HemaSphere
Powered by EHA

EHA EUROPEAN HEMATOLOGY ASSOCIATION

HemaTopics
OPEN ACCESS

TEAMM Work Saves Lives in Myeloma

By Simon Hallam

Correspondence: Simon Hallam (e-mail: Simon.Hallam@bartshealth.nhs.uk).

Receiving a diagnosis of myeloma is a life-changing event. In the clinic we try to paint a realistic picture, of an incurable disease, which may nonetheless remit for several years following successful induction therapy. Once first-line treatment is complete, and in the absence of devastating bone disease or renal failure, these should be years of relatively well-preserved quality of life.

However, too often even this proves to be optimistic. Despite improvements in response rates to first-line therapy, early mortality remains unacceptably high. One in 10 patients die within 10 weeks of receiving their diagnosis, most commonly from infection.[1] This figure may in fact be an underestimate, as the number is likely higher outside clinical trials, in older, frailer patients with multiple comorbidities. Far too many of our patients are dying from complications before they have a chance to remit, with disease that might otherwise have been well-controlled for several years.

The immunotherapy revolution seems set to rewrite the clinical history of myeloma. Living longer with disease control, even achieving functional cures, is a realistic and exciting prospect for the coming years. But these exciting developments will be of no benefit to the 1 in 10 who continue to die early from infection, and as response rates to front-line myeloma therapies improve, the relative impact of early infections on mortality will increase.

The TEAMM study (Tackling Early Morbidity and Mortality in Myeloma) takes a step toward addressing this increasingly pertinent challenge.[2] Led from the University of Birmingham, the United Kingdom (UK), this is the largest ever prospective, double-blinded trial of antibiotic prophylaxis during induction therapy in myeloma. Presentation of its findings at the 59th American Society of Hematology Annual Meeting and Exposition has captured the attention of the myeloma community. In this commentary, I will review the data presented so far, and explore why this could be such an important study for our patients.

TEAMM study design

The broad aim of the TEAMM study was to assess the impact of antibiotic prophylaxis on rates of infection and early death in newly diagnosed myeloma. A randomized, double-blind, placebo controlled multicenter phase III study, it recruited patients in the UK aged over 21 years with newly diagnosed myeloma who had started, or were planned to start, myeloma-directed therapy within 14 days of commencing the trial.

The quinolone antibiotic levofloxacin at 500 mg once daily (adjusted for renal function) was compared with placebo, both delivered continuously for 12 weeks. Other supportive antimicrobials were permitted according to standard of care in local practice, including co-trimoxazole. Study subjects were screened regularly for carriage or acquisition of resistant organisms with 4 weekly throat swabs for methicillin-resistant *Staphylococcus aureus* (MRSA), and fecal samples for *Clostridium difficile* and extended-spectrum beta-lactamase positive (ESBL+) gram-negative bacteria.

The primary end point was a composite measure of the number of febrile episodes (defined as a temperature of >37.9°C treated with anti-infective agents) and/or death from any cause within the first 12 weeks. The secondary end points included death, infection, and the occurrence of severe sepsis at any time in follow-up.

Results

Between August 2012 and April 2016, 977 subjects were recruited across 93 UK centers. The median age was 63 years, 63% were male, and 24% had renal impairment (estimated glomerular filtration rate <50 mL/min). The majority (71%) had documented bone disease at diagnosis, and

Simon Hallam
St Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom
Funding/support: None.
The authors have indicated they have no potential conflicts of interest to disclose.

HemaSphere (2018) 2:1(e24)
Citation: Hallam S. TEAMM work saves lives in myeloma. *HemaSphere*, 2018;2:1. http://dx.doi.org/10.1097/HS9.0000000000000024

93% had an Eastern Cooperative Oncology Group performance status of 0 to 2. Approximately half of the patients (54%) were undergoing treatment with an intention to proceed to high-dose therapy with autologous stem cell rescue.

In the placebo arm, there were 134 events in 488 subjects (27%), of which 112 were febrile episodes, 15 were deaths, and 7 were febrile episodes with death. In the arm receiving levofloxacin, there were 95 events in 489 subjects (19%), of which 87 were febrile episodes, 4 were deaths, and 4 were febrile episodes with death. This was a significant benefit for levofloxacin, with a hazard ratio of 1.52 (95% confidence interval 1.17–1.97, $P=0.002$). As a stand-alone outcome measure, all-cause deaths within 12 weeks were also significantly higher in the placebo arm at 22 compared with 8 deaths in the levofloxacin arm ($P=0.02$), but after 52 weeks of follow-up, there was no difference in overall survival between the arms.

Of the 291 organisms isolated from study subjects in both arms, 192 were from patients in the placebo arm and 99 in the levofloxacin arm. The main difference in type of organism isolated was a reduction in gram-negative bacteria in the levofloxacin arm, with very similar numbers of gram-positive isolates. No difference was detected between the 2 arms in respect of carriage or acquisition of infection with *C difficile*, MRSA, or ESBL+ gram-negative bacteria.

Subgroup analysis according to physicians' choice to use co-trimoxazole prophylaxis revealed that the 315 subjects receiving co-trimoxazole had fewer febrile episodes and deaths than the 662 not receiving it. Controlling for this in a post hoc analysis, the benefit of levofloxacin remained. The beneficial effect of co-trimoxazole appeared to be independent of, and additive to, the beneficial effects of levofloxacin prophylaxis.

Commentary

To date this study has been presented in abstract form only, and we must therefore be cautious about placing too much emphasis on the findings. More in-depth analysis of the mature data might reveal subtle but significant nuances, and we await the final published article with great interest.

It is understandable, however, that the findings have already drawn significant attention. This was a multicenter study recruiting large numbers of patients in a relatively short space of time, with clearly defined and identifiable end points of major clinical relevance. The study population was more representative of the real-world myeloma population in terms of age, comorbidities, and renal dysfunction than many clinical trials in this disease. Of particular value, this study asked immediately important questions of a low-technology, low-cost intervention that could be accessible to the global population of myeloma patients.

The early mortality rate of 4.5% in the control arm was lower than reported in historical controls. Nonetheless, these data demonstrate a clear reduction in febrile episodes, deaths and febrile deaths from a 12-week course of prophylactic antibiotics, the total cost of which is <50 Euros. Such a low-cost intervention seems likely to reduce the number of far more costly (from both a health and economic perspective) in-patient admissions. Moreover, the reduced use of broad-spectrum antibiotics during in-patient stays to treat febrile episodes may reduce the overall risks of antibiotic resistance and nosocomial infection in those taking prophylaxis. Comments on social media already bear testimony to the enthusiasm of opinion leaders in myeloma to incorporate these findings into daily clinical practice.

There are still a host of questions for the investigators to consider, and it will be interesting to see the details of myeloma-directed therapies received between groups, including steroid use. Why was the reduction in mortality at 12 weeks (when prophylaxis stopped) not apparent at 52 weeks? Could further benefit be derived from prolonging prophylaxis, or might this lead to increased problems with resistant strains? Was the reduction in deaths in the levofloxacin arm due solely to a reduction in sepsis-related mortality, or did the avoidance of febrile episodes permit improved delivery of planned myeloma-directed therapy? Might this data hint at a previously unrecognized antimyeloma activity of levofloxacin?

It seems likely that this study will be practice changing, and levofloxacin prophylaxis may rapidly become standard of care in myeloma. This strategy is cheap, easy to deliver and receive, and can be implemented swiftly within existing infrastructures. It is hoped that it may lead to improved outcomes in newly diagnosed myeloma across a range of healthcare economic settings, although the impact may vary by location—local pathogen and resistance patterns might be quite different between Northern Europe and, for instance, Southern Europe or North Africa. This important study exemplifies that, in a market of exciting but expensive novel therapies, high-quality clinical research asking patient-focused questions has the potential to change lives globally, without having to cost the Earth.

References

1 Augustson BM, Begum G, Dunn JA, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002—Medical Research Council Adult Leukaemia Working Party. *J Clin Oncol* 2005; 23:9219–9226.

2 https://ash.confex.com/ash/2017/webprogram/Paper106598.html. Accessed February 5, 2018.