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PRELIMINARY ANALYSIS OF IMMUNE SUBSETS AND PRO-INFLAMMATORY CYTOKINES IN MRONJ PATIENTS

SECTION: *5A*

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Background: Medication-Related Osteonecrosis of the Jaws (MRONJ) is a severe side effect observed in patients taking anti-resorptive drugs (ARDs) such as amino-bisphosphonates (N-BPs), like zoledronic acid (ZOL), and monoclonal antibodies, like denosumab (DMAB). Clinical signs of MRONJ include necrotic bone exposition and wound healing impairment; symptoms appear mostly late and the related radiographic findings may be challenging to interpret. According to current literature, the pathogenesis of MRONJ appears to be multifaceted and evidence supporting a central role of immune dysfunction consistently grew over time. To evaluate whether different ARDs could induce MRONJ through different mechanisms of action, we investigated circulating immune subsets and pro-inflammatory cytokine release. Adding insights in the pathogenesis of MRONJ is fundamental to improve the clinical management of patients undergoing treatment with such medications.

Patients and methods: In a 1-year study conducted at the Department of Oral Surgery of C.I.R. Dental School (A.O.U. Città della Salute e della Scienza, Turin, Italy) we selected 8 bone metastatic breast cancer patients, treated with ZOL or DMAB, who developed MRONJ (following diagnostic criteria proposed by the Italian Society of Maxillo-Facial Surgery and the Italian Society of Oral Medicine and Pathology, SICMF-SIPMO 2020). All the patients were scheduled to undergo a sequestrectomy, a type of bone resective surgery to remove necrotic bone tissue affected by MRONJ. On the day of surgery, a peripheral blood sample was obtained, peripheral blood mononuclear cells (PBMCs) were isolated and was used for an immunophenotypic analysis of some immune cell subsets (γδ T cells, CD4+ T helper cells, CD8+ T cytotoxic cells, along with their activation markers CD25 and CD69) by flow cytometry. A multiplex analysis of different cytokines in sera (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p70), IL-13, IL-17, GM-CSF, IFN-γ, MCP-1, MIP-1β, TNF-α) was performed to assess the presence of differences between the two MRONJ groups.

Results: In the group of patients with MRONJ induced by ZOL, we observed a significative higher level of CD4+ and CD8+ cells and a decreased level of CD4/CD69+ T cells compared to patients with DMAB-induced ONJ. The level of γδ T cells was lower in patients who developed Zol-induced ONJ compared to patients with DMAB-induced ONJ. Significative differences also emerged by the analysis of cytokine and chemokine in sera, showing a higher level of IL-8, IL-17, MIP-1β and TNF-α in ZOL-induced MRONJ patients compared to DMAB-induced MRONJ patients.

Conclusions: The two ARDs considered revealed a different capability to modulate immune subsets and pro-inflammatory cytokines release. These preliminary data deserve further investigations since could help to identify the different regulation of immune cell subsets exerted by ZOL and DMAB, opening also new therapeutic perspectives.