

Meeting Report

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Nutrition in advanced cancer patients

In the last session of the ESMO symposium on nutrition in cancer, 5 key aspects were discussed. The co-chairs, Ylva Orrevall, Sweden, and Florian Strasser, Switzerland, guided the discussion around the role of anti-cancer treatments to manage cachexia, pharmacological interventions which are available and under study, important aspects of psychosocial consequences of patient and family members having involuntary loss of weight, and newer data on home parenteral nutrition in patients in the palliative cancer care setting at home. The final discussion addressed aspects of targeted therapy, including but not limited to, pharmacological interventions, with a focus on an increasing role of a new cancer classification.

Dr. Alessandro Laviano from Sapienza University Roma, reported that chemotherapy can improve anorexia

if the tumor shows a tumor response, citing the paper of Geels from JCO 2000. In contrast, he presented data which showed that during combined multi-modality treatment for head and neck cancer, in the duration from diagnosis and treatment to revalidation, the energy intake per kg/body weight decreases during chemo-radiation treatment, but less during radiotherapy or surgery alone. The number of patients was very small; however this paper showed an important trend. This study was confirmed by data from Ohno (Gyn.Oncol. 2006) which compared radiotherapy alone with radio-chemotherapy with Cisplatin lower versus high dose in patients with a cervical cancer, which clearly showed that radiotherapy alone causes less loss of appetite and weight loss.

Also, the question of whether chemotherapy can directly cause effects on skeletal muscle and contribute to

fatigue and muscle loss was discussed. The recent study from Van Norren (BJC 2009) demonstrated that in animal models the maximum muscle force decrease was associated with a higher dose of Doxorubicin.

A wealth of data demonstrates that pro-inflammatory cytokines are associated with cancer specific survival and also cancer cachexia.

Recent data showed that genotypes with alterations in the IL6 gene, the IL10 gene, the IL12 gene or the TNF-alpha gene, were clearly associated with weight loss (Deans D AMJ Clin.Nutr.2009). Laviano also discussed data on cyclooxygenase inhibitors and 3-fatty-acids, which have strong data *in vitro*; however clinical studies are still controversial.

The data from Lundholm *et al.* in Cancer 2004 combining nutritional intervention with Cyclokinase inhibitors and with Erythropoetin are relatively difficult to extrapolate; the data concerning N3-fatty-acid have been shown not to be consistent in large randomized controlled trials.

New data combining fish oil, specifically oligonucleotide mixture or high protein/leucin, suggest that combined interventions including fish oil or omega-3-fatty acid hold promise for the future; papers on this topic include Van Norren (British Journal of Cancer 2009) and Fabre J (British Journal of Cancer 2008).

Dr. Laviano concluded that the best treatment for cancer associated catabolism is an effective anti-tumor therapy, but that anti-neoplastic strategies also may worsen nutritional status. Therefore there is a strong argument for anti-inflammatory interventions.

Prof. Giovanni Montovani summarized the wealth of new pharmacological interventions for the multifactoral cancer cachexia syndrome.

He briefly outlined the pathogenesis including the metabolic and endocrine changes, with specific focus on the importance of pro-inflammatory cytokines. A key point was that combined treatments are likely to be the future, either administered alone or in conjunction with more tailored patient-centered interventions, depending on the pre-dominant pathogenetic driver of the cancer cachexia syndrome.

He summarized the ineffective treatments, including drugs commonly used and drugs with a strong rational design, that failed or did not show unequivocal results in clinical trials. He also discussed emerging drugs under clinical evaluation, and future trends.

With regard to progestins, he stated clearly that fewer than thirty percent of patients treated with Megestrol experience appetite stimulation and there is a lack of improvement in quality of life or survival. Interestingly, he showed that the *in vitro* production of cytokines and serotonin involved in anorexia, and cachexia and emesis in cancer patients is reduced by Megestrol. However, in summary, the recent Cochrane review supports that Megestrol Acetate stimulates

appetite and weight gain, but without any conclusion about quality of life. Interestingly the Megestrol Acetate nanocrystal oral suspension which was designed to optimize drug delivery and improve bio-availability seems to have the potential to produce a more rapid clinical response; currently clinical trials are being planned to evaluate this drug.

Corticosteroids were mentioned to be effective, but clearly only for 1 or 2 weeks, and should be used exclusively in far advanced cachexia.

Professor Mantovani specifically mentioned drugs which have a strong rational and also a pre-clinical data set that have shown equivocal results in clinical trials so far. Those include substances which influence the synthesis and/or release of cytokines (such as omega-3-fatty-acid, Melatonin, Cox-2-inhibitors and Thalidomide), those which inhibit the cytokine action (anticytokine-antibodies or anti-inflammatory cytokines such as IL12 or IL15), and those which inhibit proteasome activity (Bortezomib). For these substances, current criteria for selected patient groups are being developed to determine who might benefit from the substances; most importantly, new clinical trials are needed for some of those substances. It is clear that, to date, all these substances cannot be deemed as a standard therapy for cancer cachexia.

Several emerging drugs were mentioned such as Ghrelin and Ghrelinmimetics, Betahydroxy-Betamethylbutyrat, Oxandrolon, and Olanzapin, as well as Aminoacids such as the branched-chain amino acids Arginine and Glutamine, and also American Ginseng.

Currently various trials are underway which explore combination treatments.

For clinical practice patients should be enrolled in clinical trials and/or pharmacological management should be part of a specialized multiprofessional team management approach that combines nutritional counseling, physical activity and a staging of cancer cachexia to individualize treatment approaches.

Ylva Orrevall from Sweden tackled the controversial theme of home parenteral nutrition in advanced cancer patients. She focused on her work with patients in a palliative home care service, who receive medical care in their homes that was available 24/7 per week. Typically, home parenteral nutrition was delivered in all in one bag, 2-7 nights per week.

A qualitative research project investigating experiences from cancer patients and their family members revealed that the benefits generally outweigh the negative aspects and that physical, social and psychological benefits arose. Most patients had prior experiences that they were unable to solve nutritional problems by themselves but with home parenteral nutrition they got a sense of relief and security, enjoyed better quality of life and also experienced weight and energy increase, more strength and were able to be more active. Also, oral food intake and meal time experience

improved since they had less stress about eating. This study was conducted with 13 patients.

An additional study involved 21 palliative home care services that performed cross-sectional interviews by telephone of 621 patients; 11% of these patients had parenteral nutrition. Interestingly, of those patients almost 75% were also able to eat orally and about half of them also used oral nutritional support products. These patients varied a great deal in their weekly treatments. In terms of tolerability, less than 10% reported discomfort related to the feeding solutions.

These data from Orrevall *et al.* suggest: 1. That patients might indeed profit from individualized combined oral nutritional intake and artificial parenteral nutrition in their homes, and 2. that those patients participating in home palliative care services had a survival often far longer than 6 months, which highlights the importance of an active total care program, as in the palliative care definition proposed by WHO and also by ASCO in its recent recommendation on palliative cancer care (Ferris F. *et al.* J Clin Oncol. 2009).

Jane Hopkinson from Southampton, UK discussed how to help people with advanced cancer and their families to live with the symptoms of the cancer cachexia syndrome. She presented her work with a literature review, followed by exploratory work to develop the McMillan approach to weight and eating (MAWE), which was then validated.

She clearly pointed out that weight loss and anorexia pose problems for clinicians, patients and family members. In a study of 199 patients, 52% had concerns about weight loss or eating less; additionally, more than 75% of all patients had either a weight loss or a problem with eating less.

The McMillan approach to weight and eating has 5 elements:

1. Breaking through the weight loss taboo, 2. telling healing stories, 3. managing conflict, 4. eating well, and 5. support for self action. Currently a randomized (cluster) trial compares two study sites, with or without this approach (MAWE).

In summary, it is very important to express the importance of the psychosocial consequences of involuntary loss of weight to patients and also to family members. Secondly, it is important to have a multidimensional approach to alleviate this suffering or concern. By normalizing experience and mediating between family members and patients, it is possible to identify patients' positive eating habits and to empower both patients and family members.

Florian Strasser highlighted the importance of a novel classification for cancer cachexia, which should guide interventions in a more targeted way. Key points were to identify patients who already demonstrate pre-

cachexia, defined as subtle weight loss, and who are already experiencing metabolic and endocrine changes.

A second point made by him was that nutritional impact symptoms, which are potentially reversible, need to be intensively searched for in patients having involuntary loss of weight (nausea, vomiting, constipation, defecation after meals, dyspnoea, depression, xerostomia, and dysphagia, etc.).

This implies that a strategy of dealing with nutritional issues in caring for advanced cancer patients is quite compatible with the modern definition of palliative cancer care (Ferris F *et al.* J Clin Oncol. 2009) and the ESMO policy of integrated oncology and palliative care (Cherny N *et al.* Ann. Oncol. 2009). The structure, the assessment and monitoring of eating related problems, as well as for pain and other symptoms, should be a standard of oncological care for advanced cancer patients. However in many clinics this monitoring is far from ideal and would require improvement.

As a third point, how to guide interventions, Dr. Strasser identified the developing cancer cachexia staging system with the emphasis that criteria for cancer cachexia require a cancer specific tool. For diagnostic purposes, an involuntary weight loss of >5% over the previous 6 months that is ongoing throughout the last 1 to 2 months is required. It is important to recognize that cancer cachexia has different characteristics, including impaired food intake, catabolic drive driven by tumor and inflammation, decreased muscle mass and strength, other metabolic and endocrine factors and, as a fifth important element, the impact of cachexia on function and psychosocial distress. Also Dr. Strasser flagged the importance of defining a late, not significantly reversible, cancer cachexia phase in patients who have a life expectancy too short to profit from nutritional interventions and a low performance status. These patients often receive typical symptom directed interventions and a goal to improve muscle function is not realistic. These patients need to be clearly distinguished from patients with secondary nutritional impact symptoms, which can be reversed, and those patients with a full cachexia syndrome.

New targeted interventions are emerging for appetite stimulation, gastrointestinal motility, anabolic metabolism and anti-inflammation. Several trials were mentioned which are on-going and emphasize the importance of including patients in clinical trials.

Interventions are not limited to pharmacological management; counseling, education and including family members are also important.

To improve eating, a cognitive control of eating intervention can be applied by counseling patients that they have a lessened innate drive to eat and that they "can be smarter than their tumor" and eat even though they don't have hunger. Also education is important to understand the catabolic process and why they have a small stomach due to gastrointestinal dysmotility.

To alleviate psychosocial distress, it's also important to counsel patients to find other means to express love and caring. An example of how palliative cancer care can be used

to relieve distress associated with eating, a typical palliative cancer care intervention is to prepare for the worst and hope for the best and also to express emotions. These combined interventions include pharmacological, educational, behavioral and psychosocial interventions that pertain to a comprehensive management of cancer cachexia; it was clearly mentioned that multi professional teams are required.

In conclusion, Dr. Strasser mentioned that nutritional issues include: 1. A spectrum from pre-cachexia to late, not significantly reversible, cachexia, 2. that a cancer specific cachexia classification is required which builds on a generic wasting definition, 3. the practice guiding multidimensional assessments may be harmonized into future collaborative clinical standards, and build the backbone of quality clinical research. Finally, it should be recognized that tailored interventions encompass cause-specific therapies, alleviating therapies, and family centered interventions, and that they all include nutrition, pharmaceutical agents, education and counseling.

At the end of the session an oral abstract was discussed, which compared a new operational definition of cachexia with simple weight loss data; this presentation highlighted the importance of further research on a cachexia classification in cancer patients.

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