Zoster-Related Pain In Haematological Malignancies: Durable Pain Relief Provided By Oxycodone In Patients Unresponsive To Standard Therapy

P Niscola, A Perrotti, G del Poeta, C Romani, M Giovannini, L Scaramucci, C Cartoni, P de Fabritiis

INTRODUCTION

Herpes Zoster Virus (HZV) outbreak is a significant cause of morbidity in the setting of blood-related malignancies, occurring mostly among patients affected by lymphoproliferative disorders (LPD) and in those submitted to haematopoietic stem cell transplantation (HSCT). Although very few epidemiological data are available in LPD, herpetic complications are mainly recorded among patients with chronic lymphocytic leukaemia (CLL). In the setting of autologous HSCT the HZV reactivation is reported between 15%-45%\(^2\), one-third of the affected patients developed post herpetic neuralgia (PHN). In addition, patients submitted to allogenic HSCT reported a HZV reactivation in proportions ranging from 41 to 59%.\(^3\) The elucidated pathological mechanisms of HZV outbreak have provided the rationale of acute zoster pain (AZP) and PHN treatment with antiviral therapy combined with neuroactive agents. Thereby, in addition to antiviral drugs, the affected patients should receive neuronal membrane-stabilising agents, such as tricyclic or anticonvulsant agents.\(^4\) The role of analgesics in this setting is less clearly established, although convincing evidence of benefits provided by opioids have been reported by controlled studies and metanalysis.\(^5\) In particular, levorphanol resulted as an effective neuropatic pain reliever, and the addition of low dose morphine to gabapentin allowed better analgesia than either single agent.\(^6\) Moreover, both oxycodone\(^7\) and tramadol\(^8\) were reported as effective to relieve neuropatic pain. We provided pain consultation and therefore treated with oxycodone 5 consecutive patients, suffering from AZP and long-lasting PHN resistant to several agents, including anticonvulsants and analgesics.

PATIENTS AND METHODS

Clinical characteristics of the 5 patients, including previous treatments received for post-herpetic complications while they were followed by other services, are shown in table 1. The history and the presenting clinical features, such as pain, allodynia, aching burning sensations, spontaneous shooting, were carefully assessed at each visit. Pain was rated as daily mean on a 0 to 10 numerical rating scale (NRS).
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The first patient was a female with a long history of follicular non Hodgkin's lymphoma (NHL) in continuous complete remission from 7 years after rituximab-containing high dose (HD) chemotherapy (CHT) followed by autologous HSCT. She kept under our attention referring a PHN lasting from 30 months, notwithstanding the early treatment with acyclovir and gabapentin, followed by escalating doses of pregabalin that the patient had received without any benefit three years before, when a painful shingles in a thoracic dermatomal region has occurred. Given the lack of response to pregabalin alone, this agent was reintroduced at standard dose (150 mg/day) in association with tramadol (200 mg twice daily). Pain relief but not favourable effect on allodynia was achieved. One month later, pain progressively increased until a pain score of 7; moreover, the associated complaints become ever more distressing, so that tramadol was replaced with oxycodone that was titrated until 10 mg thrice daily, allowing a rapid pain relief; however, tactile allodynia persisted, for which topical capsaicin 0.075 percent cream to relieve it was applied.

The second PHN patient was a man affected by acute lymphoblastic leukaemia treated with steroids and vinca alkaloids. During the advanced course of his disease, he had presented a shingles in a thoracic dermatome for which acyclovir was given. Because of pain and neuropathic complaints, patient received gabapentin, achieving only transient and limited benefits. So, complaining a severe PHN lasting from 4 months, he was managed by us with the addition of oxycodone, at the dose of 5 mg thrice a day, to gabapentin. This combination therapy allowed for a rapid pain relief that was maintained until his death due to disease progression.

Patients 3, 4 and 5, affected by small lymphocytic NHL, multiple myeloma and CLL respectively, presented a similar herpetic clinical course. Indeed, they have received some chemotherapy regimens, including fludarabine in the former, and long-term steroids administration in addition to melphalan and clorambucil in the cases 4 and 5 respectively. All have received antivirals associated with non-opioid analgesics and gabapentin or pregabalin, without significant benefits. We successfully treated them with the combination gabapentin-oxycodone without no remarkable side effects.

DISCUSSION

Patients with haematological malignancies are at high risk to develop HZV reactivation, given the presence in this population of the most recognized predisposing factors, such as the underlying malignancy, the older age, the age-related immune decline, the waning of specific cell-mediated immunity induced by, cytotoxic treatments and steroids, and the care for transplantation\textsuperscript{12}. The most aims of therapy of HZV outbreak are to prevent complications, such as PHN, and to achieve painlessness. Systemic antiviral therapy acyclovir or its prodrugs (famiciclovir and valaciclovir), started early in the course of HZV reactivation, can short the healing process and can significantly reduce the risk and the duration of PHN\textsuperscript{6}. For the HZV-related neuropathic complaints, neuronal membrane stabilising agents, such as gabapentin and pregabalin, are the therapy of choice. Pain management should depend on the pain intensity. Treatment of severe pain should include an opioid, given the growing evidences of their provided benefits also in patients with neuropathic pain\textsuperscript{10}. Notwithstanding these evidence, no universally accepted recommendations are to date available regarding the role of opioids in the AZP and PHN management and some aspects of their applications, together some debates regarding adverse effects, the fear of addiction and legal restrictions, remain unresolved. These concerns may reflect, in our consternations, in too many onco-haematological patients, including those with herpes-related pain states, which are still poorly treated. In this report we provided favourable results achieved by oxycodone in 5 consecutive oncohaematologic patients with herpetic pains. The small case series may limit the value of our observations. However, our cohort represent the subset of patients with otherwise intractable herpetic pains, all responding to oxycodone given as rescue option. In conclusion, our findings suggest that a strong opioid should be taken into account in patients with painful HZV outbreak or PHN; in this light, oxycodone, may represent a suitable

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Table 1: clinical features, disease's histories and zoster-related pain outcome of the patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Disease</th>
<th>Disease Duration and History</th>
<th>Pain Location</th>
<th>Previous Antiviral Therapy (Max. Dose)</th>
<th>Previous Neuronal Membrane Stabilising Agents</th>
<th>Opioid</th>
<th>Neuronal Membrane Stabilising Agents</th>
<th>Last Pain Relief</th>
<th>Mean Dose of Treatment</th>
<th>Time to Response</th>
<th>Mean Dose of Treatment</th>
<th>Time to Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>F</td>
<td>NHL</td>
<td>7 yrs continuous complete remission from 7 years after rituximab-containing HD CHT followed by autologous HSCT</td>
<td>Thoracic dermatome</td>
<td>Acyclovir 800 mg Tid</td>
<td>Pregabalin 300 mg Qd</td>
<td>Tramadol 200 mg twice daily</td>
<td>Oxycodone 10 mg thrice daily</td>
<td>Topical capsaicin 0.075 percent cream</td>
<td>6</td>
<td>2</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>F</td>
<td>NHL</td>
<td>3 yrs continuous complete remission from 3 years after rituximab-containing HD CHT followed by autologous HSCT</td>
<td>Thoracic dermatome</td>
<td>Acyclovir 800 mg Tid</td>
<td>Pregabalin 300 mg Qd</td>
<td>Tramadol 200 mg twice daily</td>
<td>Oxycodone 10 mg thrice daily</td>
<td>Topical capsaicin 0.075 percent cream</td>
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option even patients who has failed a first opioid. However, some questions, such as the opioid of choice, its combination with other class of neuroactive drugs, the time to administration in the course of herpetic painful complications, the duration of treatment, and so on, remain to explore and may represent the basis of further research.

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