Author's response to reviews

Title: Long term disease free survival in advanced melanomas treated with nitrosoureas: mechanisms and new perspectives.

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**Manuscript title**: Long term disease survival in advanced melanomas treated with nitrosoureas : mechanisms and perspectives.

**Reviewer**: Demetrius Kokkinakis

**Reviewer’s report:**

General

Significant corrections in the language and style are required. The manuscript has been submitted to Biomedes (as suggested) for english improvement.

**Abstract:**

The characterization of cystemustine as a new nitrosourea is questioned since the authors mention its use in 1985 or earlier : « new » has been deleted. *(Abstract, line 4)*

Long term survival (has) already been described (in the literature), : sentence corrected as suggested. *(Abstract, line 6)*

3) Methionine may be involved in the regulation of MGMT expression. this sentence has been deleted as suggested by Biomedes.

**Introduction:**

Melanoma, although a relative uncommon cancer. In what country? It is an uncommon cancer in France. This cancer is rather common and is increasing in the USA , especially in the sun belt. The sentence has been deleted. *(Introduction, first sentence)*

Even if for the early. *(Modify language)*. : This sentence has been changed to “Even though, most cases are cured by surgery alone in the early stages of the disease, advanced melanoma has a poor prognosis” *(Introduction, second sentence)*
some authors have reported cases after chemotherapy treatment (References missing): references added (2-6). (Introduction, line 9)

Cystemustine is a new CENU derived ..... (Something is missing here) Sentence changed to: “Cystemustine \(N'-(2\text{-chloroethyl})-N\{2-(\text{methyl sulphonyl})\text{ethyl}\}-N'\text{-nitrosourea}\) is a CENU derived from 2-chloro-ethyl-nitroso-carbamoylcysteamine (CCNC); it is synthesised in INSERM U484, Clermont-Ferrand (7).” as suggested by Biomedes. (Introduction, line 10-12)

than the CENU analogues currently used (References): reference added (8). (Introduction, line 14)

Patients:

Remaining patients (were) received: This sentence has been changed to “30 patients were included in a phase II national and multicentric study, whereas other 23 patients received Cystemustine compassionate treatment. » as suggested by Biomedes. (Patient second sentence)

They received Cystemustine 60 or 90 mg/m² (This is repeated 3 times in the paragraph. The authors should streamline the text to avoid repetition). “A series of 53 patients has been treated with Cystemustine 60 or 90 mg/m² every two weeks. The drug was administered as a 15 min IV (intra-venous) infusion. » has been changed to « A series of 53 patients has been treated with Cystemustine administered as a 15 min iv infusion every 2 weeks. » to avoid repetition. (Patient first sentence)

number of cystemustine cycles was (1-27)... All these references? It was number of cycles, this has been changed to “The median number of Cystemustine cycles was 3 (range, 1 to 27 cycles)” (patient line 7)

These last ones have led to dose. (Revise) As Biomedes has not corrected this sentence, no correction has been done.

Except these haematopoetic toxicities. (Revise) Sentence changed to “Except for the haematological toxicity, ...” as suggested by Biomedes. (Results, patient 3, line 9)

In July 1998, myelodisplasic syndrome (was) diagnosed. "was" has been added in the sentence. (Results, patient 3, line 13)

One (patient 1) (has) died... As Biomedes has not corrected this sentence, no correction has been done.

Discussion:

580 patients were treated (with) dacarbazine: “with” has been added in the sentence. (Discussion line 4)

(hydroxyurea): “hydroxyurea” changed to “hydroxyurea”. (Discussion line 5)

the full name for MGMT is O6-methylguanine-DNA methyltransferase: “O6-alkylguanine-DNA alkyltransferase” changed to “O6-methylguanine-DNA methyltransferase”. (Discussion line 26)

To improve cystemustine efficacy... (In order to improve.. is more correct): “To improve cystemustine” changed to “In order to improve”. (Discussion line 43)

MGMT (mRNA) “mARN” changed to “mRNA”. (Discussion line 46)

Reviewer: Andreas Teufel
Reviewer's report:
1) Generally, the written English is of poor quality and needs to be edited. The manuscript has been submitted to Biomedes (as suggested) for English improvement.

2) In 1999 the same group reported on a EORTC phase II trial on cysteustine at as a first- or second-line treatment in advanced malignant melanoma. In this publication the group observed five patients with partial responses, nine with stable disease and 28 showing progression. None of the 44 patients underwent complete remission. Summarizing their results, the authors reported a limited efficacy of this treatment. However, in contrast with these data the authors now report on the long term survival of five patients under the same treatment (nearly 10% of the total collective of patients). Thus, these long term survivals need to be critically discussed in context of the group’s previous, own work. Cure H, Souteyrand P, Ouabdesselam R, Roche H, Ravaud A, D’incaen M, Viens P, Fargeot P, Lentz MA, Fumoleau P, Hanauske A, Chollet P. Results of a phase II trial with cysteustine at 90 mg/m(2) as a first- or second-line treatment in advanced malignant melanoma: a trial of the EORTC Clinical Studies Group. Melanoma Res. 1999 Dec;9(6):607-10.
First, thank you to the reviewer to have mentioned this study, because there was an error in the patient description: the described phase II was not an EORTC one but it was a phase II national multicentric study. So the sentence has been changed from “30 of them were included in a phase II EORTC (European Organisation for Research and Treatment of Cancer) study,...” to “30 patients were included in a phase II national and multicentric study,...”.
In this study none of the patients underwent complete remission, and Mr TEUFEL seems to be surprised by our result. But the aim of case report is precisely to describe uncommon results, and not to conclude about the cysteustine efficacy.

3) A conclusion is missing. Do the authors warrant further studies, also the EORTC trial did not result in promising results? the following sentense has been added for the conclusion of our report: “Even if it remains rare, long term survival may be the outcome of patient presenting with metastatic melanoma treated with chemotherapy. It appears crucial to propose new therapeutic approaches to increase these response rate.”

4) As the long term survival patients are part of a series of 53 patients, is there anything that distinguishes the long-term survivors from the remaining collective? there was nothing that could distinguish the long-term survivors from the other patients treated with cysteustine, neither in primary tumor localisation, nor in general medical history, that’s why we don’t have mentionned the medical datas concerning the other patients treated with cysteustine.

5) Patients 1-4 had their primary melanoma on their extremities. Was localization on extremities a positive selection marker in the remaining 48 patients? No this location was not « a positive selection marker as at least ¾ of patients presenting with primary lesion on extremities. Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

6) Localisation of the primary site of the melanoma of patient 5 remained unspecified. « cutaneous melanoma » has been changed to « cutaneous thoracic melanoma » (Results, patient 5, line 1)

7) It seems unreasonable to discuss potential biochemical mechanisms as long as controlled studies do not result in clear increased general survival. In addition, the corresponding paragraph of the discussion does not lead to any conclusion. It should be deleted or moved to the introduction section. We don’t agree with this comment: It would be of particular interest to understand the mechanism(s) involved in these long-term disease free survival to be able to propose new therapeutic alternatives. In our case, on the basis of the previous experimental results, we have initiated a phase-I clinical trial of dietary methionine restriction.