



Results of a Randomized Study of Three Schedules of Low-dose Decitabine

In Higher Risk Myelodysplastic Syndrome and Chronic Myelomonocytic Leukemia

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Epigenetic therapy with hypomethylating drugs is now standard of care for patients with myelodysplastic syndrome (MDS), though response rates remain low, and mechanism-based dose optimization has not been reported.

We have investigated the clinical and pharmacodynamic results of different dose-schedules of decitabine. Adults with advanced MDS or chronic myelomonocytic leukemia (CMML) were randomized to one of 3 decitabine schedules:

- 1) 20 mg/m² IV daily x 5;
- 2) 20 mg/m² SQ daily x 5; and
- 3) 10 mg/m² IV daily x 10.

Randomization followed a Bayesian adaptive design favoring the arm associated with higher complete response (CR) rates. Global methylation was measured by bisulfite pyrosequencing of LINE1 repeats and P15 expression was measured by qPCR.

Ninety-five patients were treated (77 with MDS, all with IPSS score >1.0, 18 with CMML). Median age was 65 years and median MDS duration was 3.2 months.

Overall 32 patients (34%) achieved CR, and 69 patients (72%) had an objective response by the new modified International Working Group criteria.

The 5-day IV schedule, which had the highest dose-intensity, was selected as optimal after the 65th patient; the CR rate in that arm was 39%, compared to 21% in the 5-day SQ arm and 24% in the 10 day IV arm ($p < 0.05$). The high dose-intensity arm was also superior at inducing hypomethylation at day 5 and at activating P15 expression at days 12 or 28 after therapy.

We conclude that a low-dose, high dose-intensity schedule of decitabine optimizes epigenetic modulation and clinical responses in MDS. **OA**