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Relevance of NF-κB and NRF2 transcription factors into multiple myeloma pathophysiology – A preliminary study

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Multiple myeloma (MM) is a mature B cell dyscrasia characterized by an abnormal proliferation of monoclonal plasma cells, the presence of CRAB symptoms and/or myeloma-defining events. Bone marrow's microenvironment and nuclear factor-κB (NF-κB) signaling pathway play a relevant role in MM pathogenesis, constituting now therapeutic targets. Furthermore, oxidative stress has been observed in several hematopoietic malignancies, being the NF-κB and the nuclear factor (erythroid-derived 2)-like 2 (NRF2) the two key transcription factors (TFs) that regulate the cellular responses to oxidative stress and inflammation. This work aims to elucidate the importance of NF-κB and NRF2 axis in the MM biology and response to treatment.

Thirty patients with MM were enrolled in the study and the bone marrow cell populations were evaluated by flow cytometry. The expression levels of NF-κB and its phosphorylated form, and of NRF2 were determined in the different cell populations, with a special focus on plasm cells, using flow cytometry. The TFs

expression levels were correlated with clinical and laboratorial data.

Our cohort of 30 MM patients included 12 females and 18 males, with a median age at diagnosis of 62 years (32–74). Two patients at diagnosis, fourteen patients in remission and fourteen in relapse. According with international scoring system (ISS) 12 patients (40%) were in stage I, 10 patients (33.3%) in stage II, 5 patients (16.7%) in stage III and the ISS was not determined in 3 patients (10%). In tumor plasma cells, we observed at diagnosis a higher percentage of cells expressing NRF2 (22.9 ± 22.7) and NF-κB (21.7 ± 21.5) comparing with observed at remission time-point (NRF2: 7.0 ± 3.1 ; NF-κB: 4.3 ± 1.5). An intermediated expression was observed (NRF2: 12.2 ± 4.3 ; NF-κB: 6.5 ± 1.8) in samples at relapse. The increase of tumor plasma cells expressing these TFs was also associated with the presence of bone lesion and kappa light-chains. All the other bone marrow populations expressed these TFs, but higher expression was observed in granulocytes.

Our preliminary data suggest an association of NRF-2 and NF-κB expression with MM pathophysiology and disease stage.

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STAT5 – A new therapeutic target in acute lymphoblastic leukemia?

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The signal transducer and activator of transcription (STAT) family members regulate the transcription of multiple genes involved in cell survival, proliferation, differentiation and apoptosis. Deregulation of STATs was associated with several hematological neoplasias such as acute lymphoblastic leukemia (ALL). ALL is a malignant transformation and proliferation of

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hyperdevelopment or mandibular hypodevelopment which leads to a class II of Angle occlusal relationship.

Effect of orthodontic tooth movement on dental pulp mineralization process.

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Aims/Context: Dental pulp stem cells in response to a variety of environmental signals are capable of generating new stem cells and engage in specific differentiation pathways, of which the odontoblastic is essential for the maintenance of pulp homeostasis. As a survival mechanism, the pulp-dentin system responds to an aggression not only with proliferation and differentiation of dental pulp stem cells but also with the production of mineralized tissue inside the dental pulp. The aim of this study was to determine the effects of orthodontic forces on the dental pulp mineralization process.

Methods: Pre-molars subjected to orthodontic forces were divided into 4 groups (control; and 1, 2 and 3 weeks of orthodontic movement) and subjected to histologic and immunohistochemistry analysis with specific mineralized tissue antibodies Osteopontin and Osteocalcin.

Results: At weeks 2 and 3 was observed the formation of mineralized tissue in the dental pulp; and an inflammatory response with differentiation of adipose tissue. The expression of Osteopontin was the same in all experimental groups, while was observed an increase in the expression of Osteocalcin at week 3.

Conclusions: In relation to Osteopontin, it can be infer that the dental pulp expresses this protein as an attempt to contradict the defense mechanism that is the pulp mineralization. The increased expression of osteocalcin in week 3 allowed us to conclude that it is at this later period that the differentiated odontoblast-like cells exist in greater numbers and are metabolically active.

Using less than 10% formalin fixed tissue samples in vimentin immunohistochemical detection: possible impact on oncobiological analysis?

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Context: There are very few circumstances where the diagnosis of malignancy is made in the absence of histopathological confirmation. For prognosis and therapeutic guidance, it is also essential to support all decisions with knowledge of the oncobiology provided by immunohistochemistry and other molecular methodologies. Regarding this goal, it is essential to obtain/preserve adequate diagnostic material. In case of tissue samples, the most widely used fixative is 10% neutral buffered formalin. However, this concentration is not supported by consistent scientific evidence.

Aim: To compare immunohistochemical results considering less than 10% formalin concentrations, in order to support the proper use of this reagent and also to explore the possibility of decreasing the formalin use, since its toxicity is known.

Methods: Three formalin concentrations (10; 7,5; 2,5%) and 70% ethanol (representing non-formalin fixation) were used to fix, for 48 hours at room temperature, similar sized human placenta samples, with a cold ischemia time of 15 minutes. For each fixative, 30 paraffin blocks were prepared, which, after sectioning, were subjected to vimentin (NCL-L-VIM-V9) immunohistochemical detection (Ventana Benchmark GX - OptiView DAB), has this structural protein is commonly used as a fixation quality biomarker. Immunohistochemical results were assessed by two experts using the Global Immunohistochemistry Score (GIS) providing a 0–100 points score. The GIS results were analysed using descriptive statistics and Kruskal-Wallis test with pairwise comparison.

Results: The results were (mean-standard deviation): 2,5% formalin (90,10–6,94); 7,5% formalin (86,77–7,22); 10% formalin (82,94–9,62); 70% ethanol (84,67–9,49). The Kruskal-Wallis test revealed statistical differences between 2,5% formalin and all the other samples ($p < 0,05$). The internal consistency between the two observers was considered satisfactory ($\alpha = 0,72$).

Conclusions: Results sustain that 2.5% formalin provided best immunohistochemical results in this context. Even considering the exploratory type of this research, it is possible to consider the reduction of formalin concentration used in fixation.

Improving peripheral venous catheterization-related outcomes in oncology patients: an action research study in Portugal

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Aims/context: Peripheral intravenous catheterization (PIVC) is not a risk-free procedure with complications rates as high as 90%. In the literature, evidence on the incidence and impact of such procedure in oncology patients is scarce. Thus, we intend to identify current clinical practices and technologies in use during the PIVC of oncology patients. Based on the initial findings, a

multimodal intervention will be implemented and its effectiveness in reducing associated complications will be assessed.

Methods: Through Action Research method, three major phases of activities were defined: i) Planning phase, where current PIVC-related practices, technologies in use and complication rates will be identified; ii) Action phase, with the implementation of a multimodal intervention to align PIVC-related practices to the latest scientific evidence; iii) Reflection phase, discussing the project's results with the ward team and the institution's board. This study will be conducted at the Instituto Português de Oncologia de Coimbra following approval from the Administration Board and Ethical Committee.

Results: An Observational Prospective study is being carried with the support of the general surgical department's medical consultant and nursing manager. Clinically stable patients age ≥ 18 years and with the indication for PIVC insertion for a period ≥ 24 hours are being recruited for study participation. Patients who received immunosuppressive or chemo/radiotherapy treatment in the three months prior to the study recruitment date are automatically excluded. Daily data collection is being undertaken focused on PIVC-related variables (e.g., gauge, selected site) and outcomes (e.g., phlebitis and infiltration rates), patient demographical and clinical variables.

Conclusions: We expect that the multimodal intervention to be developed substantiates higher quality and safety standards during PIVC-related care provision, with the potential to be replicated in other oncology settings.

Pain Evaluation for Health Professionals - Impact on Patient Care

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Introduction and Goals: Pain is a symptom that affects the quality of life of millions of people around the world, constituting the main reason for the demand for health care by the population

It is a morbidity and mortality factor associated with longer-lasting hospital stays and increased consumption of health resources.

In this study the authors aim to:

- 1) Analyze the use of tools for pain assessment in a hospital environment
- 2) Document the main analgesic strategies used
- 3) Evaluate the quality of the approach of the hospitalized patient with pain by health professionals

Methods: A retrospective observational cross-sectional study (1 month) was designed. The study population included 2 groups N1 = 125 health professionals from an hospital service

N2 = 192 patients hospitalized for at least 72 hours

Exclusion criteria considered: length of stay less than 72 h, complete absence of procedural records

Statistical analysis: calculation of frequencies and medians

Results: Less than half of the reviewed clinical files (47.4% medical records and 45.3% nursing records) document pain on admission and less than one-sixth of the clinical records (13.5%)

report the type of analgesia actually administered and the therapeutic response obtained-

Only about half of the therapeutic tables (50.5%) include indications for assessing the patient's pain during hospitalization, although 11.5% have prescription painkillers

Most hospitalized patients experience pain during hospitalization and pain complaints have been poorly documented, conditioning their therapeutic approach

Best practices in addressing pain have been inconsistently applied

Conclusion: The proper assessment and the institution of individualized analgesia that contemplates the different aspects of pain should be considered as an integral part of daily clinical routines

An integrated approach to pain is essential for defining analgesic strategies, improving the quality of care provided to inpatients

Study shows the need to implement surveys and pain assessment scales for hospitalized patients in the clinical interview and adequately document complaints whenever pain is confirmed, it should be continuously monitored and treated.

Multidisciplinary meeting to support family of oncological patients

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Introduction and Goals: In holistic care for the severely ill person, we cannot fail to identify family problems and concerns that will be the key to adapt the person to the disease.

Most of caregivers in palliative care emerge from family. Their roles have an impact on the life and quality of care provided. Health teams must be aware of these changes and plan supportive interventions, with measures that prevent the collapse of his life.

The aims are:-Hold multidisciplinary meeting with professionals and family.

-Assess family needs, opportunities and resources to support safe home return.

-Promote symptomatic relief and fulfillment of the patient's wishes.

Methodology: An exploratory study was elaborated, with quantitative data. A multidisciplinary premeeting questionnaire was applied to all families of patients admitted to oncology service and at the end of meeting a new questionnaire was applied. Responses were voluntary, anonymous and confidential.

Results: Fifty-two pre and post meeting questionnaires were applied. Regarding pre meeting questions 86% of the families wanted information about the patient's clinical situation and how to take care of patient. In post meeting questions 100% of the families expressed satisfaction in holding the meeting, considering it a necessity and an asset and a perk.

This multidisciplinary meeting clarified, reassured and relieved family's anguish. At the end 90% of the families did not express doubts or difficulties regarding how to take care of their patient, allowing safe return home.

It was evidenced that they are clear about the patient's condition and how to intervene according to the needs of each moment. Families also highlight the fact that this is a meeting with a multidisciplinary team in which the family is considered an active member.

Conclusion: The families acquired knowledge and skills allowing them to make decisions about how to care the patient, with fewer referrals to palliative care facilities. The results confirm the need of family involvement in care process of their ill member, contributing to improvement of the quality of life of all and of the care provided, namely with the satisfaction of the patient's wishes.

The use of chlorhexidine gluconate dressings in central venous catheters

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Introduction: The use of chlorhexidine gluconate dressings is recommended to protect the insertion site of short-term central venous catheters (CVC), and is specifically indicated to reduce infections associated with CVC. The dressing consists of transparent adhesive film and a gel pad impregnated with 2% chlorhexidine gluconate, an antiseptic agent with broad spectrum antimicrobial / antimycotic activity, and also contains a plastic fixing device, on a breathable base in adhesive. silicone, less aggressive to the skin, which when replacing the fixation points reduces the entrance doors to microorganisms.

Methods: This study aims to evaluate the effectiveness of using chlorhexidine gluconate dressings in CVC, as well as its importance in reducing CVC-associated infection in a clinical hematology service. This is a descriptive and quantitative study, with a non-probabilistic sample, with a number of 32 patients, between April and June of 2019. The questionnaires were completed by the nurses who performed the treatment at the CVC insertion site according to the training performed. All ethical procedures inherent to the study were followed.

Results: The results revealed that patients had a predominant pathology of multiple myeloma, with the subclavian vein being the preferred site for CVC insertion. The dressings applied in comparison with the semi-permeable transparent polyurethane films, placed previously, allowed to increase the replacement frequency to 7 days in half of the evaluations. In the rest, the dressing was replaced because it was damp, loose or dirty and inflammatory signs were observed in 31.8% of the evaluations compared to the previous ones, which was 50%.

Conclusion: The use of chlorhexidine gluconate dressings requires less manipulation, therefore less risk of infection. The gel allows a continuous application of chlorhexidine gluconate at the puncture point and as they are transparent dressings they allow visualization of the insertion site without removing it. The gel was able to absorb liquids (sweat, blood or exudate) without interfering with antiseptic activity. In turn, the fixation device allows strong adhesion and is less aggressive to the skin.

ROS1 positive Non-Small Cell Lung Cancer clinical case

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Introduction: The identification of molecular targets has become indispensable for the treatment of lung cancer and has revolutionized its prognosis. However, the percentage of mutated patients who can benefit from these therapies is low. ROS1 gene rearrangement is present in only 1–3% of the lung adenocarcinomas.

Clinical case: A 67 year old non-smoker woman presented to the emergency department with dyspnea and cough for the last 3 months. She had a chest CT scan with a 41x47 tumor lesion in the left lower lobe, homolateral pleural effusion and multiple adenopathies.

Bronchoscopy (27/07/2018) revealed tumor lesion with obliteration of the left lower lobe bronchus. Biopsies revealed lung adenocarcinoma.

On August 14, she was hospitalized for serious worsening of dyspnea. CT angiography showed a significant worsening of the left hilar mass with left principal bronchus obliteration with atelectasis, worsening of the pleural effusion and bilateral lung metastases. She repeated bronchofibroscopy (21/08) with significant worsening with infiltration of practically all left main bronchus and total obstruction of the lobar orifices.

Awaiting molecular study she started chemotherapy with cisplatin and pemetrexed on August 23 and was discharged with PS2 and on oxygen therapy. Revealing to be ROS1 positive she started Crizotinib on 28/09. After 2 weeks of treatment, there was significant radiological and symptomatic improvement (PS1 and no more need for oxygen therapy). Currently, more than one year after starting therapy, she has PS 0 and CT scan revealing complete response.

Conclusion: We describe a case of an aggressive lung cancer with complete response maintained after 1 year of therapy.