Research Article

OSTEONECROSIS OF THE JAW (ONJ) IN CANCER AND MYELOMA PATIENTS. A 16-YEAR EXPERIENCE OF "RETE ONCOLOGICA PIEMONTE–VALLE D'AOSTA" CANCER NETWORK

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Abstract

Incidence of Medication-Related Osteonecrosis of the Jaw (MRONJ) related to cancer and myeloma treatments is yet to be assessed, with scarce epidemiologic data available from surveys of limited investigated populations. A 16-year (Jan 1 st , 2003 - Dec 31 st , 2018) regional-wide, multicenter retrospective survey was carried out through the regional database of the cancer network in North-Western Italy (Rete Oncologica di Piemonte e Valle d'Aosta), aiming to assess overall frequency, raw incidence and main characteristics of MRONJ cases among myeloma/cancer patients, over a population of 4.4 million inhabitants. Main characteristics: 691 patients (261 M, 430 F); mean age: 68 (38-90) years. Underlying diseases: metastatic breast cancer (43.8%), myeloma (24.1%), metastatic prostate cancer (19.1%), other cancer (13%). Main treatment: zoledronate (71.9%), denosumab (5.3%), other drugs/sequences (22.8%). Sites of MRONJ: mandible (63.3%), maxilla (27.7%), maxilla and mandible (9%). Median number of MRONJ cases: 44 (range: 3-66) cases/year. MRONJ occurrence was registered mostly after 12-36 months of treatment (range: 1-227 months). As a result of cases observed in the regional cancer network centers, we estimated a raw unadjusted incidence ranging between 4.8 and 13 cases/million/year,

with a mean of 9.5 cases/million/year and a median of 10.1 cases/million/year. The present, decades-long multicenter retrospective study represents un almost unprecedented collaboration between Oncology, Hematology, Oral Medicine / Surgery and Oral Maxillo-Facial Surgery units, to investigate the issue of MRONJ, in Italy. According to these data, MRONJ does not seem to be a rare event in metastatic cancer and myeloma populations, and should require the pursuit of such a multidisciplinary effort both in prevention and treatment.

Background: Medication-Related Osteonecrosis of the jaw is a relatively new disease, firstly described in 2003 ([1]), observed in patients undergoing treatment with antiresorptive or antiangiogenic agents. A restricted definition of MRONJ as exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region, persisting for more than 8 weeks in a patient with no history of radiation therapy ([2]; [3]) has been largely questioned, due to clinical evidence of cases with no bone exposure and the lack of imaging evaluation ([4]; [5]; [6]; [7]). Epidemiology of MRONJ is still unknown, with a variable, estimated incidence ranging from 2/million/year ([8], [9]) to 7.8/million/year ([10] [9]). Aim of the present work was to retrospectively describe time trend of MRONJ cases in myeloma and metastatic cancer patients in a 16-years timespan, among the 4.4 million of inhabitants of Piedmont-Valle d'Aosta territory.

Materials and Methods: After cross-checking reports from medical oncology, hematology, and oral care units, data of MRONJ were retrospectively collected from January 1st 2003, to 31st December 2018. Cases without bone exposure and with Computed Tomography evidence of jawbone alterations were included, in concordance with Italian SIPMO-SICMF recommendations ([4], [11], [12]). The main data acquired included: underlying disease, type of drug (bisphosphonate(s) and/or denosumab; eventual antiangiogenic agents); year of MRONJ diagnosis; and site of MRONJ onset.

Results: Between 2003 and 2018, data were collected over a sample of 691 individuals (261 M, 430 F) with a mean age of 68 (range: 38-90) years. Underlying diseases were metastatic breast cancer (44%), myeloma (24%), metastatic prostate cancer (19%), other cancer (13%). The main bisphosphonate administered was zoledronate, either alone (72%) or combined with pamidronate (9,8%). Since 2014, 8.6% of cases were related to denosumab, either alone (5.3%) or as part of a zoledronate/denosumab sequence (3.3%). Between 2011 and 2016, 8 cases of antiangiogenics-related MRONJ were detected, of

which 4 by sunitinib, and 4 by bevacizumab. MRONJ involved mandible (63.3%), maxilla (27.7%), maxilla and mandible (9%).

Most cases of MRONJ arose between the end of the first year and the third year of treatment, but with a wide range of onset, where isolated reports of MRONJ arised either after few months of treatment, or after more than 10 years since beginning of treatment (range: 1- 227 months). Throughout the years, a median number of 44 (3-66) cases was detected. The median number of MRONJ cases per year was 43 in the 2003-2006 period, 44 in the 2007-2010 period, 48.5 in the 2011-2014 period, and 35.5 in the 2015-2018 period.

Conclusions: As a result of cases observed in the regional cancer network centers, we calculated a raw unadjusted incidence ranging between 4.8 and 13 cases/million/year, with a mean of 9.5 cases/million/year and a median of 10.1 cases/million/year. Overall, MRONJ does not seem to be a rare event in metastatic cancer and myeloma populations and should require continuous awareness by prescribing doctors, oral physicians, and maxillofacial surgeons.

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