BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

British Society for Haematology

Edited by: John Barrett
Impact factor: 5.518
2019 Journal Citation Reports (Clarivate Analytics): 14/76 (Hematology)
Online ISSN: 1365-2141

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COVID-19 and Myeloma Clinical Research – Experience from the CARDAMON Clinical Trial

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COVID-19 – caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – has spread to more than 213 countries and territories, with 15,785,641 cases, including 640,016 deaths, reported to WHO by 26 July 2020[1]. At the time of writing, there were 298,681 laboratory-confirmed cases and 45,738 COVID-19 associated deaths in the UK alone[2]. Self-isolation and physical distancing measures were implemented in most jurisdictions to limit the spread of the virus. Changes to clinical practice saw the short-term reduction of routine and non-emergency care in an effort to liberate much-needed capacity in medical facilities, while minimising the risk to patients and healthcare workers by eliminating avoidable face-to-face interactions.

Haematology patients are perceived as being particularly vulnerable to SARS-CoV-2 infection, and in need of shielding; hence alternative management plans and new ways of delivering care were implemented wherever possible to reduce individual patient risk. Various guidelines were issued at

unprecedented speed to guide clinical management, including recommendations for multiple myeloma (MM) and patients needing autologous stem cell transplantation (ASCT)[3–5]. Conducting clinical trials poses unique challenges, having to strike a balance between patient safety, maintaining trial integrity, and ensuring adherence to good clinical practice (GCP) standards. The EMA, the EU Commission and the UK MHRA all published guidance to help stakeholders manage clinical trials during the COVID-19 pandemic[6–8].

We report the challenges and adaptations made to the CARDAMON trial during the peak of the COVID-19 outbreak in the UK in March–June 2020. CARDAMON is a phase II, randomised, open label clinical trial in transplant-eligible newly diagnosed MM (NDMM), to assess the benefit of upfront (ASCT) (clinicaltrials.gov identifier NCT02315716). Patients are treated with carfilzomib (30 minute intravenous infusion), cyclophosphamide and dexamethasone (KCd) as induction, then randomised to standard consolidation with ASCT or to a further 4 cycles of KCd, following which all receive 18 months of maintenance with weekly single agent carfilzomib (d1, 8 and 15)[9]. Aside from standard serological response assessments, minimal residual disease(MRD) was assessed by bone marrow(BM) sampling at pre-specified timepoints, and by CT-PET for those patients on an imaging sub-study.

When the UK went into lockdown on 24th March 2020, 70 patients were still receiving carfilzomib maintenance and 173 patients were on follow-up. Following discussions within the Trial Management Group (TMG), adaptations to the trial protocol were agreed, allowing CARDAMON to continue with minimal disruption. Local Principal Investigators (PIs) were informed of these changes, with open communication by email or telephone facilitating rapid resolution of further queries and smooth trial management throughout.

Assessments conducted locally or remotely

Pre-treatment blood tests could be completed locally, either via the GP or at local hospitals, to save patient travel and footfall in the trial site, with results sent to the site for review before carfilzomib dosing. Monthly follow-up visits could be conducted via telephone or video conferencing, initiating in-person assessment and/or investigations when clinically indicated.

Pragmatic approach to treatment delays during carfilzomib maintenance

Patients who had completed at least 12 months of maintenance could stop treatment at the PI's discretion and the patient's wishes. Patients who completed <12 months of maintenance were encouraged to continue if possible, allowing delays of up to 14 weeks, compared to 4 weeks in the pre-COVID-19 era. For those who had completed maintenance therapy, end of maintenance assessments could be completed outside of the 14-day time-window.

Re-starting carfilzomib maintenance with step-up dosing after treatment break

Initiation of carfilzomib therapy is routinely done with a step-up dose from 20mg/m^2 to target dose (56mg/m^2 in Cardamon). To reduce the risk of infusion reactions and adverse events, such as thrombotic microangiopathy occurring on resuming therapy after a break[10], an urgent safety measure was implemented. Where carfilzomib maintenance was delayed for >4 weeks, treatment was to be restarted at 20mg/m^2 on day 1 of the new cycle before escalating to the full 56mg/m^2 or last tolerated dose.

Postponement of 6-month MRD assessment during maintenance

BM sampling for MRD assessments, due at 6 months of maintenance, could be delayed for up to 3 months, and similarly for the follow up PET-CT scan, also due at 6 months.

Impact on CARDAMON Trial Activity

During lockdown, 15 patients stopped carfilzomib maintenance completely; 14 carried on uninterrupted and 41 patients had their treatment paused with plans to re-start once COVID-19 infection rates improved. Due to these protocol amendments, 55 (79%) patients who would otherwise have stopped trial treatment were able to stay on carfilzomib maintenance on the CARDAMON study. Of 25 outstanding MRD BM assessments, 20 were delayed by an average of 2 months, with investigations resuming when restrictions eased in June. As of 5th August 2020, 8 of the delayed BM assessments have been performed and 3 were missed. Nine PET-CT scans were also delayed, of which two have been performed.

Effect on Data Analysis and Interpretation

~~Since all patients completed the randomised component of treatment by 29th February 2020, neither arm has been impacted by the pandemic. Also, the delays/alternations to maintenance therapy are not anticipated to diminish the validity of the primary endpoint comparison of progression free survival between arms.~~ Although all patients had completed the randomised component of trial treatment by 29th February 2020, delays and alterations to maintenance therapy may not have affected the two arms equally. There is the potential for bias, with some investigators perhaps being more willing to alter treatment if patients had had a favourable response. Therefore, sensitivity analyses will be performed with and without the inclusion of those patients affected to assess the significance of the measures taken on patient outcomes. Secondary outcomes will also be assessed as originally intended as well as in pre- and post-COVID scenarios.

Prompt and pragmatic action successfully mitigated the unavoidable disruption of trial functioning; trial conduct was maintained while preserving scientific integrity and protecting patient safety. The

post-pandemic environment comes with risks of missing or delayed data collection in ongoing trials, with impact on data analysis and interpretation. This global crisis should encourage the rethinking of study designs to make future clinical trials more flexible and pragmatic, whilst retaining successful adaptations to current trials[11].

[*998 words*]

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