MANUSCRIPT Scientific Services...
www.manuscriptscientific.com

Journal of Pharmaceuticals Sciences and Drug Discovery

Case Report

Squamous Carcinoma of the Cervix: A Difficult Management of Pain

Tirelli W[1*], Basti G[2], Malgaroli A[3], Gianinazzi N[3], Casadio R[4], Lombardo L[1], Ginobbi P[1], Penco I[1], Tirelli MS[1] and Citro G[5]

[*1]*Hospice Fondazione Sanità e Ricerca Rome, Italy*

[2]*Pontifical Lateran University Philosophy Department, Vatican City*

[3]*Center for Behavioral Neuroscience Università San Raffaele Milano, Italy*

[4]*Department of Pharmacy and Biotecnology University of the Bologna, Italy*

[5]*Consultant Hospice Fondazione Sanità e Ricerca Rome, Italy.*

Corresponding author: Walter Tirelli, Hospice Fondazione Sanità e Ricerca Rome, Italy, Tel: 0339-06588991; E-mail: w.tirelli@fondazionesr.it

Abstract

The IASP (International Association for the Study of Pain) defines pain: "An unpleasant sensory and emotional experience associated with current or potential tissue damage or described in terms to represent such a type of damage, pain is always subjective".

Cancer pain is a very serious and frequent manifestation of cancer; it is estimated, according to a recent systematic review, that the prevalence of cancer pain is about 33% in patients in active care and 64% in patients with metastatic or terminal disease. The clinical management of pain is consolidated by WHO guidelines revised later and which see opioids as the cornerstone of analgesic therapy. In Italy, cervical cancer is the fifth most frequent cancer in women under 50 years of age and in total 1.3% of all those diagnosed. In the world in 2020 there were 604 thousand new cases and 342 thousand deaths, representing the fourth cancer by incidence in women. It is also estimated that about 84% of cervical cancer cases currently occur in developing countries. The case described in this report indicates how currently the management of pain therapy is often, in many cases, unmanageable, bringing out ethical-professional implications. It is important that scientific research is oriented towards the identification of specific molecular targets to generate effective personalized pain therapy. Artificial intelligence, associated with scientific knowledge in genetics and using current instrumental methodologies offers great possibilities for achieving this goal.

Keywords: Cancer pain, WHO, Artificial intelligence, Methodologies

INTRODUCTION

The difficult control of oncological pain in the exposed clinical case suggests that the greatest obstacle that is encountered in the management of antalgic therapy is the variability of the response to analgesic therapies. This variability is closely linked to both genetic and epigenetic factors in patients [1-11]. Genetics related to polymorphisms of the metabolic pathways of drugs and epigenetics strictly dependent on lifestyles and individual clinical history. There are numerous individual differences in response to opioid therapy. The reasons for this variability are partly due to incorrect drug administration and pharmacokinetic differences, while genetic variations can lead to differences in absorption, distribution, metabolism and excretion of drugs that ultimately affect the effectiveness of the drug and its toxicity [12,13]. The individual response to opioids is conditioned by polymorphisms of opioid receptors and polymorphisms of metabolism enzymes. Polymorphisms of opioid receptors determine relevant clinical effects such as in the case of polymorphisms of OPRM1 genes encoding mu receptors for opioids that are linked to morphine response variability [14]. The polymorphisms of metabolic enzymes in much of the hepatic enzyme system cytochrome 450 (CYP 450) determine a considerable variability in the clinical response to several opioids [15]. Even today there are few molecular targets of drugs in this discipline to obtain an effective therapeutic response over time. In our case studies, as well as in the exposed clinical case, there are initially sensitive patients who during drug treatment show a resistance that requires an increase in the initial dose as well as resistant patients who do not fully respond to known treatment protocols and need more combinations of increased medication or medication doses.

CASE REPORT

The case concerns a female patient of 51 years old B.R.

Received: *December 13, 2022;* ***Revised:*** *January 01, 2023;* ***Accepted:*** *January 04, 2023*

Citation: Tirelli W, Basti G, Malgaroli A, Gianinazzi N, Casadio R, et al. (2023) Squamous Carcinoma of the Cervix: A Difficult Management of Pain. J Pharm Sci Drug Discov, 2(1): 1-3.

whose clinical history began in January 2017 with diagnosis of Squamous Cervical Cancer (Stage FIGO IIIB) who was treated with neo-adjuvant chemotherapy according to the scheme Carboplatin/Taxole weekly (Dose-dense scheme). After about a month the patient underwent radical hysterectomy, pelvic and lumbo-aortic lymphadenectomy, with distal resection of the left ureter and ureteral replanting (Hitch left bladder-psoas). After two months he started adjuvant chemotherapy with weekly Carboplatin and Taxol (Dose-Dense Scheme). On 22 February 2018, the patient was subjected e.g. PET that showed a progression of disease at the level of the paracavala nodes of the right and therefore carried out six cycles of chemotherapy with Carboplatin, Taxol and Bevacizumab; then eight cycles of maintenance with Bevacizumab. In March 2019, he performed four rounds of chemotherapy with Tisotumab Vedotin with progression at the psoas level. In July 2019, the patient underwent radiotherapy in right retroperitoneal para-caval for progression of abdominal disease, and for progression of disease at bone and abdominal level in November 2019 carried out 2 cycle's sec. Protocol REGENERON and for pathological vertebral fracture performed six cycles of chemotherapy with weekly Taxol and zometa with addition to the fifth cycle of Pembrolizumab. On August 4, 2020, Total-Body CT was performed which showed pathological tissue in the right retroperitoneal area along the right ileo-psoas muscle infiltrating the inferior vena cava under-renal and ureter homolateral and presence of neoplastic tissue at the level of the lumbar vertebral canal with invasion of the soma of L3 with invasion of the left conjugation channel up to L2. For this reason he began chemotherapy treatment according to the scheme Carboplatino q21 but was interrupted for evidence of further progression of the disease localization in the right retroperitoneal with increased lumbar vertebral involvement both somatic that intracanalare/ conjugation foramen with the onset of a painful symptomatology that required the intervention of an pain specialist. On 3-09-2020, the patient entered the pain therapy department for lumbar Algie irradiated to the lower limbs and began therapy first with minor opioids (codeine 180 mg/day) and then, for insufficient pain rilief, with morphine sulfate (120 mg/day). Due to uncontrolled pain, an epidural catheter was implanted on 07.09.2020 for the continuous infusion of local anesthetics but was removed on the same day. For exacerbation of the lumbar pain radiated to the lower limbs refractory to the drugs was implanted intrathecal pump delivering morphine with reported benefit. During hospitalization neurological consultation was required: patient suffering from advanced uterine neoplasm with myeloradicular infiltration already being treated for pain therapy, Vigilant collaborating, with evidence of lack of strength in the lower limbs with occasional paresthesia in the feet; was advised to continue the antalgic therapy set by analgesists. On 19-09-2020, due to exacerbation of pain, the administration of intrathecal morphine was suspended and systemic therapy with Metadone 40mg /day associated with Fentanyl 400 mcg was initiated for episodes of Breakthrough pain [16]. Due to the poor control of pain began a stubborn escalation of cocktails of analgesic and adjuvant drugs that ended with the following therapeutic scheme:

Methadone 25 mg x 2/day, Naproxen 750 mg /day, Prednisone 25 mg x 2, Amitriptyline 14 drops twice daily, Pregabalin 300 mg x 2 /day, Haloperidol 20 drops in the evening, Buprenorphine 52.5 mcg/h /72 hours, Fentanyl 400 mch when needed (the patient took at least 5 times a day) Quetiapine 25 mg in the evening and medical cannabis 5 drops x 2 /day. On October 6, 2020, the patient was transferred to our hospice for inclusion in a residential palliative care program. In hospice, because of the pain reported by the patient, antalgic therapy was rationalized by proposing to the patient (carrier of port-a-Cath) a more complex therapeutic scheme using, with the patient's consent, a continuous infusion of morphine e.v. by PCA electronic pump with suspension of most of the drugs previously prescribed and according to the following therapeutic scheme: morphine hydrochloride 60 mg+ Ketorolac 60 mg + dexamethasone 8 mg in 24 hours with immediate pain relief but with a decalant analgesia in the third day. For this reason we were forced to increase the dosage of morphine to 90 mg /day and get a good control of pain except for a few episodes of Breakthrough pain well controlled by therapy with Fentanyl 800 via sub-lingual. After about 20 days of severe pain intensification and new escalation to 120 mg of morphine hydrochloride /day. With discreet pain control for about 7 days and re-adjustment of the morphine dosage with less and less pain effects. The patient on 05-02-2021 died after palliative sedation in the company of her loved ones.

CONCLUSIONS

A proportion of patients receiving opioid therapy are cancer patients [17]; for such patients we have observed that there are different responses to opioid therapy. Even today it is not possible to stratify the quality of the response to opioids with the stage of the disease; in fact many patients before responding to therapies, become resistant during treatment [18,19]. For these patients the bio-molecular mechanisms responsible for resistance are not known, and in the scientific literature, to date data on this topic have not been highlighted. It has been suggested that an individual's genetic predisposition affects opioid response; there is limited evidence of correlation between some polymorphisms of human genes and variability in analgesia: studies investigated the effect of polymorphisms both for analgesia and for the toxic effects induced by opioids [20,21]. To give an answer to the understanding of this phenomenon, Our institution is engaged in a research project for the identification of genetic polymorphisms of opioid receptors and enzymes of their metabolism in cancer patients by evaluating any differences [22,23]. The comparison of all

the data coming from the analyses of both responders and non-responders could lead to the identification of specific targets responsible for resistance to treatment and of specific molecular analogues to be tested in different situations pharmacogenomics [24]. These results will ultimately be used to generate predictive mathematical models of response in order to identify strategies for therapy personalization.

REFERENCES

1. No authors listed (1979) International Association for the Study of Pain, Subcommittee on taxonomy of pain terms: a list with definitions and notes on us-age. Pain 6: 249-252.
2. Van den Beuken-Van Everdingen MH, De Rijke JM, Kessels AG, Schouten HC, van Kleef M, et al. (2007) Prevalence of pain in patients with cancer: A systematic review of the past 40 years. Ann Oncol 18: 1437-1449.
3. World Health Organization (1996) Cancer Pain Relief with a guide to opioid availability. World Health Organization, Geneve.
4. Ventafridda V, Saita L, Ripamonti C, Connoet F De (1985) WHO guidelines for the use of analgesics in cancer pain. Int J Tissue React 7(1): 93-96.
5. Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, et al. (2012) Use of opioids analgesics in the treatment of cancer pain: Evidence-based recommendations from the EAPC. Lancet Oncol 13(2): 58-68.
6. Aiom-Airtum (Italian Association of medical Oncology-Italian cancer registry Association) (2020) The numbers of cancer in Italy.
7. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, et al. (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 71(3): 209-249.
8. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, et al. (2018) Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68(6): 394-424.
9. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, et al. (2015) Global cancer statistics, 2012. CA Cancer J Clin 65(2): 87-108.
10. Kadiev E, Patel V, Rad P, Thankachan L, Tram A, et al. (2008) Role of Pharmacogenetics in variable response to drugs: Focus in opioids. Expert Opin Drug Metab Toxicol 4(1): 77-91.
11. Sweatt JD, Meaney MJ, Nestler EJ, Akbarian S (Eds.) (2013) Epigenetic regulation in the nervous system, Academic Press, Elsevier, Amsterdam.
12. Stamer UM (2007) Genetic factors in pain and its treatment. Curr Opin Anaesthesiol 20: 478-484.
13. Lotsch J (2006) Current evidence for a genetic modulation of the response to analgesics. Pain 121: 1-5.
14. Campa D (2008) Association of ABCB1/MDR1 and OPRM1 gene polimorphisms with morphine pain relief. Clin Pharmacol Ther 83: 559-566.
15. Rogers JF, Nafzinger AN, Bertino Jr JS (2002) Pharmacogenetics effects dosing, efficacy and toxicity of cytochrome 450-metabolized drugs. Am J Med 113: 746-750.
16. Portenoy RK, Hagen NA (1990) BreakThrough Pain: definition, prevalence and characteristics. Pain 41: 273-81.
17. Hanks GW, De Conno F, Ripamonti C (1996) Morphine in cancer pain: Modes of administration. An expert working group of the European Association for Palliative Care. Br Med J 312: 823-826.
18. Ueda H, Ueda M (2009) Mechanisms underlying morphine analgesic tolerance and dependence, in Frontiers in Bioscience 14: 5260-5272.
19. Vanderah TW, Ossipov MH, Lai J, Malan TP Jr, Porreca F (2001) Mechanism of opioid-induced pain and antinociceptive tolerance: Descending facilitation and spinal dynorphin. Pain 92 (1-2): 5-9.
20. Skorpen F, Laugsand EA, Klepstad P (2008) Variable response to opioid treatment: Any genetic predictors within sight? Palliat Med 22(4): 310-327.
21. Klepstad P, Fladvard T, Skorpen F (2011) Influence from genetic variability on opioid use for cancer pain: A European genetic Association Study of 2294 cancer pain patients. Pain 152(5): 1139-1145.
22. Pan L, Xu J, Yu R, Xu MM, Pan YX (2005) Identification and characterization of six new alternatively spliced variants of the human mu opioid receptor gene, Oprm. Neuroscience 133(1): 209-220.
23. Kraus J (2009) Regulation of mu-opioid receptors by cytokines. Front Biosci 1(1): 164-170.
24. Arcuri E, Ginobbi P, Tirelli W, Froldi R, Citro G (2002) Preliminary *in vivo* experimental evidence on intratumoral morphine uptake. Possible clinical implications in cancer pain and opioid responsiveness. J Pain Symptom Manag 24(1): 1-3.