Author’s response to reviews

Title: Emergency Etoposide-Cisplatin (Em-EP) for patients with germ cell tumours (GCT) and trophoblastic neoplasia (TN)

Authors:
Charleen Chan Wah Hak (charleen.chanwahhak@nhs.net; charleen.chan@gmail.com)
Christopher Coyle (chriscoyle@doctors.org.uk)
Arwa Kocache (arwa.kocache@nhs.net)
Dee Short (dee.short@nhs.net)
Naveed Sarwar (naveed.sarwar1@nhs.net)
Michael Seckl (m.seckl@imperial.ac.uk)
Michael Gonzalez (Michael.Gonzalez@icr.ac.uk)

Version: 1 Date: 15 Jul 2019

Author’s response to reviews:

Department of Medical Oncology
Charing Cross Hospital
Fulham Palace Road
London
W6 8RF

15 July 2019

BMC Cancer

Editor-in-Chief

Dear Dr Linda Gummlich,

Re: Manuscript BCAN-D-19-00796 resubmission.

Thank you for the opportunity to revise our manuscript entitled “Emergency Etoposide-Cisplatin (Em-EP) for patients with germ cell tumours (GCT) and trophoblastic neoplasia (TN)”.
We appreciate the insightful comments and suggestions offered by the Reviewers. Many thanks to both for their time and Specialist input, which we feel has strengthened the paper. Revisions have now been incorporated in the version submitted here.

We hope that the revised manuscript is suitable for publication in BMC Cancer and remain grateful for your kind consideration.

Yours sincerely,

Dr Charleen Chan Wah Hak

Reviewer Comments, Author Responses and Manuscript Changes

Christa Nagel (Reviewer 1):

Comment 1: On page 8 line 20 in results change commonest to most common.

Response: This has been amended in the Results section, page 9, line 18, to read “Intra-uterine (n=44, 42%) and gonadal (n=41, 39%) primary sites were the most common.”

Comment 2: On page 8 line 21 of results you state most patients received Em-EP at their initial diagnosis. How many received it for a recurrence?

Response: This has been clarified in the Results section, page 9, line 20. The sentence now reads “The majority of patients received Em-EP at their initial diagnosis (n=100, 96%) rather than for recurrent disease (n=4, 4%).” There is further detail within the same section on the patient subtypes who had received Em-EP for recurrence: “One male GCT patient (5%), 1 female GCT patient (3%) and 2 TN patients (4%) had previously received standard chemotherapy and presented with disease relapse.”

Comment 3: In the clinical outcome section of the results you say that 2 patients died at less than 4 weeks and a total of 20 patients died with a 6 month minimal follow up. You may want to reference table 2 here for the causes of death. You may also want to break down the causes to within the first 4 weeks and within the initial 6 months.

Response: The relevant section has been re-written. We have included in the Results section, page 12, line 47: “Within the entire cohort, 102 patients (98%) remained alive at 4 weeks after their first Em-EP administration, with only 2 early deaths (2%) observed at less than 4 weeks after Em-EP. Therefore, with full escalation and full support, Em-EP can be a life-saving intervention in patients with advanced GCT and TN who present with life-threatening disease.”
The 2 patients who died within 4 weeks included 1 male GCT patient and 1 non-gestational TN patient. A 45 year-old gentleman of no fixed abode presented at our ECTC with an advanced seminoma that had arisen within an undescended right-sided pelvic testis resulting in right hydronephrosis. Right para-aortic lymphadenopathy was also present. He sadly died elsewhere from an unknown cause on Day 25, having received Em-EP on Day 4 following admission and having initiated BEP chemotherapy on Day 9. The second patient died on Day 11 at a Respiratory ICU, transferred from our own ICU for extracorporeal membrane oxygenation. She was a 40 year-old lady admitted with septic shock and respiratory failure from a symptomatic right-sided pleural effusion that was exudative and had required multiple intercostal drains for prompt symptomatic relief, as well as a video-assisted thoracoscopic surgical pleurodesis that had proved unsuccessful. Pleural fluid analysis had already identified both Staphylococcus aureus and extended-spectrum beta-lactamase-producing bacteria. The baseline serum HCG was elevated at 4772 IU/L. Em-EP had been administered within 24 hours of admission, whilst intubated, ventilated and on both inotropes and intravenous antibiotics.”

As Table 2 includes clinical outcome data for bona fide GCT and TN patients rather than the overall cohort, later, in the Results section, page 13, line 42, when this group is described we reference Table 2. “Specifically, there were 15 deaths in the cohort of 95 patients (45 GTN, 20 male GCT, 30 female GCT) excluding non-gestational TN patients, patients with cancer of unknown primary without confirmed histology, poorly-differentiated tumour marker-secreting tumours or lung cancer treated empirically as GCT or GTN (Table 2).” We also now include values for patients who remain alive at 6 months in Table 2.

Comment 4: On page 14 line 11 of the discussion you state that the mortality of induction chemotherapy with Em-EP with 98% of patients alive at 4 weeks. I recommend adding the mortality rate with standard chemotherapy regimens for comparison.

Response: As far as we are aware, studies using standard chemotherapy regimens have not described early clinical outcomes in patients with advanced GCT treated in the acute setting. This was our principle study objective. For TN, however, EP induction chemotherapy administered at our Centre to 23.1% high-risk patients (33 of 140) with a large disease burden was associated with a low early death rate at 0.7% compared with 7.2% for patients who proceeded with immediate conventional-dose chemotherapy on the EMA-CO regimen (manuscript reference: Alifrangis et al. 2013). In our study, the TN subgroup recruited after 2012 differs from the cohort originally described by Alifrangis et al who received low-dose chemotherapy up until 2010. The TN cohort serves as an important comparator and we demonstrate here that early mortality at 4 weeks is equivalent for both GCT and TN.

We have added a paragraph to Discussion section, page 15, line 20, to address the Reviewer’s comment: “There is a lack of published data on early outcomes in advanced GCT patients treated within the acute setting for symptomatic high-burden disease, with or without organ failure, either at low or conventional doses. For high-risk TN patients with a large disease burden, a study at our Centre by Alifrangis et al (Alifrangis et al. 2013) identified a low early death rate at 0.7% with upfront Em-EP compared to 7.2% for patients who proceeded with immediate conventional-dose EMA-CO chemotherapy. In our study, the TN subgroup recruited after 2012
differs from the cohort originally described by Alifrangis et al who received low-dose chemotherapy up until 2010. The TN cohort serves as an important comparator and we demonstrate here that early mortality at 4 weeks is equivalent for both GCT and TN.”

Comment 5: In the results you state 9% of patients developed neutropenic sepsis. This seems high and that consideration for prophylactic GCSF may be given to this patient population who is already compromised. You may want to discuss this further in the discussion section.

Response: We are grateful to the Reviewer for this comment. We have added the following to Discussion section, page 14, line 54: “There were 5 cases of neutropenic sepsis (5%) that occurred post Em-EP and prior to their first cycle of standard chemotherapy. Chemotherapy regimens with a febrile neutropenia rate at 10% or more could be offered prophylactic GCSF routinely. Given the context described within our cohort and the high risk for concomitant sepsis, we are working towards offering prophylactic GCSF routinely to all patients at our ECTC who embark on Em-EP.”

Debra Richardson (Reviewer 2):

The authors have written an interesting manuscript regarding emergency Em-EP for patients with malignant germ cell tumors and GTN.

Comment 1: In the abstract- you state out of hours- please define- somewhere in the manuscript- 8pm-8am is mentioned. Please define the hours for M-F. I assume Sat and Sunday would be out of hours

Response: Thank you for this important point. Due to word count limitations, we had not defined “out-of-hours” in the Abstract, however, we have clarified this in our Patients and Methods section, page 7, line 40, with the statement: “Out-of-hours is defined as 8pm to 8am on weekdays from Monday to Friday and all hours at the weekend on Saturday and Sunday”

Comment 2: On page 6- you state you use FIGO score- isn't this typically referred to WHO score? FIGO adopted it.

Response: FIGO is the specific score we have used in our data collection, which is consistent with the majority of the cited literature in our manuscript (manuscript references: Alifrangis et al. 2013; Lurain et al. 1982, 1987; McGrath et al. 2010; Seckl et al. 2010).

Comment 3: How long is the chemo good for after it is mixed- how many hours? Page 7 you note the pharmacists prepare the chemo in advance of the weekend. What if a patient had a BSA >2? Have there been any dosing errors using this premixed chemo?
Response: Thank you for this important point. Cisplatin has a 7-day expiry and Etoposide has a 4-day expiry. Patients with a BSA>2 m² are dose-capped at 2 m² for emergency treatment only. Thereafter the dose can be tailored according to BSA from Cycle 2 onwards as the chemotherapy can be made up within working hours in an elective, planned manner. As far as we are aware there have been no errors in using pre-mixed chemotherapy in the last 10 years at Imperial College Healthcare NHS Trust. There are robust guidelines for the resident pharmacist to check that the dose and volume administered are both correct.

Comment 4: Page 9- please define "PV" bleeding- I think you may mean vaginal bleeding- would be best not to use unnecessary abbreviations.

Response: “PV bleeding” has been replaced with “vaginal bleeding” for clarity in the Results section, page 10, line 54.

Comment 5: Page 9- define ERPC

Response: We can confirm that the term has previously been defined in the Results section, page 10, line 52.

Comment 6: On page 13 you note you can treat sepsis with antibiotics and treat with chemo. Do you have any safety data regarding that approach? I have never given chemo when someone is actively being treated for a serious infection.

Response: With regards to safety, the favourable early clinical outcome suggests that concomitant antibiotics will be effective and safe within the context described, given that higher-level support is available 24/7 for acutely unwell GCT and TN patients. In the emergency setting chemotherapy administration remains our priority for all acutely unwell GCT and TN patients given the rapid proliferation rates associated with both malignancies.

Comment 7: Table 1- you note one patient have a gestational choriocarcinoma- that was an ovarian primary. I am confused- gestational choriocarcinoma arises in the uterus- unless this was from an ovarian ectopic?

Response: Yes, we acknowledge that this was not clearly stated. The patient highlighted in Table 1, postscript c, had a term pregnancy prior to presentation with a left adnexal ovarian mass that was confirmed on biopsy to be a choriocarcinoma. We have revised this Table 1, postscript c, for clarity to “One patient with an ovarian primary disease site was diagnosed as an ectopic gestational choriocarcinoma.”