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## Thalidomide in multiple myeloma: state of art

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Since the first report by Singhal *et al.* on the use of thalidomide in multiple myeloma (MM),<sup>1</sup> an increasing bulk of evidence has confirmed the striking activity of this drug in the treatment of patients with advanced and refractory disease.<sup>2-6</sup> The overall response rate in most studies so far reported averages approximately 30%. The mechanisms by which thalidomide exerts its action are as yet poorly defined and include induction of plasma cell apoptosis,<sup>7</sup> either directly or through inhibition of secretion of interleukin (IL-6) and tumor necrosis factor (TNF)- $\alpha$  by bone marrow stromal cells,<sup>8</sup> antiangiogenic activity<sup>9</sup> and, above all, modulation of T-cell immune response.<sup>10,11</sup> Based on these multiple modes of action, thalidomide can be regarded as the prototype of a novel class of antimyeloma agents targeting both the tumor cell and its interaction with the bone marrow microenvironment to overcome conventional drug resistance. Side effects most frequently reported during the first weeks of thalidomide therapy, such as lethargy, constipation and skin rash, are dose-dependent and easily manageable. Furthermore, thalidomide is virtually non-cytotoxic, thus representing an ideal agent for the management of heavily pretreated patients on an outpatient basis, as Corso *et al.* further point out in the present issue of *Haematologica*.<sup>12</sup> More serious, and as yet poorly investigated, side effects of thalidomide include bradycardia, hypothyroidism and, above all, peripheral neuropathy which is more frequently observed in patients treated for longer than one year.<sup>13</sup> Disturbances of sensation due to peripheral neuropathy may be reversible or persist after thalidomide discontinuation and should be carefully checked and monitored in patients being treated with this drug. More recently, the occurrence of deep vein thrombosis in patients receiving thalidomide has been reported,<sup>14</sup> with the estimated risk increasing from less than 5%<sup>1</sup> to approximately 30%<sup>15</sup> according to whether the drug is administered alone or in combination with anthracycline-based chemotherapy.

Several important issues concerning thalidomide therapy for MM are still matter of debate and should be addressed in future clinical trials. First, conflicting results have been reported on the optimal dose to use. Barlogie *et al.* recently analyzed the results of thalidomide dose escalation up to a

maximum of 800 mg daily<sup>13</sup> and found a relationship between tumor cell mass reduction and a cumulative dose of thalidomide exceeding 42 g at three months. In contrast, other groups<sup>4,16</sup> achieved comparable results using much lower, and less toxic, doses of the drug. Secondly, the activity of thalidomide in combination with other drugs should be further investigated. It now seems ascertained that thalidomide and dexamethasone are synergistic, the addition of dexamethasone increasing the response rate of patients with advanced and refractory disease to approximately 50% or above,<sup>17</sup> and allowing the rescue of a certain fraction of patients refractory to previous therapy with thalidomide alone. Combined treatment with thalidomide and multiple cytotoxic drugs<sup>18,19</sup> was reported to further raise the probability of response up to 60%, even at the cost of increased deep vein thromboses. Third, the role of thalidomide as remission induction or maintenance therapy and its optimal duration of administration still need to be investigated. Based on favorable results obtained in heavily pretreated patients, clinical trials on the use of thalidomide, either alone or combined with other drugs, in newly diagnosed patients have been recently started in both Europe and USA. Preliminary data on thalidomide alone in a small series of patients with smoldering MM showed a response rate that was comparable with that obtained in relapsed-refractory patients,<sup>20</sup> whereas combined thalidomide-dexamethasone therapy for symptomatic MM produced responses in 65-70%.<sup>21</sup> Whether thalidomide-dexamethasone may provide an alternative to conventional chemotherapy as first-line treatment for patients with newly diagnosed MM is still an open issue which is currently being addressed in ongoing phase II-III clinical trials. Concerns regarding potential impairment of peripheral blood stem cell collection in patients receiving thalidomide therapy were initially raised, even though more recent experience has shown an adequate yield of CD34<sup>+</sup> cells can be obtained upon interrupting thalidomide before the mobilization procedure.<sup>17</sup>

In conclusion, the exciting results that have been obtained so far with thalidomide in both previously treated and untreated MM patients demonstrate that, after more than three decades of unsuccessful clinical trial research, we actually possess a truly innovative therapeutic weapon for this still incurable malignancy. Efforts should be made in order to elucidate further the mechanism of action of, and resistance to, thalidomide, as well as to explore its best combination with other drugs. In

this light, new more selective thalidomide derivatives aimed at producing a more potent antimyeloma activity without increasing the systemic toxicity have recently been developed. At present, immunomodulatory derivatives (IMiDS) are showing promise in phase II clinical trials,<sup>23</sup> although definitive results are still awaited.

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#### Funding

*This work was supported in part by the Università di Bologna, progetti di ricerca ex-60% (MC).*

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