Management of neuromuscular dose limiting toxicity at the early stage of drug development

Non-hematological toxicities, including neuromuscular toxicity, occurring during phase I trials may prevent novel compounds from undergoing further drug development. Toxicity may also result in the recommendation of low doses and inappropriate schedules with no antitumor activity, rapidly reducing the interest of clinical investigators, pharmaceutical companies, and/or business investors. In the early stages of drug development a few compounds such as imatinib mesylate [1] and sunitinib malate [2] will provide straightforward evidence of efficacy in well characterized tumor types and good safety profiles, allowing fast-track drug registration. For those drugs, very little support would be sufficient for a convincing and unequivocal demonstration of their potential benefit as anticancer drugs. Many other compounds in development with a narrow spectrum of activity, sporadic activity in a limited number of (often undefined) tumor types, and risky toxicity profile will require deeper clinical tutoring from investigators and sustained support from sponsors to properly balance the benefits/risk and identify the clinical niche of activity.

The occurrence of neuromuscular toxicity has been an issue over the last 10 years, compromising the development of several novel anticancer agents. Oxaliplatin-development remains an emblematic story of a drug in which cumulative neuropathy, and limited antitumor activity as a single agent in colorectal cancer, prevented it becoming a reference drug in this disease in combination with 5fluorouracil/folinic acid [3–6]. The increasing prevalence of oxaliplatin/cisplatin- and paclitaxel-based regimens as first/second line chemotherapy in several malignancies further exposed patients to neuro muscular toxicity. Therefore, neuromuscular toxicity became an important issue for the development of several novel anticancer agents with neurological and muscular toxicity [7].

Didemnin B was extensively investigated in the 1990s. In phase I trials, didemnin B was shown to induce severe neuromuscular toxicity that led to the recommendation of safe, although relatively low, doses for phase II studies. Further phase II studies showed sporadic responses but failed to demonstrate clinically relevant evidence of antitumor activity, preventing further development of didemnin B as an anticancer agent. In this issue of Annals of Oncology, Marroun et al. [8] report the results of a phase I clinical trial with aplidine, a novel marine compound derived from didemnin B, infusions given five times a day every four weeks. This trial was one of the five phase I schedules evaluated with aplidine in 215 patients with advanced cancers (Table 1). In several of these clinical trials, aplidine demonstrated evidence of muscular toxicity. Maroun et al., who performed extensive neurological evaluation, further demonstrated that this toxicity was not associated with peripheral neuropathy. Muscular events were dose limiting toxicities in all phase I schedules, including muscle pain, muscular weakness and/or increases in creatine kinase. In our experience [9], muscular pain in shoulders, neck and/or thighs was the earliest symptom and appeared 3–4 weeks after the beginning of therapy with aplidine. When present, muscular weakness started one week later. The median time to detect an increase in creatine kinase from the first drug exposure was 35 days. In those patients with enough follow up, the toxicities recovered after onset in a median of 10–20 days. This recovery time was shorter for laboratory abnormalities than for muscular weakness. At the recommended doses, about 45% of the patients had reversible elevations in creatine kinase, mostly grade 1–2. Apparently, that proportion was higher in the schedules with longer duration of infusion. In the overall study program, and in our experience, myalgia has been reported in 41% of the patients treated with the recommended doses, most of them experiencing grade 1 pain as worst toxicity. Despite this frightening toxicity, aplidine given as a single agent also displayed encouraging evidence of antitumor activity that consisted of prolonged tumor stabilization and objective responses in patients with non-small cell lung carcinoma and orphan diseases, such as neuroendocrine and medullar thyroid carcinomas (Figure 1).

Careful clinical investigation suggested that aplidine muscle toxicity was consistent with a type II fiber atrophy myopathy commonly responsible for painful muscular weakness, followed by creatine phosphokinase and aldolase elevation. Indeed, neural and muscular biopsies performed in some patients with muscular dose-limiting toxicity showed type II fiber atrophy with minimal or no necrosis with no inflammatory signs, unspecific accumulation of glycogen and autophagocytic vacuoles, with or without disappearance of thick filaments of myosin (Figure 2). Although the precise mechanism of aplidine muscle toxicity remains unknown, aplidine inhibits the palmitoyl protein thioesterase I [10], a protein closely related to carnitine palmitoyl transferase 2, a muscular enzyme for which deficiency leads to congenital myopathy in children [11]. Another possible mechanism of toxicity may involve the interaction with elongation factors (eIFs), impairment in translation efficiency being known to decrease muscular protein synthesis [12]. Interestingly, the use of carnitine seems to facilitate the recovery of muscular toxicity and increases the dose intensity of aplidine in phase I trials. Preclinical studies showed that carnitine does not
Table 1. Phase I clinical trials of aplidine given intravenously in patients with advanced malignancies

<table>
<thead>
<tr>
<th>Aplidine trials</th>
<th>Schedules</th>
<th>Centers</th>
<th>No. of patients</th>
<th>Initial dose(^a)</th>
<th>Maximum dose administered(^a)</th>
<th>Maximum dose intensity(^b)</th>
<th>MTD(^a)</th>
<th>DLT at MTD</th>
<th>RD(^a)</th>
<th>Dose intensity at the RD level(^b)</th>
<th>Clinical benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>001a</td>
<td>24 h infusion days 1, 8, 15 every 28 days</td>
<td>Beatson Oncology Centre, Glasgow, UK</td>
<td>Hospital 12 de Octubre, Madrid, Spain</td>
<td>35</td>
<td>0.13</td>
<td>4.50</td>
<td>3.58</td>
<td>3.50</td>
<td>Muscular hepatic</td>
<td>3.75</td>
<td>2.81</td>
</tr>
<tr>
<td>001b</td>
<td>3 h infusion days 1, 15 every 28 days</td>
<td>Beatson Oncology Centre, Glasgow, UK</td>
<td>Hospital 12 de Octubre, Madrid, Spain</td>
<td>27</td>
<td>0.30</td>
<td>6</td>
<td>3.50</td>
<td>6</td>
<td>Renal, hepatic, muscular et al.</td>
<td>5</td>
<td>2.50</td>
</tr>
<tr>
<td>002</td>
<td>1 h infusion days 1, 8, 15 every 28 days</td>
<td>Western General Hospital, Edinburgh, UK</td>
<td>Instituto Catalán de Oncología, Barcelona, Spain</td>
<td>49</td>
<td>0.13</td>
<td>3.60</td>
<td>2.70</td>
<td>3.60</td>
<td>Muscular</td>
<td>3.20</td>
<td>2.40</td>
</tr>
<tr>
<td>003</td>
<td>24 h infusion days 1, 15 every 28 days</td>
<td>Institut Gustave-Roussy, Villejuif, France</td>
<td></td>
<td>39</td>
<td>0.20</td>
<td>7</td>
<td>3.50</td>
<td>6</td>
<td>Muscular</td>
<td>5</td>
<td>2.50</td>
</tr>
<tr>
<td>003+c</td>
<td>24 h infusion days 1, 15 every 28 days + L-carnitine</td>
<td>Institut Gustave-Roussy, Villejuif, France</td>
<td></td>
<td>28</td>
<td>0.60</td>
<td>8</td>
<td>4</td>
<td>8</td>
<td>Asthenia</td>
<td>7</td>
<td>3.50</td>
</tr>
<tr>
<td>004</td>
<td>1 h infusion days 1–5 every 21 days</td>
<td>Ottawa Regional Cancer Center, Ottawa</td>
<td>Centre Hospitalier Universitaire de Montreal</td>
<td>37</td>
<td>0.08</td>
<td>1.50</td>
<td>2.50</td>
<td>1.35</td>
<td>Cutaneous diarrhea</td>
<td>1.20</td>
<td>2.00</td>
</tr>
</tbody>
</table>

\(^{a}\)Doses given in g/m\(^2\).

\(^{b}\)Dose intensity given in g/m\(^2\)/month.
interact negatively with aplidine cytotoxicity in cancer cells [13]. The prophylactic use of high-dose carnitine allowed the recommended dose of aplidine to be increased without severe muscular toxicity, but with a slight increase of grade 1–2 diarrhea, a toxicity also related to carnitine.

Aplidine illustrates the complexity of developing natural compounds with potential antitumor activity but unexpected non-hematological toxicity, especially with delayed onset. Another example of problematic toxicity was recently illustrated with irofulven, a novel semi-synthetic derivative of illudin S displaying visual troubles that consisted of halo or blurred vision under bright lights and ‘flattened’ colour vision with no modification of visual acuity [14]. Although mild and reversible, this potentially detrimental side effect of patient quality of life prevented further dose-escalation of irofulven in phase I trials. Occurrence of visual toxicity became unlikely to be considered as a limiting factor for further development of irofulven.

The usual methodology of phase I trials may be sometimes recognized as inappropriate or insufficient for drugs with cumulative neuromuscular toxicity. Most phase I trials will use standard definitions of maximum tolerated dose based on dose-limiting toxicity occurring during the first cycle. These unusual non-hematological toxicities will require careful observation and inference. In addition, poor performance status at study entry, rapid tumor progression and/or sub-effective dosing will prevent most patients from receiving more than two cycles in phase I studies. Neuromuscular toxicity, which often occurs after repeated dosing, will therefore be difficult to explore in the course of classical phase I trials and may not be considered in the final dose recommendation, based on toxicity at cycle 1. In our experience, occurrence of neuromuscular toxicity has often required redefining the appraisal of maximum tolerated and recommended doses, based on dose-limiting toxicity occurring not only during cycle 1 but at any cycle in a subset of 9–12 patients who were capable of receiving at least three to four cycles (i.e. the median duration to toxicity onset). Considering that only one among three patients with performance status ECOG 0–1 entering phase I will be able to receive three cycles, this revised definition requires an increase in the number of patients treated at the maximum tolerated dose. Increasing the number of patients and the duration of follow-up for ≥3 cycles at the latest stage of phase I trials while launching phase II studies might be considered an unnecessary waste of time and money. Conversely, we believe that it offers the unique opportunity to avoid critical mistakes in dose recommendations that will be carried over and which may jeopardize the overall phase II/III program by requiring further dose and schedule adjustments and delays. Furthermore, it offers the chance to develop a clinical database that might help to better describe the toxicity, understand its physiopathology, and/or sometimes

0.50 mg/kg irofulven given on day 1 and 8 or day 1 and 15 can be recommended in patients with advanced cancer. At this dose, the estimated rate of visual event was about 25% with no patient requiring the withdrawal of treatment for unacceptable tolerance. Considering that irofulven was likely to be used in combination at doses ≤0.50 mg/kg, based on our study, visual toxicity became unlikely to be considered as a limiting factor for further development of irofulven.

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Figure 1. Evidence of antitumor activity of aplidine given as a single 24 hour infusion every other week in a patient with bronchial carcinoid tumor refractory to cisplatin and etoposide.

Figure 2. Electron microscopy of a muscle biopsy from a patient with aplidine dose-limiting muscle toxicity showing accumulation of glycogen (a) and disappearance of some thick filaments of myosin.
offer counteracting and developing prophylactic measures against neuromuscular toxicity.

In summary, although sometimes difficult to manage, neuromuscular toxicity does not prevent a drug from being used as an anticancer agent providing there are appropriate and safe dose and schedule recommendations. At early stages of clinical evaluations, neuromuscular toxicity that often appears after repeated cycles requires careful clinical management, reappraisal of classical phase I methodology, as well as good cooperation from physicians and sponsors that are far beyond usual contract commitments. Recent studies demonstrated that this approach may bring benefits to drugs, allowing continuing drug development, and also to patients permitting them to get safe access to active novel anticancer agents.

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references