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Italian Journal of Medicine 2013; volume 7:253-258

Treatment of cancer cachexia in the very advanced or terminal phase: a systematic review

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ABSTRACT

The therapeutic approach to refractory cancer cachexia represents an unmet need and an important research priority in the field of palliative care. Unfortunately, clinical studies in this area are scarce, both regarding nutritional and pharmacological approach. We performed a systematic literature search through Pubmed. The search algorithm considered: the clinical context, the related pathology, the therapeutic approach. The abstracts obtained were entered in a spreadsheet and analyzed in full text. The results were then analyzed according to the PRISMA method. Overall, 258 records were screened: 244 were excluded (not in English, n=44; no abstract, n=12; literature reviews, n=108; not relevant for not advanced phase or phase II studies, n=80). The remaining 14 papers were read in full text: 10 were excluded (4 phase II studies, 4 including patients with a performance status score of ≥70%, 2 including patients concomitantly treated by palliative chemotherapy). The remaining 4 studies of qualitative synthesis included: a study on megestrol acetate; a comparison between supportive treatment with/without melatonin; a placebo-controlled study on intravenous adenosine 5'-triphosphate; a comparison of indomethacin plus erythropoietin with/without nutritional support. The reported data do not allow us to draw any conclusion concerning the efficacy of pharmacological or nutritional treatment for cancer cachexia in very advanced or terminal phase and specific studies are, therefore, awaited.

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Key words: cachexia, advanced cancer, terminal phase, systematic review.

Contributions: GL collected and analyzed data; GL, GA, SG, IG and SN wrote the manuscript; SD, RI and BT reviewed the manuscript.

Conflict of interests: the authors declare no potential conflict of interests.

Acknowledgements: the authors would like to thank Mrs. Caroline Edeh, for her support in reviewing the English text.

Conference presentation: part of this paper was presented at the XIX National Meeting of the Italian Society of Palliative Care (SICP), Turin, Italy, Oct. 2012.

Received for publication: 22 February 2013.
Revision received: 6 May 2013.
Accepted for publication: 7 May 2013.

Italian Journal of Medicine 2013; 7:253-258
doi:10.4081/itjm.2013.253

Introduction

In recent years, there has been a growing interest and many resources have been invested in the care and management of cancer patients in the very advanced or terminal phase, with the objective of improving patient comfort and quality of life (QoL). Nevertheless, the therapeutic approach to clinically refractory cancer cachexia still represents an unmet need[1] and, therefore, represents one of the most important research priorities in the field of palliative care.[2] Unfortunately, clinical studies aimed at dealing with this are extremely scarce, both for nutritional and for pharmacological approach. With regards to nutritional support, there is no definitive evidence to support the use of parenteral nutrition (PN) in patients at end of life and, in general, long-term PN is recommended only in selected patients who are likely to die from starvation before tumor progression.[3] Enteral and parenteral nutrition may help improve QoL, but these benefits appear to be limited.[4] A Cochrane Systematic Review on the use of medically assisted nutrition in palliative care patients concludes that *There are insufficient good quality studies to make any recommendations for practice*.[5] Therefore, according to a recent position paper,[6] the decision to administer parenteral nutrition should be tailored to individual patients on a clinical basis and should be consistent with the goals of patient care.

As regards the pharmacological approach, there only three systematic reviews have been published. In the first,[7] about thalidomide, there is inadequate evi-

dence to recommend its use in clinical practice. In the second,[8] the same conclusions are reported for the use of fish oil, while in the last review,[9] about non-steroidal anti-inflammatory drugs, some evidence is shown of positive therapeutic effects on QoL, performance status, inflammatory markers, and weight gain and survival, but there is insufficient evidence for widespread use in clinical practice.

Methods of research

A systematic search of the scientific literature was performed by consulting Pubmed® in the attempt to answer the questions concerning the effectiveness of pharmacological treatment of cancer cachexia in the very advanced phase, and the effectiveness of nutritional approach in the same context. Therefore, a complex search algorithm was used (Table 1) taking into account the following eligibility criteria: i) the clinical context (advanced or terminal phase or palliative care or hospice care); ii) the related pathology (cachexia or wasting syndrome); and iii) the therapeutic approach (pharmacological treatment or nutritional support).

The inclusion criteria of the search were: i) publications in English with an available abstract; ii) from between January 1972 to October 2012. The abstracts obtained were entered in a spreadsheet and analyzed, if necessary evaluating the full text. We used the following exclusion criteria for the abstract analysis: i) literature review papers; ii) studies not concerning the advanced phase; iii) phase II studies; iv) studies including patients with Karnofsky performance status ≥50%; and v) studies allowing concomitant palliative chemotherapy.

After this selection procedure, the suitable papers were then analyzed in full text according to the PRISMA method,[10] reporting the study design, the characteristics of included patients, the treatment arms, and the clinical results evaluated according to outcome: quality of life, symptom measurements, survival, adverse effects.

Results

The detailed Prisma flow chart is reported in Figure 1. A total of 255 records were identified through the first step of the Pubmed® search. Then, 6 additional records identified through other sources (reported in the bibliography of review articles) were added; 3 duplicate records were removed, leading to 258 screened records. In the second step, 244 records were excluded: 44 because they were not in English, 12 because they had no available abstract, 108 were literature reviews, 80 studies did not concern the advanced setup or were phase II studies or included patients with Karnofsky performance status ≥50% or allowed concomitant palliative chemotherapy.

All the remaining 14 papers were read in full text. Ten of them were excluded from the final analysis because 4 were phase II studies[11-14] (Table 2), 4 studies included patients with a Karnofsky performance status ≥50%,[15-18] 2 studies included some patients concomitantly treated by palliative chemotherapy.[19,20] The detailed characteristics of the remaining 4 studies included in the qualitative synthesis are reported in Table 3 while Table 4 shows the reported outcomes.

The first reported study[21] concerned the use of megestrol acetate 160 mg/day for ten days with crossover in patients with advanced non-hormone responsive solid tumors. An improvement in appetite (P=0.005), activity (P=0.007) and wellbeing (P=0.03) was registered, whereas no change in body weight, nutritional parameters, energy intake or QoL score was obtained. The second study[22] concerned the comparison between supportive treatment plus melatonin 20 mg/day and supportive therapy alone. While there was no change in food intake, a greater than 10% weight loss was registered in 4% only of patients adding melatonin to supportive treatment, in comparison with 32% of patients submitted to supportive treatment alone (P<0.01). The third study[23] was a placebo-controlled study on adenosine 5'-triphosphate by intravenous intermittent slow infusion. A significant improvement in body weight (P=0.002), serum albumin level (P=0.006), muscular strength evaluated by a hand-held dynamometer (P=0.02) and in QoL score (P=0.0001) was registered during the trial period. A longer but not statistically significant survival (median

Table 1. The detailed Pubmed® search algorithm.

PUBMED search:

("palliative care"[All Fields] OR ("hospices"[MeSH Terms] OR "hospices"[All Fields] OR "hospice"[All Fields] OR "hospice care"[MeSH Terms] OR ("hospice"[All Fields]

AND "care"[All Fields]) OR "hospice care"[All Fields]) OR "terminal care"[All Fields] OR "terminally ill"[All Fields])

AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])

AND (("cachexia"[MeSH Terms] OR "cachexia"[All Fields]) OR ("wasting syndrome"[MeSH Terms] OR ("wasting"[All Fields] AND "syndrome"[All Fields]) OR "wasting syndrome"[All Fields]))

AND (("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR ("nutritional support"[MeSH Terms] OR ("nutritional"[All Fields]

AND "support"[All Fields]) OR "nutritional support"[All Fields])

Table 2. List of the excluded full text studies.

Author (ref.)	Treatment	Reasons for exclusion
Strasser *et al.*[11]	i.v. Ghrelin	Phase II
Tassinari *et al.*[12]	Thalidomide	Phase II
Bruera *et al.*[13]	Thalidomide	Phase II
Hopkinson *et al.*[14]	MAWE	Phase II
Kraft *et al.*[15]	L-Carnitine	PS>50%
Daneryd *et al.*[16]	Indomethacin +/- erithropoietin	PS>50%
De Conno *et al.*[17]	Megestrol acetate	PS>50%
Bruera *et al.*[18]	Fish oil	PS>50%
Chasen *et al.*[19]	Peptide-nucleic acid OHR118	Some patients in palliative CT
Lundholm *et al.*[20]	Indomethacin + erithropoietin + nutritional support +/- insulin	Some patients in palliative CT

i.v., intravenous; MAWE, Macmillan approach to weight loss and eating difficulties; PS, performance status score; CT, chemotherapy.

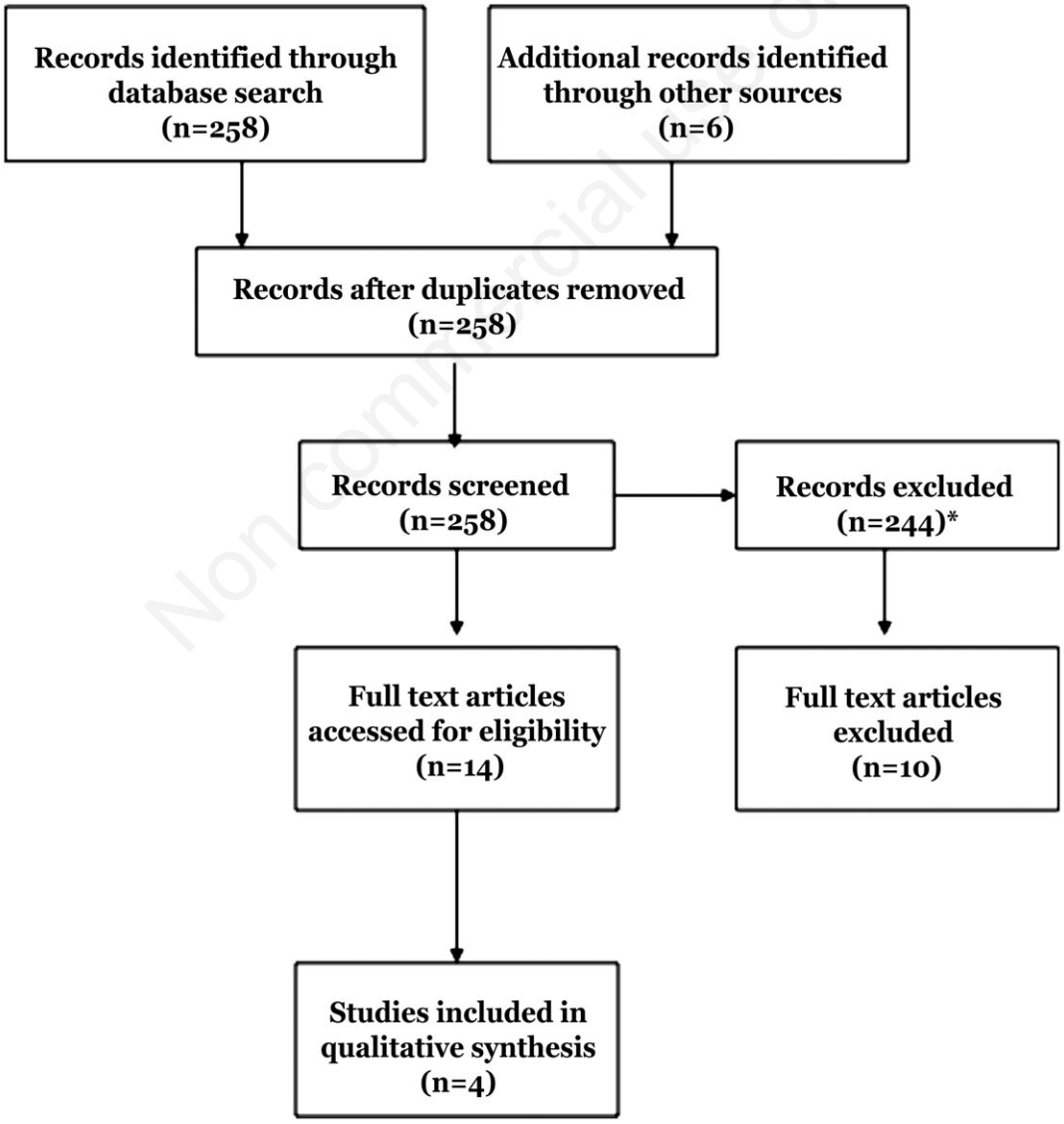

Figure 1. The Prisma flow-chart. *The details of the excluded studies are reported in the text.

Table 3. Detailed characteristics of the studies included in qualitative synthesis.

Author, year (ref.)	Study design	Patients' characteristics	Total no. of patients included	Evaluable patients (experimental arm)	Experimental arm	Evaluable patients (control arm)	Control arm
Bruera *et al.*, 1998[21]	RCT phIII, DB, cross	AST, NHST	84	53 (cross)	MEG 160 mg×3/d×10 dd, then cross	53	Placebo
Lissoni *et al.*, 1996[22]	RCT phIII	AST, OffTh	100	45	ST+melatonin 20 mg/d	41	ST alone
Agteresch *et al.*, 2000[23]	RCT phIII, open	NSCLC stage IIB-IV, OffTh	58	28	ATP 20 ⟶75 µg/kg/min ×30 h i.v. q 2-4 wks ×10 (tot. 28 wks)	30	Placebo
Lundholm *et al.*, 2004[24]	RCT phIII	AST (mostly GI), OffTh, WL>5%	309	107	INDO + EPO (12-30 MU/wk)+NS	139	INDO+EPO

RCT, randomized clinical trial; phIII, phase III; DB, double blind; cross, cross-over; AST, advanced solid tumors; NHST, not hormone-sensitive tumors; MEG, megestrol acetate; d, daily; dd, days; OffTh, off therapy; NSCLC, non-small cell lung cancer; ATP, adenosine 5'-triphosphate; wks, weeks; GI, gastrointestinal; WL, weight loss; INDO, indomethacin; EPO, recombinant human erythropoietin; wk, weekly; NS, nutritional support (orally, or home parenteral nutrition).

Table 4. The reported outcomes of the studies included in qualitative synthesis.

Author, year (ref.)	QoL	Symptoms	Survival	Adverse effects
Bruera *et al.*, 1998[21]	Better activity and wellbeing. No change in FLIC scores	Improvement in appetite. No change in BW, nutritional parameters, energy intake	NR	NR
Lissoni *et al.*, 1996[22]	NR	Reduction in WL; no change in food intake	NR	No melatonin toxicity
Agteresch *et al.*, 2000[23]	Mantained physical QoL score during treatment period	Gain in BW, albumin, muscular strength	Longer for experimental arm pts	Chest discomfort, dyspnea, flushing, nausea, headache, sweating, mood alteration, palpitations, injection side reaction
Lundholm *et al.*, 2004[24]	NR	Improved energy balance; no change in BW	Longer for experimental arm patients	NR

QoL, quality of life score; FLIC, Functional Living Index-Cancer; BW, body weight; NR, not reported; WL, weight loss.

5.6 *vs* 4.7 months; P=0.51) was reported in the experimental arm. The last study[24] evaluated a combination of a COX inhibitor (indomethacin, 50 mg twice daily) and recombinant erythropoietin (15-40,000 IU/week administered subcutaneously) along with oral nutritional support and home total parenteral nutrition. The addition of nutrition led to a prolonged survival (P<0.01) that was accompanied by improved energy balance (P<0.001) and a greater maximum exercise capacity (P<0.04).

Discussion

This systematic review has some methodological weaknesses that make the interpretation of results difficult. First, the apparently negative results of our systematic review might be a consequence of the choice of too wide a context of research, including studies with heterogeneous inclusion criteria and end points. Splitting the literature analysis into two parts, *i.e.* efficacy of drugs and efficacy of the nutritional treatment, might have led to different results. Furthermore, the search was limited to Pubmed, therefore, we cannot exclude the possibility that we might have *lost* some relevant articles cited on other databases. Finally, data collection and analysis were performed by only one author (GL) and this could have led to a possible misinterpretation of the results.

Nevertheless, the above reported data show that even now there is a complete lack of studies directed at verifying the efficacy of pharmacological or nutritional treatment for cancer cachexia in the very advanced or terminal phase. In particular, as regards drugs, the scarcity of available data does not allow us to draw any conclusions that could be translated into

clinical practice. The single study about progestins[21] confirms their efficacy, according to a wide meta-analysis,[25] even if the latter was not aimed specifically at the very advanced phase.

Concerning the nutritional approach, the single reported study[24] seems to show an advantage in its use, even if the Cochrane review[5] and the available guidelines[3,26] seem to exclude a real advantage for parenteral nutrition in the refractory phase of cancer cachexia.

In the clinical context, a careful nutritional evaluation of all cancer patients remains a general objective for improvement, and it should lead to an early clinical staging of cachexia before the initiation of the pre-cachexia-cachexia-refractory cachexia chain.[27]

The optimal management of the patient in the particular context of palliative care requires adequate education and counseling for patients and families, and a significant interaction between patients, caregivers and the medical staff.

The interruption of artificial support could be a cause of distress for patients and family members. Moreover, the uncertainty about the evaluation of prognosis, psychosocial factors and the perceived benefits of artificial nutrition support its employment in terminally ill patients. In the light of this, we can reasonably recommend a 3-step approach for clinical practice: a careful pre-treatment evaluation of patients with any grade of cancer cachexia (including nutritional status, and evaluation of performance status and of the prognostic factors), a prognosis-oriented decision-making process (excluding from artificial support those patients in the end-of-life phase), and, finally, an informed consent for patients and families on the consequences of cancer cachexia and its treatment, as regards quality and duration of life.

In consideration of this approach, in case of uncertainty about the benefits and risks of parenteral nutrition in the individual patient, it would be appropriate to have a brief trial period after which the clinical benefits and risks could be reassessed. The final decision should also take into account the emotional involvement of the patient and the family, in complete agreement with the conclusions of the position paper already referred to.[6] Once again, even though we recognize the complexity involved in carrying out such studies, we are waiting hopefully for specific studies in the context of cancer cachexia in the very advanced or terminal phase.

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