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ORIGINAL ARTICLE

Prospective comparison of 5- and 7-day administration of azacitidine for myelodysplastic syndromes: a JALSG MDS212 trial

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Abstract

The hypomethylating agent azacitidine (AZA) significantly extends overall survival (OS) in patients with higher risk myelodysplastic syndromes (MDS), when compared with other conventional care regimens, including supportive care and low-dose and intensive chemotherapy. However, the effects of 5- and 7-day treatment schedules of AZA (AZA-5 and AZA-7, respectively) on the OS of MDS patients had not been compared prospectively. We started a phase 3 trial comparing the effects of AZA-7 and AZA-5 on MDS patients with refractory anemia with excess blasts (RAEB) and RAEB in transformation (RAEB-T). However, this trial was prematurely terminated because of poor recruitment. Using all data, there was no significant difference in the OS of patients between AZA-7 (92 patients) and AZA-5 (95 patients), with the 2-year OS rates of AZA-7 and AZA-5 at 36.4% and 25.8%, respectively ($P=0.293$). Adverse event profiles were similar between the two groups. Interestingly, data of the centrally diagnosed RAEB and RAEB-T cases showed that AZA-7 significantly prolonged the time to leukemia transformation compared with AZA-5 ($P=0.022$), confirmed by multivariate analysis. Although this trial could not provide definite evidence, the results support the use of AZA-7 for RAEB and RAEB-T. (UMIN Clinical Trials Registry UMIN000009633).

Keywords Azacitidine · Myelodysplastic syndromes · Higher risk · Treatment schedule · Leukemia transformation

Introduction

The treatment for myelodysplastic syndromes (MDS) has drastically improved with the introduction of hypomethylating agents (HMAs) such as azacitidine (AZA) and decitabine [1]. A pivotal phase 3 trial of AZA for higher risk MDS, the AZA-001 study, in which an AZA dose of 75 mg/m^2 was administered for 7 days (AZA-7) in a 28-day cycle, clearly demonstrated the survival benefit of AZA treatment over the conventional care regimens, including classical intensive chemotherapy, low-dose chemotherapy, and supportive care [2]. AZA also significantly prolonged the time to transformation to acute myeloid leukemia (AML) in the same study. On the basis of these data, AZA has been preferred as the first-line treatment for higher risk MDS patients who are ineligible for allogeneic hematopoietic stem cell transplantation (allo-HSCT). This is the first trial that prospectively demonstrated the survival benefit of a medication for higher risk MDS. Since then, the treatment schedule of AZA administration has been explored in several prospective and retrospective studies. A randomized phase 2 study comparing 5-day AZA (AZA-5) and AZA-7 administration showed similar hematological response rates between the two schedules for patients with lower and higher risk MDS, but those undergoing AZA-5 had less hematological toxicities and infectious events [3]. Another phase 2 trial

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