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

Citation

P Niscola, A Perrotti, G del Poeta, C Romani, M Giovannini, L Scaramucci, C Cartoni, P de Fabritiis. *Zoster-Related Pain In Haematological Malignancies: Durable Pain Relief Provided By Oxycodone In Patients Unresponsive To Standard Therapy*. The Internet Journal of Hematology. 2006 Volume 3 Number 1.

Abstract

Acute Herpes Zoster-related pain and post herpetic neuralgia (PHN) are significant cause of morbidity in the setting of blood-related malignancies. Standard treatments of these complications include specific antiviral drugs, anticonvulsants and analgesics. We recently observed 5 patients with lymphoproliferative disorders who were affected by acute zoster pain and by long lasting PHN, unresponsive to standard treatments, including several analgesics. So, they were treated with oxycodone achieving a durable and stable pain relief without any adverse effect.

This anecdotic experience suggests that, in the setting of refractory zoster pain this agent can be offered as useful rescue option.

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)[1]. 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%[2,3]; one-third of the affected patients developed post herpetic neuralgia (PHN)[4]. In addition, patients submitted to allogenic HSCT reported a HZV reactivation in proportions ranging from 41 to 59%[5]. 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 trycyclic or anticonvulsant agents[6]. 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[7,8,9]. In particular, levorphanol resulted as an effective neuropatic pain reliever[7] and the addition of low dose morphine to gabapentin allowed better analgesia than either single agent[8]. Moreover, both oxycodone[9] and tramadol[11] 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).

Figure 1

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

Patient (Pain)	Age (years), Sex	Diagnosis (Disease Duration and status)	Previous HZ outbreaks	Primary Analgesic Therapy (Max Dose)	Basal Pain Rate	Oxycodone			Last Pain Rate
						Initial doses (mg)	Time to Response* (Days)	Mean Doses (Days of Treatment)	
1 (PHN)	61, F	NHL (15 years, remission)	1	PGB (1800 mg) Tramadol (400 mg)	9	20	2	30 mg (340)	0-1
2 (PHN)	69, M	ALL (2 years, death)	1	GB (1200 mg)	8	15	3	15 mg (105)	1-2
3 (AZP)	52, F	NHL (1 year, remission)	0	GB (900 mg)+ AMP (3000 mg)	7	15	1	15 mg (31)	0
4 (AZP)	71, M	MM (4 years, advanced)	0	PGB (300)	7	15	1	20 mg (29)	0
5 (AZP)	83, M	CLL (7 years, death)	2	GB (1800) + NSAIDs	4	15	3	15 mg (33)	1

HZ: Herpes Zoster; PHN: Post Herpetic Neuralgia; AZP: Acute Zoster Pain; F: female; M:male, NHL: Non-Hodgkin Lymphoma; ALL: Acute Lymphoblastic Leukemia; MM: Multiple Myeloma; PGB: Pregabalin; GB: Gabapentin; NSAIDs: Non-Steroidal Antinflammatory Drugs; AMP: Acetaminophen. * Reduction of almost 50% of pain rate with respect to the baseline level.

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[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 (famciclovir 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[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[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 oxicodone 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

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.

CORRESPONDENCE TO

Pasquale Niscola M. D. Haematology Division, Tor Vergata University, Sant'Eugenio Hospital, Via dell'Umanesimo 10, 00144 Rome. Phone: +390651002509 Fax: +39065915965 E-mail: pasquale.niscola@uniroma2.it

References

1. Niscola P, Arcuri E, Giovannini M, Scaramucci L, Romani C, Palombi F, Trape G, Morabito F. Pain syndromes in haematological malignancies: an overview. Hematol J. 2004; 5(4): 293-303.
2. Leung TF, Chik KW, Li CK, Lai H, Shing MM, Chan PK, Lee V, Yuen PM. Incidence, risk factors and outcome of varicella-zoster virus infection in children after haematopoietic stem cell transplantation. Bone Marrow Transplant. 2000 Jan;25(2):167-72.
3. Bilgrami S, Chakraborty NG, Rodriguez-Pinero F, Khan AM, Feingold JM, Bona RD, Edwards RL, Dorsky D, Clive J, Mukherji B, Tutschka PJ. Varicella zoster virus infection associated with high-dose chemotherapy and autologous stem-cell rescue. Bone Marrow Transplant. 1999 Mar;23(5):469-74.
4. Offidani M, Corvatta L, Olivieri A, Mele A, Brunori M, Montanari M, Rupoli S, Scalari P, Leoni P. A predictive model of varicella-zoster virus infection after autologous peripheral blood progenitor cell transplantation. Clin Infect Dis. 2001 May 15;32(10):1414-22.
5. Koc Y, Miller KB, Schenkein DP, Griffith J, Akhtar M, DesJardin J, Snydman DR. Varicella zoster virus infections following allogeneic bone marrow transplantation: frequency, risk factors, and clinical outcome. Biol Blood Marrow Transplant. 2000;6(1):44-9.
6. Baron R, Wasner G. Prevention and treatment of postherpetic neuralgia. Lancet. 2006 Jan 21; 367(9506): 186-8.
7. Rowbotham MC, Twilling L, Davies PS, Reisner L, Taylor K, Mohr D. Oral opioid therapy for chronic peripheral and central neuropathic pain. N Engl J Med. 2003 Mar 27;348(13):1223-32.
8. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med. 2005 Mar 31;352(13):1324-34.
9. Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. Neurology. 1998 Jun; 50(6): 1837-41.
10. Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomised controlled trials. JAMA. 2005 Jun 22;293(24):3043-52.
11. Hollingshead J, Duhmke R, Cornblath D. Tramadol for neuropathic pain. Cochrane Database Syst Rev. 2006 Jul 19;3:CD003726.
12. Insinga RP, Itzler RF, Pellissier JM, Saddier P, Nikas AA. The incidence of herpes zoster in a United States administrative database. J Gen Intern Med. 2005 Aug;20(8):748-53.

Author Information

Pasquale Niscola
Haematology Division, Sant'Eugenio Hospital, Tor Vergata University

Alessio Pio Perrotti
Haematology Division, Sant'Eugenio Hospital, Tor Vergata University

Giovanni del Poeta
Haematology Division, Sant'Eugenio Hospital, Tor Vergata University

Claudio Romani
Armando Businco Cancer Centre

Marco Giovannini
Umberto I Hospital

Laura Scaramucci
Haematology Division, Sant'Eugenio Hospital, Tor Vergata University

Claudio Cartoni
Human Biopathology and Haematology Department, "La Sapienza" University

Paolo de Fabritiis
Haematology Division, Sant'Eugenio Hospital, Tor Vergata University