High dose Simvastatin does not reverse resistance to Vincristine, Adriamycin, and Dexamethasone (VAD) in Myeloma

In a prospective phase II study, we evaluated the combination of high dose simvastatin and VAD chemotherapy in patients with refractory or relapsed multiple myeloma. Although treatment was feasible with mild side effects, only 1 of 12 patients achieved a partial response. According to our predefined criteria this was insufficient to continue the study.

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Letter to the Editor

Simvastatin is a HMG-CoA-Reductase inhibitor widely used for the treatment of

hypercholesterolemia. In vitro, statins are cytotoxic against myeloma cells by inducing apoptosis and inhibiting proliferation. We previously showed synergistic activity of simvastatin with doxorubicin and dexamethasone in vitro.[1] In a recent phase I study of simvastatin combined with chemotherapy in relapsed or refractory myeloma and lymphoma patients, the maximum tolerated dose of simvastatin was 15 mg/kg/day for 7 days.[2] Dose limiting toxicities were gastrointestinal complaints and neutropenic fever.

To further explore its potential anti-myeloma activity, and to confirm the feasibility of the phase I study, we conducted a phase II study of high dose simvastatin combined with chemotherapy in patients with relapsed or refractory multiple myeloma. Patients under the age of 75 years were eligible if they had received at least 2 lines of chemotherapy which included anthracyclines and dexamethasone and had acceptable organ function (total bilirubin and transaminases ≤2 x upper limit of normal and creatinine clearance ≥40 mL/min, no severe cardiac dysfunction).

Simvastatin 15 mg/kg/day was prescribed orally on days 1-7 of a 28 day cycle, divided into two daily dosages, followed by rapid intravenous infusion of vincristine (0.4 mg) and doxorubicin (9 mg/m^2) and dexamethasone 40 mg (VAD) orally on day 7 to 10. Response according to EBMT criteria was determined after 2 cycles. In case of stable disease or response, 2 additional courses could be given. In case of progressive disease during therapy, treatment was discontinued. All patients received prophylactic treatment with cotrimoxazole. The protocol was approved by the Medical Ethical Board of our hospital and all patients signed informed consent before start of treatment.

Based on literature,[3] we defined that for this category of patients a response rate (defined as complete response plus partial response) below 10%, and a non-haematological toxicity rate WHO grade 3-4 larger than 30% would be unacceptable. Using Fleming's two-stage design, 40 patients were needed, with a planned interim analysis after 12 patients. Accrual would stop if less than 2 responses were observed after 12 patients.

The median age of the first 12 patients was 64 years (range 38-71). They received a median of 4 (range 2-6) previous anti-myeloma treatments. Seven were VAD resistant before study entry. A median of 3 study cycles (range 1-4) was given. Evaluation showed a PR in 1 patient, stable disease in 6 patients, and progressive disease in 5. Among patients with stable disease, 5 out of 6 had progressive disease before study treatment. Two of them reported a marked reduction of pain, already during simvastatin treatment alone. One patient had a plasma cell leukaemia that was stable during treatment, but rapidly progressed after the end of the study. Patients with stable disease remained stable during a median of 103 days (range 94-258 days). The patient with the partial response relapsed after 230 days from start of treatment. According to our predefined criteria, one partial response was insufficient to continue the study and accrual was stopped.

The main adverse event was hematological toxicity. WHO grade 3-4 neutropenia occurred in 8 patients and grade 3-4 thrombocytopenia in 2 patients. This effect was more prominent in the second course. No neutropenic fever occurred. One patient experienced grade 3 gastro-intestinal toxicity with dehydration due to nausea and vomiting after the first treatment cycle. No other toxicities ≥ grade 3 were observed, especially no rhabdomyolysis.

To our knowledge, this is the first clinical study with high dose statins in myeloma. Although statins are very effective in vitro, high dose simvastatin in vivo did not convincingly reverse clinical resistance to VAD chemotherapy. An explanation for this finding may be that although plasma levels of statins that are effective in vitro can be reached in vivo,[4] these levels should probably be maintained for a prolonged period of time. Such prolonged high serum levels may not have been achieved in our patients due to the short half life of simvastatin. Possibly, simultaneous rather than subsequent treatment with anti-myeloma agents proves to be a more effective regimen. Alternatively, heavily pretreated patients may have developed multiple anti-apoptotic pathways, which are not all influenced by statins.

In conclusion, our design of high dose statins followed by VAD chemotherapy in refractory myeloma can not be recommended for further exploration. Other strategies are required to determine if statins deserve a place in the treatment of myeloma. These strategies include prolonged or simultaneous administration with other anti-myeloma agents in less heavily pre-treated patients.

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