < .01$). Early death (during chemotherapy and up to 6 weeks afterward) was not observed in patients receiving aspirin, statins, or both but occurred in 6% of nonusers. Patients receiving both statins and aspirin had median PFS and OS of 6.1 and 9.2 years, respectively, compared with 1.6 years and 3.7 years in nonusers (PFS $P = .003$; OS $P = .05$; Figure 1). Compared with nonusers, patients who took both statins and aspirin had a 66% reduced risk of disease progression and a 60% reduced risk of death (PFS hazard ratio [HR] = 0.34, 95% confidence interval [CI] = 0.18-0.65, $P < .001$; OS HR = 0.40, 95% CI = 0.21-0.79, $P = .008$).

In a fitted multivariate model controlling for clinicopathological characteristics found to be statistically significant from univariate analyses including Rai stage, cytogenetic abnormalities, the number of previous treatments, refractoriness to fludarabine, IgVH mutation status, β2-microglobulin, hemoglobin, platelet, lactate dehydrogenase, and creatinine level, use of both medications was also associated with a much more favorable outcome (PFS adjusted HR = 0.27, 95% CI = 0.14-0.53, $P = .001$; OS adjusted HR = 0.29, 95% CI = 0.15-0.58, $P < .001$), whereas single-agent use of aspirin or statins did not affect PFS or OS.

Our findings demonstrate for the first time that concurrent administration of statins and aspirin to CLL patients with relapsed/refractory disease receiving salvage FCR significantly improve both response rate and survival. This is consistent with previous preclinical studies suggesting the possible synergistic effect between statins and chemotherapy.10 Therefore, a prospective study aimed at evaluating the effects of statins and aspirin in CLL patients receiving chemoimmunotherapy is warranted.

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Figure 1. Kaplan-Meier estimates for PFS and OS by aspirin and statin use. Patients receiving both statins and aspirin (n = 20) had a median PFS (A) and OS (B) of 6.1 years and 9.2 years compared with 1.6 years and 3.7 years for patients on neither medication (n = 221) (PFS P = .003; OS P = .05). The number of events per total number of patients is denoted in the box. The P value was derived from a log-rank test.

Y.K.C. and L.T. contributed equally to this study.

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References

To the editor:

Mutations in GATA2 are rare in juvenile myelomonocytic leukemia

GATA2 encodes a transcription factor that regulates hematopoiesis and vascular development, and germline mutations cause MonoMAC syndrome,1,2 Emberger syndrome,3 and some cases of mild chronic neutropenia.4 Patients with each of these disorders are predisposed to myelodysplastic syndrome (MDS) and acute myeloid leukemia that is frequently associated with somatic acquisition of monosomy 7.5,6

Juvenile myelomonocytic leukemia (JMML) is an aggressive childhood malignancy with overlapping features of an MDS and myeloproliferative neoplasm (MPN) that is caused by mutations that aberrantly activate Ras/MAPK signaling. Mutations in NF1, NRAS, KRAS, PTPN11, and CBL are found in 85% to 90% of newly diagnosed patients.7,8 Given the frequent occurrence of somatic monosomy 7 in JMML as well as the fact that there are several germline syndromes that predispose children to developing both transient and aggressive forms of JMML, we hypothesized that mutations in GATA2 play a role in its development.

Specimens from 57 patients with JMML were screened for GATA2 mutations. Patient samples and clinical data were collected from the Children’s Oncology Group trial AAML0122.9 DNA was extracted from peripheral blood or bone marrow as per previous protocols and whole genome amplified using Qiagen REPLI-g kits. We performed bidirectional Sanger sequencing (Beckman Coulter Genomics, Danvers, MA) of the entire coding region of GATA2 (NM_001145661.1) and aligned the sequences using CLC software (CLC Bio, Aarhus, Denmark). Only missense, splice site, or nonsense mutations were evaluated using SIFT (Sorting Tolerant from Intolerant)10 to predict the impact of identified mutations on the structure and function in the resultant protein.

GATA2 was mutated in only 1 of 57 JMML specimens. Peripheral blood from patient J384 contained a nonsense point mutation at c.988C>T (R330X), which has been reported as a germline mutation in patients with mild chronic neutropenia.4 Patient J384 also carried a second missense point mutation at c.962T>G (L321R), which was predicted to be damaging by SIFT, PolyPhen 2.0, and Mutation Assessor. Subcloning of the mutant amplicon using a TA cloning kit with pCR 2.1 vector (Invitrogen) followed by directed sequencing of individually transformed colonies revealed that the 2 sequence variants only occurred in a trans configuration. Out of 40 amplicons sequenced, 20 displayed the c.988C>T transition, 16 had the c.962T>G variant, and 4 were wild-type. We therefore hypothesize that c.988C>T was inherited as a germline event, whereas c.962T>G represents a somatic acquisition. Unfortunately, granulocyte-macrophage progenitor colonies at diagnosis were not available for analysis, nor was parental DNA. Previous studies of patient J384 revealed a subclonal KRAS G12D mutation (c.35G>A) as well as monosomy 7 in his JMML bone marrow.

Patient J384 met the World Health Organization diagnostic criteria for JMML based on having splenomegaly, an absolute monocyte count >1000 (1 × 10⁹/L), <20% bone marrow blasts, absence of t(9;22) or BCR/ABL, and presence of myeloid precursors in peripheral blood with a white blood cell count >10 000 (10 × 10⁹/L).9 However, he also possessed features less common in JMML, including older age at diagnosis (4 years and 10 months) and, in particular, a normal response in myeloid progenitor cells to the cytokine granulocyte-macrophage colony-stimulating factor in methylcellulose culture, which is rarely seen in JMML.11

We speculate that a somatic “second hit” in the normal GATA2 allele accelerated the onset of MDS in patient J384, with monosomy 7 and the oncogenic KRAS mutation cooperating to drive clonal evolution.

Figure 1. Identification of 2 distinct GATA2 mutations in patient J384. (A) Bidirectional sequencing of patient sample J384 revealed 2 distinct sequence variants in both the forward (shown here) and reverse strands. Sequencing of 40 individual colony picks after subcloning revealed that each sequence variant occurred in a trans configuration (CP9 and CP13 are shown here as examples). In addition, 10% of colony picks (ie, CP32) revealed a wild-type sequence, indicating that at least 1 of the 2 variants was a somatic event. (B) Schematic representation of the GATA2 gene highlighting the proposed germline and somatic mutations identified in patient J384. Both mutations are present in coding region 3, which translates to the zinc finger 1 region of the protein.
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