Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force

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Received 10 October 2013; revised 4 February 2014; accepted 5 February 2014

Background: Weight loss and cachexia are common, reduce tolerance of cancer treatment and the likelihood of response, and independently predict poor outcome.

Methods: A group of experts met under the auspices of the European School of Oncology to review the literature and—on the basis of the limited evidence at present—make recommendations for malnutrition and cachexia management and future research.

Conclusions: Our focus should move from end-stage wasting to supporting patients’ nutritional and functional state throughout the increasingly complex and prolonged course of anti-cancer treatment. When inadequate nutrient intake predominates (malnutrition), this can be managed by conventional nutritional support. In the presence of systemic inflammation/alteration metabolism (cachexia), a multi-modal approach including novel therapeutic agents is required. For all patients, oncologists should consider three supportive care issues: ensuring sufficient energy and protein intake, maintaining physical activity to maintain muscle mass and (if present) reducing systemic inflammation. The results of phase II/III trials based on novel drug targets (e.g. cytokines, ghrelin receptor, androgen receptor, myostatin) are expected in the next 2 years. If effective therapies emerge, early detection of malnutrition and cachexia will be increasingly important in the hope that timely intervention can improve both patient-centered and oncology outcomes.

Key words: cancer cachexia, malnutrition, nutritional support, systemic inflammation, review

introduction

Malnutrition and cachexia (which differs from simple starvation/malnutrition in that it cannot be fully reversed by conventional nutritional support) have for many years been relatively under-researched and under-resourced aspects of cancer supportive care. This has been the case despite the well-documented scale of the problem: more than 50% of advanced cancer patients experience cachexia and more than 10% die with or from it [1]. Weight loss is also a major source of distress for cancer patients and their carers. In part, this is because wasting of muscle—frequently perceived as distressing—‘makes the disease visible’ and is taken as signifying the proximity of death...
[2]. On the other hand, it is perhaps the very association with advanced and incurable disease that has bred a reluctance to discuss the issue openly, a certain nihilism with regard to potential treatment, and the lack of a proactive and systematic approach to assessment and management [3].

It is therefore welcome, especially with the emphasis on patient-centered care, that there is growing interest in cancer-associated malnutrition and cachexia. Our concept of its impact has expanded from anorexia and weight loss to encompass functional components such as decreased exercise capacity and muscle strength (with resulting adverse effects on quality of life, self-care and independence), systemic inflammation, the emotional consequences of the syndrome and its impact on the tolerability and effectiveness of treatment [4]. Knowledge about the underlying pathophysiology has also increased substantially, particularly with regard to the central role of systemic mediators of inflammation [5–8].

**new developments**

In cancer-related anorexia and the abnormalities of anabolism and catabolism that underlie cachexia, we appear to be on the threshold of effective new interventions based on the identification of novel drug targets [5]. To sound a caution, we must have the results of large, randomized trials (some nearing completion) demonstrating safety, efficacy and cost-effectiveness before any of these agents can be considered for clinical practice [9]. Even so, in anticipation of effective novel therapies, and with our more sophisticated use of existing nutritional support, the early assessment of malnutrition and detection of cachexia is increasingly important. With timely use, there is hope that these developments will alter both patient-centered and oncological outcomes.

As an encouraging model, a recent randomized trial by Temel et al. in patients with newly diagnosed metastatic non-small-cell lung cancer (NSCLC) showed that integrating palliative and supportive care along with standard oncologic care early in treatment significantly improved both quality of life and survival when compared with standard oncologic care alone [10]. A >2-month prolongation of median survival was evident in the early palliation group (11.6 versus 8.9 months, P = 0.02) even though they had less aggressive end-of-life care. Although this study did not involve nutritional support specifically, some of the benefits may have been through improved management of pain and constipation which affect nutritional status.

But how do we best identify patients at risk of malnutrition, weight loss and functional decline? Do we need to add variables to the classification systems already developed? Are particular groups more likely than others to benefit from earlier intervention?

In this context, a group of clinicians with a background in cancer nursing, dietetics, surgery, medical oncology or palliative care and with a publication record in cancer nutrition or cachexia convened in December 2012 under the auspices of the European School of Oncology to pool their experience, review the literature and make recommendations (summarised in Table 1) as the basis for further discussion. There was no attempt formally to assign levels of evidence to these recommendations. This article summarises what we know and what we still need to know. Its aim is to increase awareness of the importance of malnutrition and cancer cachexia and to facilitate research.

**impact of weight loss on cancer outcome**

Even before diagnosis and treatment, weight loss is common. In one series of more than 3000 cases, the frequency of weight loss ranged from 31% in patients with good-risk non-Hodgkin’s lymphoma to 87% in those with gastric cancer [11]. A systematic review recently found a negative relationship between health-related quality of life and loss of weight [12]. Weight loss is also an indication of adverse prognosis. In 9 of 12 Eastern Cooperative Oncology Group (ECOG) protocols, median overall survival (OS) was significantly shorter in patients with pre-chemotherapy weight loss than in those who had maintained their weight [11]. Weight loss was associated with poor prognosis in non-NSCLC, prostate and colorectal patients. The effect was seen within categories defined by Performance Status (PS) and the anatomical extent of tumour. In patients with advanced breast cancer, response rates were also lower among those who had lost weight before chemotherapy.

Cachexia reduces patients’ ability to tolerate anti-cancer treatment. In a prospective study of 100 NSCLC patients undergoing chemotherapy, those who were malnourished and hypoalbuminaemic experienced major toxicities significantly more frequently than those who were not [13]. Retrospective review of data gathered in 1555 consecutive chemotherapy patients with gastrointestinal cancer showed that those with self-reported weight loss before treatment experienced more frequent and severe toxicities despite being treated for a shorter period [14]. Pre-chemotherapy weight loss correlated with shorter failure-free and OS and decreased response rate, quality of life and PS. Weight loss at presentation was an independent prognostic variable. In lung cancer, weight loss before chemotherapy is an independent predictor of OS [15]. And in both resected and non-resected pancreatic cancer, cachexia is significantly associated with poorer survival despite the fact that cachectic and non-cachectic patients did not differ in tumour size or lymph node status [16].

**current clinical practice**

For cancer patients suffering predominantly from simple starvation (malnutrition) [17], there are clear treatment pathways such as stenting an obstructive oesophageal cancer, tube feeding for patients with head and neck cancer undergoing radical chemoradiotherapy/surgery and home TPN for slowly progressive ovarian cancer causing multi-level obstruction. The nutritional status, physical functioning and quality of life of patients receiving radiotherapy for cancers of the gastrointestinal tract or head and neck can also be helped by intensive dietary counselling and recommendations regarding the fortification of food and modifying its texture [18]. In an randomized, controlled trial (RCT) conducted among colorectal cancer patients undergoing radiotherapy, early and individualized counselling and education about their usual foods improved quality of life and prognosis (over a median follow-up of over 6 years) when compared with groups of patients who did not receive such advice [19]. These findings are worthy of further evaluation and confirmation in similar or related groups of patients. However, there is little specific therapy for patients with predominant hypermetabolism/catabolism (such as the small-cell lung cancer patient with rapid weight loss who is eating well).
Most patients lie somewhere between these extremes and the clinical problem is to identify those in the anorexia–cachexia spectrum who might gain demonstrable clinical benefit from current modes of nutritional support and our limited armoury of other therapies. For this majority of patients, the rationale for intervention relies more on inherent plausibility, on the well-documented adverse effects of malnutrition and on individual trials/opinion than it does on benefit proven by meta-analysis of large multicentre trials conducted in a contemporary setting and during concurrent anti-cancer therapy. One key aid to progress would be an agreed classification of cancer cachexia (using clinical variables and biomarkers) to be used in conjunction with a series of large RCTs designed to provide a robust evidence base.

**definitions of cachexia**

Several attempts have been made to define cachexia in a way that would facilitate diagnosis, management and clinical trials. Weight loss of 10% or more continues to be regarded as clinically significant [20]. However, this can conceal a disproportionately higher loss of muscle mass [4], and weight loss alone is often insufficient to capture the complexity of cachexia [21, 22]. The addition of reduced food intake and systemic inflammation (as indicated by C-reactive protein, CRP) to the criterion of 10% or greater weight loss produced a three-factor profile identifying patients with poor function and adverse prognosis [21].

Using a prospective database, Bozzetti and Mariani validated a classification based on loss of body weight and the presence or absence of at least one symptom (anorexia, fatigue or early satiety) significantly related to clinical features such as tumour type, cancer stage, ECOG PS and symptom severity [23]. Subsequently, Fearon et al have attempted to achieve international consensus on a framework to develop a classification...
for cachexia akin to the tumour–node–metastasis system for cancer staging (Table 2) [24].

These and other definitions of cachexia have in common a criterion based on weight loss (albeit varying from 2% to 10%). The majority also include the presence of inflammatory markers (notably elevated CRP, but some definitions also encompass low albumin or low muscularity).

### assessment of body composition and early markers of cachexia risk

Certain variants among the genes underlying an individual’s innate immune system appear to confer a predisposition to cachexia. The P-selectin genotype is one example [25]. Such factors are likely to be relevant only in a proportion of the population. However, just as the tumour transcriptome is now being used to guide cancer treatment, it is conceivable that analysis of the skeletal muscle transcriptome might one day be used to select the most appropriate therapy in cachectic patients (even though hundreds of genes are up- or down-regulated) [26].

Though none is ready for clinical use, early changes in relevant biomarkers may have the potential to identify patients needing intervention before they develop overt cachexia. Among them are several plasma markers of inflammation. Gioulbasanis et al. studied a wide group of potential markers including haemoglobin, albumin, CRP, ghrelin, adiponectin, leptin and IGF-1 [27]. CRP appears to be the most robust, with relevance to several tumour types [28, 29]. In relation to muscle breakdown, the ubiquitin proteasome pathway is clearly of interest as, in the urine, myosin heavy chain [30] and proteolysis-inducing factor. The various models of cachexia appear to account for 25%–50% of cachexia risk, of which CRP accounts for around a third [31].

A computed tomography (CT) scan at the lumbar vertebrae level 3–4 can measure skeletal muscle mass as distinct from fat. Analysis of routine diagnostic CT scans can quantify whole-body adipose and muscle mass with a reproducibility of around 2%, detects small changes in body composition and has been used to detect early cachexia [32, 33]. Though muscle mass does not always equate to function, this would help identify the increasing number of patients who have low muscularity while also being obese. However, CT is limited as a routine assessment to those patients with a clinical need for scanning. Bioimpedance is also a potentially useful measure of lean mass, and has been investigated as a prognostic indicator in breast and advanced colorectal and pancreatic cancer [34, 35]. While bioimpedance is helpful for evaluating groups of patients, it is not sufficiently accurate for longitudinal follow-up of individuals.

### drug targets arising from pathophysiology

The pathophysiology of cachexia is multifaceted. Anorexia is an important factor in some patients, but the major or compounding element is abnormal metabolism [9, 36]. Cancer cells not only produce tumour-specific cachectic factors but also interact with host cells to produce cytokines which lead to an acute phase response, neuro-endocrine activation and a chronic state in which catabolism dominates anabolism. The ESPEN guidelines of 2009 suggest that around 50% of patients with weight loss are hypermetabolic [37]. Changes in metabolism may be accompanied by anorexia, fatigue and nausea which, in turn, exacerbate weight loss.

The presence of a systemic inflammatory response is indicated by the Glasgow Prognostic Score (GPS) which combines data on elevated CRP (>10 mg/l) and hypoalbuminaemia (<35 g/l). The GPS is prognostic in unselected cancer patients, in those with operable or inoperable disease and in those undergoing chemoradiotherapy [38, 39]. The GPS was as prognostic as PS and, when used along with it, added prognostic accuracy. It also appears able to identify patients who are likely to develop cachexia, emphasizing the importance of systemic inflammation as a target for therapeutic intervention.

Such targets can be upstream (e.g. inflammatory mediators) or downstream (e.g. conserved mechanisms of muscle anabolism or catabolism) (Table 3). Targets range from antagonists of pro-inflammatory cytokines such as IL-6 and IL-1α and activin type II receptors (ActRIIB) and its ligand myostatin to selective agonists of the androgen receptor, β2 adrenergic receptor or ghrelin receptor whose activation should have direct or indirect potential to stimulate anabolism [40] and/or improve appetite. Results from several major phase II and III trials are awaited.

### principles and nature of intervention

**Multi-modality treatment and early intervention during cancer therapy.** Patients should be assessed for malnutrition and cachexia only if assessment is likely to lead to appropriate intervention: for a patient, to know that a problem has been identified brings an expectation that it can be addressed. Increasingly, this is likely to be the case. Conventional management of cachexia is often focused on the use of oral nutritional supplements. In some centres, attention is also paid to the control of systemic inflammation with either n-3 fatty acids or NSAIDs. Some centres also advise physical activity and therapeutic exercise.

1. Oral nutritional supplements: Individual studies have shown that general nutritional support can be effective in reducing loss of weight in patients undergoing cancer therapy [41]. However, a meta-analysis of 13 RCTs in malnourished patients found that studies were of variable quality and outcome: compared with routine care, oral nutritional interventions improved some aspects of quality of life but did not decrease mortality [42]. Some centres have emphasized the clinical benefits of nutritional counselling in colorectal cancer patients receiving radiotherapy [19, 43]. However, a recent study which provided nutritional support to patients with thoracic cancer via a dedicated rehabilitation service table 3.

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<th>Class</th>
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<td>II</td>
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showed that such support failed to prevent weight loss and did not improve survival [44]. One key issue with oral nutrition supplements is patient compliance. While the taste and texture of current supplements is better than that of their predecessors, it is hoped that further developments in the science of hedonics will help improve compliance.

(ii) n-3 fatty acids: A meta-analysis of 38 papers evaluating fish oil/n-3 fatty acids in advanced cancer cachexia found that while some smaller trials, often without a control group, reported benefit, the majority of the larger RCTs did not find significant effects [45]. However, a recent review of supplementation with eicosapentaenoic acid identified limitations with current studies and suggested methods that might enhance the value of future clinical trials [46]. A second recent review found that oral or enteral omega-3s maintained body weight and quality of life in cancer patients [47].

(iii) NSAIDs: of 13 studies included in a recent review of intervention using NSAIDs, all but two showed improvement or stable weight or lean body mass but 7 studies had no comparator [48]. The conclusion was that the small size of studies, flaws in some and the risk of false positives resulting from multiple outcome measures meant that the evidence was insufficient to recommend NSAIDs outside trials.

(iv) Exercise: It is difficult to engage all patients in a programme of therapeutic exercise. However, this should not promote an attitude of nihilism. Effects of exercise include enhancing muscle protein synthesis, attenuating the catabolic effects of cachexia and modulating levels of inflammation [49]. Strategies to make exercise more accessible therapy include offering it early in the course of disease, at lower intensities and in different forms.

In short, meta-analyses of the many studies (using different inclusion criteria) involving general nutritional intervention, supplementary fish oils and NSAIDs have shown generally unimpressive results. A limitation of these studies is that they involved nutritional interventions or NSAIDs in isolation: until the start of the Multimodal Exercise/Nutrition/Anti-inflammatory treatment of Cachexia (MENAC) study (see below), there had been no attempt to combine ‘optimal’ nutritional support with optimal anti-inflammatory therapy. Yet the complexity of cancer-associated weight loss, coupled with the fact that cancer treatment in general utilizes the paradigm of multimagent therapy, suggests that cachexia treatment will necessitate more than one concurrent intervention [50].

Given the multifaceted nature of the problem, the solution is likely to lie in a multi-modality approach. This would encompass general medical and oncological management, stimulation of appetite, nutritional counselling and supplementation, the encouragement of exercise and one or more pharmacological agents.

Another principle is that intervention is more likely to be effective when given early, before pronounced metabolic abnormalities produce resistance to nutritional intervention [51]. Weight gain induced by corticosteroids, progestins and parenteral nutrition in cachectic AIDS or intensive care patients is predominantly fat [52]. Such evidence of anabolic resistance in skeletal muscle in these models of cachexia suggests that every effort should be made to ‘prevent’ muscle loss rather than relying on attempts to regain what has been lost.

Clinical trials to date have largely been conducted in late-stage patients with poor PS. By this stage, both cachexia and cancer are refractory to treatment and the proportion of patients discontinuing trials because of toxicity, disease progression and death is often >50%. The earlier phase of active anti-cancer therapy, which frequently achieves good control of tumour, offers a window of opportunity for intervention against malnutrition and, by reducing catabolic drive, against cachexia. At this stage, it should also be possible to demonstrate cost-effectiveness using outcomes such as a greater intensity of chemotherapy delivered, fewer cases of treatment failure and improved quality of life. Recent studies of n-3 fatty acid supplementation during chemotherapy for NSCLC have suggested not only preservation of lean body mass, PS and quality of life, but also possible benefits in oncological outcome [53, 54]. These small studies require confirmation in large randomized trials.

The MENAC trial will test the efficacy of a multi-modal approach during chemotherapy: patients are randomized to standard care or standard care plus oral nutritional supplements, exercise and NSAIDs. Those eligible have inoperable pancreatic or advanced lung cancer, are about to start chemo- or chemoradiotherapy, and have a KPS of 80 or above. Underpinning this multi-modal approach are meta-analyses (summarized above) suggesting that each of the intervention’s components—while not unequivocally associated with improved outcome—is more likely than not to be beneficial. The primary objective is to determine whether the intervention achieves a difference in skeletal muscle index of more than 1.5 kg/m² at 6 weeks (at which point control patients may cross-over to the intervention arm). Oncological outcomes will also be assessed.

Recognizing heterogeneity among patients. A third principle is that attention should be paid to the heterogeneity of patients both with respect to cause of malnutrition and cachexia and with respect to their severity. As noted, in some patients, the dominant cause underlying loss of weight and muscle mass is a systemic inflammatory response (cachexia) while, more rarely, it is dysphagia or obstruction of the lower gastrointestinal tract by tumour (starvation/malnutrition). Cachexia and starvation can co-exist.

When considering muscle wasting, it is important to remember that the average age of a cancer patient is generally 65–70 years. Such individuals frequently have varying degrees of age-related sarcopenia irrespective of other co-morbidities (such as heart failure, chronic renal failure and chronic obstructive pulmonary disease) that can compound cancer-related muscle wasting. In addition, it is important to recognize the importance of chemotherapy or radiotherapy-induced muscle loss [55].

In relation to severity, Martin et al. have shown that mortality risk depends both on the extent of weight loss and on baseline BMI [56]. In a series of more than 1000 medical oncology patients, mortality among those with >20% loss of weight and a baseline BMI of <21 kg/m² was four times that of patients with <6% weight loss and a BMI above 27. Risk-adapted cut-offs to determine the intensity of intervention are therefore feasible.

Clearly, risk of malnutrition and weight loss also varies according to tumour type and treatment. The great majority of pancreatic cancer patients develop cachexia, as do those with gastro-oesophageal tumours undergoing neoadjuvant therapy.
However, women with breast cancer having adjuvant endocrine treatment are more likely to gain weight than to shed it.

Recent data also point to the possibility that some of the newer, more targeted anti-neoplastic agents give rise to muscle wasting, although the mechanisms responsible remain speculative. For example Antoun et al. analysed results from a randomized trial in renal cell cancer to explore the effects of sorafenib on muscle [57]. Serial CT revealed that sorafenib-treated patients lost skeletal muscle steadily at both 6 months (decrease 4.9%; \( P < 0.01 \)) and 12 months (decrease 8.0%; \( P < 0.01 \)). Whereas placebo patients had stable body weight, patients who received sorafenib lost 2.1 ± 0.6 kg \( P < 0.01 \) by 6 months and 4.2 ± 0.7 kg \( P < 0.01 \) by 1 year. These data give rise to the possibility that newer classes of cancer agents may have direct erosive effects on muscle, thus further contributing to the heterogeneity of patients with a cachectic phenotype.

**intervention to permit therapy and minimize toxicity.**

Chemotherapy can produce significant loss of body mass and femoral bone density [58], especially when it involves multiple, sequential treatments undertaken over many years. There has been a move from interest in cachexia in the setting of palliation to an awareness that ensuring adequate nutrition plays a part in optimizing outcome throughout the increasingly complex and prolonged care pathway. A patient with colon cancer and liver involvement might undergo neoadjuvant chemotherapy, resection of the primary and hepatic metastases, adjuvant therapy and resection of subsequent pulmonary metastases followed by palliative chemotherapy for further recurrent disease. All of these interventions may deplete muscle and fat mass and can lead to a cumulative burden of cachexia.

**delivering and monitoring the package of supportive care.**

The personnel involved in delivering interventions to correct malnutrition and ameliorate cachexia will vary by country and health system but are likely to include oncologists, oncology nurses, dietitians, physiotherapists and specialists in palliative medicine. The ultimate responsibility should be that of the surgical and medical oncologists in charge of overall management. Providing nutritional information and metabolic support during each phase of chemotherapy should become as standard as giving instructions on how to care for a central line.

Both in and out of hospital, the family have a role in encouraging compliance with diet and exercise. This would be helped by ensuring patients themselves understand the steps that can be taken to counter weight loss. In established cachexia, families may demand that patients have an unrealistically high calorie intake, in the mistaken belief this will reverse weight loss; and coping with the psychosocial effects of cancer cachexia would benefit from carers being provided with more information about the condition [59].

With adequate knowledge about the pre-cachectic phase, it may be that patients themselves can request appropriate assessments and interventions. Web-based resources would be useful in providing information. Portable electronic devices held by patients could enable advice to be obtained easily and provide a convenient way for them to record changes in weight, symptoms and pain and communicate these to professional and family carers.

**discussion**

Cancer cachexia is complex and challenging. However, having been an under-resourced aspect of supportive and palliative care, it is now a focus of interest. The question of how best to transfer this enthusiasm to mainstream oncology remains. It has become clear that, along with anorexia, a chronic systemic inflammatory response results in the major features of the condition—i.e. progressive loss of weight (especially of lean tissue), elevated resting energy expenditure (demonstrated for many but not all tumours), functional decline and poor outcome. Together with weight loss, raised CRP is included in most definitions of cachexia. As with weight loss per se, recent scoring systems based on markers of inflammation, such as the GPS, are prognostic.

None of the existing classification schemes for cachexia is sufficiently well validated to be recommended for routine clinical use. However, they are helpful as a research tool and as a means of better defining the nature of patients investigated. All current classifications make clear that cachexia is multifaceted. The corollary is that its management will require a multi-modal-ity approach, and selection of the right treatment of the right patient at the right time. Although there are no well-validated biochemical markers of impending cachexia, the concept of ‘pre-cachexia’ has utility if defined as an ‘expected’ deterioration in nutritional and/or functional status resulting from uncontrolled progression of disease or with aggressive cancer treatment. Identifying the pre-cachectic patient is therefore within the expertise of the oncologist. We can envisage nutritional support as part of a package of supportive care which would include anti-emetics and pain relief. Where resources allow, this approach would be complemented by the expertise of nutritionists. However, it has to be acknowledged that advocating nutritional intervention currently relies more on the well-documented adverse effects of malnutrition than on benefits proven by well-conducted clinical trials.

Therapy to maintain normal body weight and composition, exercise capacity and the ability of a patient to benefit from anticancer treatment should be considered an integral part of the package of care offered at each stage of disease. Loss of muscle mass and fatigue, central elements in cachexia and a frequent side-effect of oncology treatment, can at least to some extent be counteracted by encouragement of physical exercise.

Early detection of cachexia becomes important if we have interventions, either nutritional or pharmacological or an integrated approach, which, when used in a timely manner, are able to alter its course. There remains a need to demonstrate that this is the case through RCTs using a common definition of cachexia and agreed outcome criteria. Given the emphasis on multi-modal intervention and integrated care, and the importance of the distress caused by cachexia, the incorporation of patient-reported outcomes such as mood and fatigue is recommended. Whether the clinical end points are related specifically to cancer survival, tolerability of treatment, response rate and quality of life or to nutrition (body weight and composition) or to both remains an open question. Its resolution will require collaboration between groups/societies such as the MASCC working group on nutrition and cachexia, the ESMO Faculty of Supportive and Palliative Care, the Society for Sarcopenia, Cachexia and Wasting Diseases, the European Association for Palliative Care (EAPC),
ESPIN and others. However, it is worth noting that the FDA now mandates that drug trials in cachexia have the dual primary end point of retention or gain of lean body mass and clinical benefit (the latter defined on a trial-by-trial basis).

acknowledgements
Alexandra Zampetti of ESO organized the Geneva Task Force meeting. Rob Stepney (medical writer, Charlbury, UK) was rapporteur at the Geneva meeting and assisted in writing this paper. We also acknowledge the kind help of the following who read and commented on a submission draft of the paper: David Currow, Australia; Vickie Baracos, Canada; Rosanna Tarricone, Italy; Egidio Del Fabbro, USA; Maurizio Muscaritoli, Italy; Dan Waitzberg, Brazil; Binghe Xu, China; Katsumasa Kuroi, Japan.

funding
The European School of Oncology (ESO) Sharing Progress in Cancer Care programme has funded the meeting of the Task Force and covered the cost of the medical writer. KP has received speaker fees, advisory board fees or grant funding from Abbott, Nutricia, Helsinn, Novartis, Ono and Acacia Pharmaceuticals. MA has had recent relationships with the following companies: Abaxis, Amgen, AstraZeneca, Bayer-Schering, Bristol-Myers, Celgene, Cephalon, Chugai, Ferring, GSK, Helsinn, Hospira, Ipsen, Johnson and Johnson, Ortho Biotech, Merck Serono, Novartis, Pfizer, Pierre-Fabre, Roche, Sandoz, Schering, Sanofi, Teva and Vifor. AJ has had recent relationships with the following companies: GTX (served as a consultant); Incyte (was affiliated with a research network that accrued to one of its trials); Entera Health (received research funding); Helsinn Pharmaceuticals (served as a consultant); and X Biotech (received research funding).

disclosure
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