Multicenter Phase II Feasibility Trial of High-Dose Tamoxifen in Patients With Refractory or Relapsed Multiple Myeloma

Despite high-dose chemotherapy with autologous stem cell transplantation, most patients with multiple myeloma relapse and eventually die. Previous studies have suggested that multiple myeloma cells express estrogen receptors and that antiestrogens induce in vitro growth inhibition and apoptosis of tumor cells (1–3). We therefore conducted a phase II feasibility trial of high-dose tamoxifen in patients with relapsed or refractory multiple myeloma who were previously treated by two or three chemotherapy regimens including thalidomide.

As in a previous phase I trial (4), tamoxifen was administered twice daily at doses of 400 mg/m² per day on day 1 and 300 mg/m² per day on days 2–6. Thereafter, doses were adjusted according to pharmacokinetic measurements to target serum tamoxifen concentrations between 4 μM and 5 μM for a total treatment duration of 39 days. Concentrations of serum tamoxifen and its main metabolites were measured using a high-pressure liquid chromatography assay (5) on days 2 and 3, 9, 16, 23, and 30 to adjust the doses administered on days 6–13, 13–20, 20–27, 27–34, and 34–39, respectively (ranges overlap because treatment doses were adjusted after morning tamoxifen administration). We based the tamoxifen dose adjustment on the estimated clearance from the analysis of concentration–time data using a nonlinear regression model (MicroPharm, Newcastle Emlyn, Camarthenshire, U.K., and INSERM, Paris, France).

Estrogen receptor α, estrogen receptor β, and progesterone receptor transcripts were quantified by quantitative real-time reverse transcription–polymerase chain reaction (TaqMan; Applied Biosystems, Foster City, CA) (6) on CD38-positive bone marrow cells.

After inclusion of the sixth patient, the overall lack of response and neurologic toxicity led us to prematurely stop patient inclusion. Tamoxifen was administered for 39 days to two patients but was discontinued at day 10, 22, 29, or 30 for the other four patients because one patient experienced ventral complication and three patients experienced multiple myeloma progression. Neurotoxicity was observed in three patients, with dizziness, vertigo, light-headedness, instability on tandem walk, dysmetria, and tremor. Evaluation of response showed disease progression after treatment in all patients. Adjusted tamoxifen doses ranged from 212 to 436 mg/m² per day (median = 330 mg/m² per day). After day 9, the median concentration was 4.0 μM (range = 2.0–6.0 μM), and four patients reached the target serum tamoxifen concentrations.

There was no relationship between tamoxifen and/or tamoxifen metabolite concentrations (mean or maximum) and the severity of side effects (Table 1). Estrogen receptor α, estrogen receptor β, and progesterone receptor expression was analyzed in a series of 12 patients, including the above six patients and six consecutive new patients to enlarge our multiple myeloma population. Before any treatment, only four of 12 tumor samples expressed estrogen receptor α: one tumor sample expressed substantial levels and the expression levels in those of the remaining three patients (including that from one tamoxifen protocol patient) were close to the positive cutoff value. Tumors from three patients (including one tamoxifen protocol patient) expressed high levels of estrogen receptor β transcripts. None expressed progesterone receptor transcripts. No correlation was observed between estrogen receptor α and estrogen receptor β expression (r = .46). Analyses of tumors from two patients performed before and after 4 months of tamoxifen treatment indicated that expression of estrogen receptor α was not modified by treatment.

In conclusion, despite high serum tamoxifen concentrations, our feasibility trial showed the absence of substantial estrogen receptor α expression in all plasmacytosis tumor cells except one tumor sample and the absence of activity against multiple myeloma by tamoxifen. Thus, our data do not support the use of high-dose tamoxifen given orally as a treatment for patients with refractory or relapsed multiple myeloma.

References


Table 1. Individual pharmacokinetic–pharmacodynamic results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment duration, days</th>
<th>Mean adjusted tamoxifen dose, mg/m² per day*</th>
<th>Highest serum tamoxifen concentration during treatment, μM†</th>
<th>Mean serum tamoxifen concentration during treatment, μM‡</th>
<th>Maximum toxicity grade during treatment‡</th>
<th>Neurotoxicity</th>
<th>Nausea–vomiting</th>
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*Mean adjusted tamoxifen dose was calculated from day 6 until the end of treatment.
†Tamoxifen concentration was defined as [C0+C3h]/2, where C0 is the concentration before morning daily oral administration of tamoxifen and C3h is the concentration 3 hours after morning daily administration of tamoxifen.
‡Grade was defined using World Health Organization criteria.


NOTES

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