Cancer-related fatigue casts a dark shadow over the quality of life of cancer patients

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Dynamic changes of cancer-related fatigue (CRF) among colorectal cancer patients treated by chemo- or radiochemotherapy and, in addition, by supportive care with a specific mistletoe preparation, were determined. Patients completed anamnestic interviews at the beginning of the post-surgical therapy, in the midst of the intended-to-treat therapy and at the end of the chemo- or chemo-radio therapy. The retrospective results suggested that inflammatory processes are involved in CRF. Comorbidities were associated with the prevalence and severity of CRF. The supportive care delivered by mistletoe application during the post-surgical treatment period was able to decrease CRF symptoms and to improve quality of life.

Keywords: quality of life; cancer-related fatigue; inflammation; anti-inflammatory drugs; supportive care; mistletoe

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Vast sums of money have been expended in the hope of finding a cure in the fight against cancer. Since the beginning of the era of modern chemotherapy, in the 50’s and 60’s of the last century, huge strides were made by modern medicine, yet the success rate for most cancers did not fulfill clinically, what we might have expected from the promise held out by the accumulation of knowledge in cancer biology.

In the near future, the management of a cancer patient will be driven by an integral of individual tumor biology, tumor microenvironment, host characteristics, and psychosocial, cognitive and social entities to identify that patient -those group of patients -who will show a favorable therapeutic response [1]. However, supportive cancer care must become in parallel a mandatory service for patients to improve quality of life when undergoing treatment and entering follow-up phases.

Cancer-related fatigue (CRF) is a disabling and distressing symptom complex and is highly prevalent -up to 70% - in cancer patients. It is a subjective state of overwhelming sustained exhaustion and decreased capacity for physical and mental work, which is not relieved by rest. CRF differs substantially from the fatigue that accompanies everyday life, which is usually temporary and relieved by rest [2, 3].

Very recently, we could demonstrate in colorectal patients, who were treated in a supportive care intention by a mistletoe preparation (ISCADOR®Qu), in addition to
chemo- or radio-chemotherapy, a beneficial effect to improving CRF [4]. However, to understand a mechanism-driven intervention, specific research efforts have to be carried out, which must be based on a solid ground to frame a scientific hypothesis. It is obvious that CRF is influenced by a number of critical factors, which have to be targeted by experimental and clinical research. CRF demonstrates striking similarities with the cytokine-induced sickness phenomenon in animal models [5]. It is a rational argument to link cytokine-induced inflammation to CRF. Smith AK et al. [6] could demonstrate that epigenetic changes were associated with inflammation and CRF in breast cancer patients treated by chemotherapy. Bower JE et al. [7] published the results of a randomized controlled trial, showing a beneficial effect of Yoga by reducing inflammatory signals in fatigued breast cancer survivors. It is an attractive working hypothesis that CRF in cancer patients is driven by the activation of the pro-inflammatory cytokine network and by activated neuro-endocrine loops. To address the neuronal part in CRF, the CNS stimulants modafinil and methylphenidate have been recommended for the treatment of CRF. However, clinical trials recently demonstrated no effect of these drugs on CRF in lung cancer patients [8] and only marginal effects when supported in docetaxel-based chemotherapy protocols [9].

The results of the retrospective clinical trial [4] posed the main question, why is a mistletoe intervention in chemo- or chemo-radiotherapy treated colorectal tumor patients successful to improve CRF? Kaveri S. et al. [10] investigated in A549 cells the activity of a mistletoe preparation (ISCADOR®Qu) on the cytokine-induced cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) activities, which play a critical role in the pathogenesis of inflammation. They found a novel anti-inflammatory mechanism of mistletoe by inhibiting cytokine-induced PGE2 via selective inhibition of COX-2.

Macrophages have classically been subdivided into M1 and M2 macrophages, depending on their roles in the immune response, wound healing, atherosclerosis and promotion or inhibition of tumor growth. M1 macrophages operate as inflammatory cells and detect and destroy invading pathogens and tumor cells. However, they differentiate under the influence of a wound healing microenvironment cytokine pattern into M2 macrophages. M2-differentiated macrophages contribute to tumor progression, tumor cell migration and metastasis formation by initiating angiogenesis and inhibiting specific antitumor T-cell response. A recent review about the association between immune-/ (genomic) markers and CRF revealed an empirical support for the association between high levels of CRF and elevated systemic inflammatory markers. Elevated systemic inflammatory markers (IL-6, IL-1β, TNF-α) can lead to CRF by themselves [11] or are drivers to differentiate M1 into M2 macrophages; M2 macrophages promote tumor growth and progression. Therefore, there is an urgent need for drugs, which are able to block the M1 to M2 macrophage switch and, concomitantly, decrease a systemic inflammatory cytokine pattern. Mistletoe preparations contain substances, which are able to determine the balance of M1 and M2 macrophages and anti-inflammatory cytokine patterns, and are therefore candidates to alleviate CRF.

The reported study on supportive mistletoe care and improvement of CRF [4] in cancer patients is, because of its research design, an observational one; that limits the ability to draw causative conclusions. The current knowledge about the mechanisms of CRF is still based on limited experimental and clinical results. The diversity of factors that contribute to multidimensional clinical symptoms might exhibit common molecular pathways, anchored within the cytokine network and the balance of cellular immunogenicity.

Conclusions

Patients, suffering from CRF, cannot wait until the identification and therapeutically targeting of causatively defined cytokine patterns associated with CRF und inflammation. Therefore, those observational results, obtained for the time being with drugs, which do not show significant adverse effects, but exhibit anti-inflammatory properties, should be considered in clinical chemo- or chemo-radiotherapy protocols, to fight at an early stage against CRF.

Further research efforts in CRF must aim to identify and, perhaps, to close gaps between molecular immunology, cytokine-triggered adverse inflammatory processes and clinical symptoms. This can only be achieved by longitudinal clinical studies and by monitoring individually the levels of immune/ inflammatory markers.

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Conflict of interest

The author declares that there is no conflict of interest.

References


