Self-assessment pain control in end-of-life children with bone tumors: a cohort study

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Abstract

BACKGROUND: INCA estimated, for 2020 – 2022, Brazil would have 8,460 new pediatric cancer cases and 5% are bone cancer. Pain is the most prevalent symptom and is present in 75% - 90%. Advanced ill patients have 40% pain undertreated. OBJECTIVE: This study was to evaluate pain in pediatric bone cancer patients and investigate if there was a difference between those who survived and those at end-of-life. PROCEDURE: Patients were registered at INCA Pediatric Department, January 2011 – October 2016, with the diagnosis confirmed of primary bone cancer and under 19 years old. Pain was evaluated and registered at three moments during their treatment: at registration, three months after and the last visit before the end of this study or patients death, using pain scores. RESULTS: 157 patients were bone cancer, 15 (9.6%) had lost the follow up; 142 were analyzed, osteosarcoma 69.7% and Ewing sarcoma 30.3%, metastatic patients 50.7%. At the registration 53.5% had pain, 69.71% were receiving pain treatment and 42.25% had pain medications changed. Comparison of the three study moments was observed a decrease of pain status, with the absence of excruciating pain, and an increased use of opioids. There was no difference ($p = 0.68$) in pain status between groups of who survived and who died (39.4%). CONCLUSION: Pain management resulted in reduction of pain complaint and reduction in pain intensity, together with increasing opioid use. End-of-life patients did not have more pain than others, but disease progression was associated to more pain.

Introduction

The Brazilian National Cancer Institute (INCA) estimated that cancer incidences in Brazil for 2020 - 2022 will be 685,960 new patients and 8,460 will be in children and adolescents [1]. Of this small population, 5% are bone cancers cases, osteosarcomas (OS) and Ewing sarcomas (ES) [1,2]. Pain is the symptom most prevalent in these types of cancer which is estimated to be present in about 75% to 90% of patients with advanced cancer[3–9] and can be present from the moment of the diagnosis to the end-of-life [10–12].

With advances in pediatric bone cancer treatment, especially the use of intensive combination chemotherapies and supportive care, pediatric bone cancer death rates have been declining [13]. However, pain continues to be the most prevalent symptom in this population, and it has an important role in their quality of life[14,15], especially in patients with advanced disease and in end-of-life period.

Although there are many pain management guidelines, as World Health Organization (WHO) and Expert Working Group of European Association for the Palliative Care. Pain undertreatment is still a problem and represent 40% of patients with advanced cancer[16–18], one of the reasons for this untreated pain is the inappropriate use of opioids [19].

This study had the objective to evaluate pain management in pediatric patients with bone tumors during

treatment and follow up and to investigate if there was difference in pain status at last evaluation between those on treatment or in disease control and those at the end-of-life.

Material and Methods

This was a retrospective cohort study of pediatric patients with the diagnosis of primary bone cancer consecutively registered at the Pediatric Oncology Department of INCA, from January 1 2011 to October 16 2016. This study was approved by the INCA Research Ethics Committee (CAAE: 67729317.5.0000.5274).

Patients under 19 years old were included, they were registered at INCA's Pediatric Oncology Department with primary bone cancer, with either the diagnosis of OS or bone ES. Patients treated at other institutions and admitted at INCA for exclusive radiotherapy were excluded. The diagnosis, OS or ES, was confirmed by INCA Department of Pathology. Whenever the diagnosis had been carried out in other institutions, they had a pathology review at INCA. All patients were registered in Latin American Cooperative Group for Osteosarcoma Protocol of Treatment (GLATO) or in Latin American Cooperative Group for Ewing Tumors Family (GALLOP). [12,20–23]

At the time of the registration, all patients were initially evaluated for pain. If they were already using some kind of pain control medication for this symptom this was modified whenever necessary according to the patient's clinical evaluation. Pain management was performed by the multidisciplinary team according to institutional clinical protocols established by the pediatric pain clinic service.

In this study, pain measurement was standardized according to Wong and Baker, who had considered 0 as no pain; 1 to 3 as mild pain, 4 to 6 as moderate pain, 7 to 9 as severe pain and 10 as excruciating pain[24–26].

Data was collected from medical records and registered in a specific chart. Three moments were considered during this cohort: at the registration moment, three months after registration and at the last visit before the end of this study or patients death. Patients were considered end-of-life when they had an evaluation up to 1 month before death [27–29].

The variables of this study were: age at diagnosis, sex, race, cancer type, presence of metastases at diagnosis, progression disease, pain complaint, pain measurement, pain relieve treatment, modification in pain relief treatment and pain status at the end-of-life.

Statistical analysis was performed using SPSS for Windows (version 22) and Stata 13.0 (*Stata Corp, LC*). The Kolmogorov-Smirnov Test was used to verify normality, results are presented as median, interquartile range (IQR) and 95% confidence intervals (95% CI). The association between categorical variables was tested by Pearson's Chi-squared test or Fisher exact test; Mann-Whitney test was used to compare continuous variables. Data was analyzed until December 31, 2016. We compared pain status in the last evaluation between those on treatment or in disease control and those at the end-of-life.

To identify possible associations between variables and pain status at the last evaluation, we performed a Poisson regression with robust estimation, log link function to determine crude prevalence ratios (CPR); patients were tested for characteristics, presence of metastasis at registration, disease progression at last evaluation and use of mild analgesics, weak opioids and strong opioids at last evaluation; variables associated to pain (CPR with p-value <0.20) were included in a multivariate model to determine adjusted prevalence ratios (APR). Considered a p-value of < 0.05.

Results

During this cohort period, INCA Pediatric Oncology registered 1,625 patients, from these, 917 patients had the diagnosis of cancer, 157 were primary bone cancer who had been included.

Fifteen patients (9.6%) were loss of some data, but these patients were analyzed: 9 (60%) with diagnosis of OS and 6 (40%) ES; median age 12 years old (IQR 8 - 14) and 4 (26.7%) died. Comparisons were made between loss of data patients and the cohort sample according to age (Mann-Whitney Test; $p = 0.42$), diagnosis (Fisher Exact Test; $p = 0.30$) and survival (Fisher Exact Test; $p = 0.24$).

The cohort study comprised 142 patients, with median age 13 years old (IQR 9-14 years old), 43.6% male sex, being 99 OS (69.7%) and 43 ES (30.3%). Median time for initial treatment after registration was 22.5 days (IQR 16.0 - 34.0 days) and 72 (50.7%) patients had metastatic disease at presentation, 46/99 OS (46.46%) and 26/43 ES (60.46%). Patients characteristics at registration are in Table 1.

We examined pain characteristics and previous treatment at registration. Seventy-six patients (53.5%) had pain evaluated by a method at that moment and 99 (69.71%) were in previous use of pain treatment.

At registration, pain treatment was modified in 60 patients (42.25%); pain treatment at that moment evaluation were prescribed to 103 patients (72.53%) in the following frequency: mild analgesics in 42 (29.57%), weak opioids in 37 (26.05%) and strong opioids in 17 (11.97%), strong opioid plus mild analgesics in 1 (0.70%), strong opioid plus mild analgesics in 6 (4.22%), anticonvulsants in 11 (7.75%), antidepressants in 21 (14.79%) and steroids in 3 (2.11%). Three patients with no pain had their pain treatment discontinued. It was initially observed a reduction in the use of mild analgesics and an increase in the use of weak and strong opioids.

Three months after registration, patients were evaluated again. Eight patients (5.63%) had disease progression. Seventy-one patients (50%) had their pain treatment changed. Pain treatment at that moment was: 21 (14.78%) mild analgesics, 29 (20.42%) mild opioids, 55 (38.73%) strong opioids, 4 (2.81%) mild and strong opioids, 2 (1.40%) mild analgesics and weak opioid, 36 (25.35%) anticonvulsants, 60 (42.25%) antidepressants and 4 (2.81%) steroids.

At last evaluation, all 142 patients had received antineoplastic treatment, 105 (73.94%) were submitted to surgery, 31 (21.83%) to radiotherapy and 62 (43.66%) to chemotherapy. Sixty-five patients (45.77%) had disease in progression. Seventy-three patients (51.41%) had their pain treatment changed. Pain treatment at that last evaluation was: 19 (13.38%) mild analgesics, 21 (14.78%) mild opioids, 63 (44.36%) only strong opioids, 3 (2.11%) weak and strong opioid (Figure 1).

The comparison of pain at registration, three months later and at last evaluation showed along the time a more frequent pain assessment and absence of patients with excruciating pain (Table 2).

A hundred and twenty-two patients had pain classified at last evaluation. Twenty patients who did not have pain assessment by scale, reported no pain at last evaluation and were classified as no pain.

According to this, data was imputed based on pain complaint at last evaluation (self-assessment). Analysis between those who survived or died, revealed no difference of pain status between groups (p = 0.68). Fifty-six patients evolved to death (39.4%), it was observed a 25% (14/56) frequency of pain complaint among those end-of-life patients and a 22% (19/86) among the others at last evaluation (Table 3).

Poisson regression to estimate CPR of pain (yes/no) at last evaluation revealed no difference of pain status between those end-of-life or not (p=0.68), as can be seen on Table 4. All variables with CPR p value <0.20 were candidates to enter a multivariate model to predict adjusted prevalence ratios (APR).

A multivariate model to estimate APR included disease progression, use of strong opioids and steroids at last evaluation. This model was adjusted for age (Table 5).

Discussion

In the present study, there was a high incidence of metastatic disease at presentation (50.70%). Pakos et al [30], in an international OS compilation, where OS Brazilian Group was included, showed 13% of the patients with metastatic disease, the same could be seen in the OS Children Oncology Group (COG) (27%) and Cooperative Ewing Sarcoma Study (CESS) group (30%) [30–34]. Patients arrived at INCA with advanced disease and this characteristic probably influenced in their pain status in all follow-up moments.

At registration, pain was related as the most frequent symptom (61.27%). Even if pain scales were not used, the majority of patients self-assessed pain as moderate to severe and three children had excruciating pain. At that moment, the most frequent drugs used for pain control were mild analgesics (paracetamol or dipyrone)

and treatment was changed in 42.25% of patients. This data contrasts with the WHO recommendation, that suggested the use of strong opioids at that level of pain, specially morphine. This undertreatment could be attributed to the fear of using opioids [16,35–38].

By contrast, end-of-life patients used strong opioids and morphine was the most frequently used, followed by anticonvulsant and antidepressant drugs, as well as other drugs and procedures, as a multimodal therapy. This has been used in agreement with international references.[27,28,35,39]

Along the follow-up period, more patients had their pain classified. Also, pain complaint decreased, and no excruciating pain was observed at last evaluation. At registration, 34.21% had no pain and at last evaluation 73.77% of all patients had no pain. These results suggest the effectiveness of the management of pain control associated during follow-up.

However, we observed association between pain at last evaluation and the presence of disease progression. Those patients presented 3.5 times more pain compared to the others. Comparing with previous international cooperative pediatric bone cancer groups studies, the influence of this variable followed the same direction, being associated to pain[20–23,31–34,40–42].

At last evaluation we observed no difference in pain complaint between end-of-life patients and the others. This suggests that pain management was effective. Also, it was observed opioid use associated to pain complaint at last evaluation, this is a reverse cause-effect association, as those who have more pain use more opioids. However,19.64% of end-of-life patients and 18.60% of those undergoing treatment or in disease control still presented moderate and severe pain, at last evaluation. We suggest that this might have occurred because of family misconception for the use of pain control drugs. Similar results were seen by Snaman et al., who revealed difficulty in pain control, with the principal obstacle being lack of information and misconceptions of opioid use. [5,29,27,43].

Conclusion

In this study, pain management together with increasing opioid use in pediatric patients with bone tumors resulted in reduction of pain complaint and in pain intensity. End-of-life patients did not have more pain than the survivors, but disease progression was associated to more pain.

Conflict of Interest

The authors have no financial or other conflicts of interest relevant to this article.

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