Continuous high dosing of lenalidomide in relapsed, refractory or older newly diagnosed acute myeloid leukemia patients not suitable for other treatment options - results from a phase I study

Lenalidomide is an immunomodulatory drug approved for multiple myeloma, relapsed mantle cell lymphoma and myelodysplastic syndrome (MDS) with deletion of chromosome 5q (del(5q)). Based on the high rate of hematologic improvement and cytogenetic responses seen in del(5q) MDS, several trials have been conducted with lenalidomide in acute myeloid leukemia (AML) and high-risk MDS irrespective of the presence of del(5q). A response rate of 30% in a high dosing schedule was reported in older newly diagnosed AML patients.[1] In contrast, in a phase I trial with refractory and relapsed (r/r-) AML patients, the response rate was lower and a high toxicity was observed when lenalidomide was given at higher doses of up to 75 mg/day over a 21-day time period.[2]

Based on the initial encouraging reports,[3,4] we performed a phase I dose escalating (3+3 design) study with single agent continuous lenalidomide. Patients with either relapsed/refractory AML or older patients with newly diagnosed AML (age >60 years) unfit for intensive treatment were eligible. *clinicaltrials.gov identifier 00839059.*

Standard in- and exclusion criteria for phase I dose-escalation trials were used including the absence of polyneuropathy at enrolment; out-patient treatment was intended. The starting dose was 25mg lenalidomide/day as continuous treatment until complete remission (CR), dose-limiting toxicity (DLT) or day 56.

Between March 2009 and June 2010, 14 patients (median age 71.5 years, range 35-83 years) were enrolled and 12 patients (1 screening failure, 1 rapidly progressive disease) were treated in 2 dose levels (25 mg, 50mg). Eight patients were male, 8 patients had r/r-AML, and 4 patients had newly diagnosed AML. Median number of prior lines of therapies was 1 (range 0-5), 8 patients (67%) had adverse cytogenetics including 5 cases with del(5q) and 4 had a normal karyotype; median white blood cell count at study entry was 3.5 G/l (range 0.7-27.3 G/l).

Five patients were treated at a dosage of 25mg/day without DLT and, subsequently, 7 patients at a dosage of 50mg/day. At a dosage of 50mg/day, 2 DLTs were observed with polyneuropathy CTC AE grade III. This is in contrast to other phase I trials with lenalidomide in AML where haematological toxicities or fatigue were dose limiting. No cytokine release syndrome was seen within the trial, but 2 patients developed drug hypersensitivity reaction CTC AE grade III with eyelid edema.

Only 7 patients (58%) were eligible for first response evaluation at day 22; the other 5 patients dropped out before due to rapid progressive disease (n=3) or severe infectious complications (n=2; urosepsis and pneumonia). None of the patients achieved a PR or CR. In 1 patient, a decrease in bone marrow blasts from 40% to 15% and blast clearance in peripheral blood was documented; treatment was discontinued at day 47 based on worsening of anemia and thrombocytopenia to CTC grade 4 and heavily impaired quality of life. Overall, treatment discontinuation was due to progressive disease (n=7), DLT (n=2), worsening of general condition (n=1), patient's wish (n=1) and death (n=1). Ten patients were hospitalized during treatment due to serious adverse events not manageable in an outpatient setting. The 30-day and 60-day mortality was 42% (5/12) and 50% (6/12), respectively. At day 140 after study entry, the last patient had died.

Our results are in line with the data from Zeidan *et al.*, showing poor feasibility and outcome of higher dosages of lenalidomide in AML.[5] DLT in our study was polyneuropathy CTC AE grade III, which has not been observed in other studies evaluating higher dosages of lenalidomide.

A combination therapy of low-dose lenalidomide with low– or intermediate-dose cytarabine showed feasibility but only minimally superior results compared to single agent treatment with cytarabine in two phase-I/II single arm trials.[6,7]

Recently, the combination treatment of a hypomethylating agent and lenalidomide was reported in AML.[8] In a randomized 3-arm study, lenalidomide was administered at a high dosage as monotherapy (50mg/day for 28 days in the first 2 cycles) or sequentially to azacytidine. Again, poor tolerability and low efficacy was reported in this elderly population with newly diagnosed AML.

The high sensitivity of del(5q) MDS to lenalidomide results from haploinsufficiency of casein kinase 1A1 (*CSNK1A1*) and degradation of this protein induces apoptosis by activating *TP53*.[9] Therefore, a prerequisite for the specific activity of lenalidomide in myeloid malignancies is a heterozygous deletion on chromosome 5 comprising the *CSNK1A1* gene as well as an intact *TP53* pathway. However, in contrast to MDS, deletion of chromosome 5 in AML is highly associated with *TP53* mutations, providing a mechanistic explanation as to why lenalidomide has no activity in AML.

In conclusion, our results add to previous knowledge that high dose lenalidomide in relapsed and refractory as well as elderly treatment naïve AML is not feasible and has limited efficacy as single agent therapy.

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