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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 6869
Title: Cachexia and pancreatic cancer - are there treatment options?
Reviewer code: 02544216
Science editor: Qi, Yuan
Date sent for review: 2013-10-30 19:13
Date reviewed: 2013-11-06 23:15

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[Y] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[Y] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

The present review is well written and structured in its composition. The authors discuss in detail the current treatment option to treat cachexia in pancreatic cancer patients, illustrating the basis for the development of new therapies. Furthermore, they specifically address the emerging pharmacological treatments and provide a lot of valid information including what kind of clinical studies have been performed or are currently in progress. The background and the cited literature is up-to-date and properly discussed, and the data of the main studies on cachexia are summarized appropriately. The author's views and suggestions are in line with the current literature in this complex field of research. In particular, one relevant conclusion is the need for multimodal treatments. The Authors might add among the references the study by Barber et al., A polymorphism of the interleukin-1 beta gene influences survival in pancreatic cancer. Br J Cancer. 2000 Dec;83(11):1443-7.

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ESPS Peer-review Report
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS
Overall this is a well written, concise summary of the currently available therapies. The authors have provided a logical flow to the review and offer a step-wise approach to treating the cachectic pancreatic cancer patient. See comments attached.

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ESPS Peer-review Report
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[Y] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

The authors presented a systemic review on cachexia in pancreatic cancer, the authors have summarized the recent defination of the mechanisms of cachexia in pancreatic cancer, as well as provided an integrative view of multiple treatment agents for cachexia. It contains indisputable logic, fluid organization and substantial content which merit publication, but there are still some problems that need to be solved. 1.In section "Current treatment options of cachexia in pancreatic cancer patients", the author mentioned that "Approximately 70% of patients are primarily resectable at first presentation". Maybe the source of the cited article is needed, from my point of view, only 20% pancreatic cancer patients are diagnozed resectable. 2.In the same section, the author mentioned "Palliative treatment of non-resectable pancreatic cancer consists of chemotherapy and supportive care". Maybe radiotherapy is also a valuable optional therapeutic agent for these patients, especially those with severe pain.

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

In their current review, Muller et al. reviewed the clinically highly relevant issue of cancer cachexia, with particular emphasis on pancreatic cancer (PC)-associated cachexia. They provide an overview on the different definitions of cachexia and its prognostic impact in PC and lung cancer (NSCLC). Furthermore, they refer to the currently applied therapeutic approaches to cachexia and cite several trials which investigated several different pharmacological agents. Moreover, the step-up therapy approach that the authors propose for treating cachexia is very plausible. Overall, the study contains a good and comprehensive summary of therapeutic approaches to cachexia, and it effectively demonstrates how little we know about cachexia and how little we probably do to treat it. In this well-written review, I feel that two major points are missing: 1) It seems that the pro-inflammatory milieu that is generated during cancer as a complex disease, and the mixture of humoral and metabolic changes in cancer contribute to cachexia. While the authors have discussed some of the humoral factors (e.g. cytokines), they did not refer to the specific metabolic changes that occur in these patients. What arms of the metabolism are affected by cancer? Lipid metabolism? Glucose metabolism? Protein metabolism? 2) One major question is, how can doctors integrate assessment of cachexia into their daily practice? The authors state that cachexia is associated with worse survival in pancreatic cancer. In this regard, every doctor dealing with PC or NSCLC should routinely monitor patients for cachexia. Is weighing the patient sufficient? Or should every CT scan of these patients be routinely used to monitor the thickness of the muscle and fat tissue, i.e. to obtain a musle mass/fat index? I think such an index and its implementation would allow objective monitoring of cachexia and the amelioration of cachexia and thus prognosis. But are there are difficulties in front of the implementation of such a measurement on a routine basis? Minor

comments: 1) Page 5, paragraph 3: the rate of resectable PC patients at first diagnosis is between 10-20%, and certainly not 70%. Please correct this together with an appropriate citation. 2) Page 6, paragraph 1: The range of caloric intake (1000-1500 kcal) seems to be rather adequate for a non-cachectic, normal individual with little regular exercise. This range should be reconsidered to be somewhat higher (i.e. close to 2,000 kcal) in the revised manuscript, or at least a supporting reference with these values should be shown. 3) I unfortunately could not locate the Figure files, so I would kindly ask for their re-upload in the revised version.

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[Y] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

This is an interesting and well written review article on cachexia and pancreatic cancer. Authors give an overview of current therapies, propose a stepwise approach for clinical practice after having well described diagnostic criteria and precisely define cachexia. There are several points to increase the quality of this review: 1- Authors should define precisely what they mean in terms of "pancreatic cancer" in the background section "Cachexia in pancreatic cancer", ie. Pancreatic Ductal Adenocarcinoma only (as ADK is only mentioned at the end of the manuscript in page 18) or do they include other types of pancreatic cancers? 2- The part: "Cachexia in pancreatic cancer: incidence, impact on prognosis and outcome" (starts at page 4) should be enriched. For example, in the section at the end of page 4, authors could described more precisely what are "other stimulators" of catabolic pathways as well as "catabolic" and "anabolic pathways" in order to describe what is known about alterations in metabolism in pancreatic cancer. Same for neuroendocrine hormones and tumor-derived factors (page 5), authors should shortly describe them. 3- Authors should define the "acute phase response in the liver" in the context of cachexia (end page 4). 4- Page 5: "70% of patients are primarily resectable at first presentation": this is not what it is usually considered, authors should mention a reference or correct the percentage. 5- Page 9 authors have to explain the side effects of the use of cannabis extract. 6- In the part "pharmacological treatment of cachexia in pancreatic cancer patient", - It is not always properly mentioned if clinical trials have been done on pancreatic cancer or on other types of tumors (excluded pancreatic cancer). - Authors should invert the parts "anti-cytokine strategies" and "anti-inflammatory drugs" to fit with Table2. - Authors have to include Figure and Table legends in the manuscript. Minor points: - Reference 21 is not properly cited (it was published on February 2013 and not an "advance online publication"). - Table 1: typo

correction: Acetyl-coA. - Figure 2: Authors could play with colors to better highlight parts/columns in Figure 2 (“Supportive therapy” can be in a different color than the rest of the figure). - Not all abbreviations are explained.