Prophylactic levofloxacin to prevent infections in newly diagnosed symptomatic myeloma: the TEAMM RCT

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Scientific summary

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Background

Myeloma is a cancer of bone marrow plasma cells that causes profound immunosuppression. There is a high early-death rate, with the biggest single cause being infection. Recent improvements in overall survival in myeloma mean that prevention of early death has become more pressing, especially as early death affects all prognosis groups.

Antibiotic prophylaxis is likely to be the single most effective measure to prevent early death in myeloma patients. Treatment with antibiotics once an infection is established is probably not sufficient, as the early-death rate in older patients has remained constant over a 20-year period, despite improvements in supportive care. The use of antibiotic prophylaxis is evidence-based established practice in some areas of medicine (e.g. neutropenia, human immunodeficiency virus) but the recent rise in health care-associated infections (HCAIs) has raised concern about the risks of antibiotic prophylaxis. Although the benefits are well established, there is concern that clinicians are withholding antibiotic prophylaxis because of fears of HCAI. Extrapolating from current data, the benefits of prophylaxis are likely to outweigh the risks of HCAI. However, there has not been a large trial looking at the benefits of antibiotic prophylaxis compared with the risks of HCAI. Examination of the organisms causing infection in myeloma suggests that levofloxacin, given for the first 12 weeks, is the best antibiotic for prophylaxis.

Reducing infection in the first 3 months from diagnosis may increase the myeloma response rate primarily by reducing the number of interruptions of antimyeloma treatment. There is also some evidence for a role for infections driving myeloma pathogenesis directly, although further proof is required to confirm this effect in vivo.

Objectives

To assess the risks, benefits and cost-effectiveness of levofloxacin in newly diagnosed symptomatic myeloma by means of a prospective, multicentre, randomised, double-blind, placebo-controlled trial.

End points

Primary outcome from start of trial treatment to 12 weeks

- Time to first febrile episode or death.
  A febrile episode is identified and counted by a single oral temperature of $\geq 38\,^{\circ}C$ (recorded either by a health-care professional *or* by the patient/carer, provided that the patient/carer has been trained and assessed as being competent in temperature taking) *and* by that patient then being given anti-infectives.

Secondary outcomes from start of trial treatment to 12 weeks

- Number of deaths and infection-related deaths.
- Number of days in hospital.
- Number of days in hospital on anti-infectives.
- Carriage and invasive infections with *Staphylococcus aureus*, *Clostridium difficile* and extended-spectrum beta-lactamase (ESBL) coliforms.

- Patient characteristics, steroid use and indices of immunocompetence and their relation to colonisation by, and development of, infection with *S. aureus*, *C. difficile* and ESBL coliforms, non-HCAIs and Eastern Cooperative Oncology Group (ECOG) performance status.
- Number of clinically documented total infections, episodes of severe sepsis (Common Terminology Criteria for Adverse Events grade 3 or 4) and suspected infections (defined as any episode in which the patient was given anti-infective treatment for a suspected infection and any recorded temperature of < 38 °C).
- Incidence of microbiologically proven infections, the pathogens and their susceptibility to antibacterials.
- Number of days on anti-infective therapy for treatment of infection.
- Response to antimyeloma therapy and its relationship to infection.

Secondary outcomes from start of trial treatment to beyond 12 weeks

- Carriage and invasive infections with *S. aureus, C. difficile* and ESBL coliforms between 12 and 16 weeks to assess for delayed effects from the intervention, which is stopped at 12 weeks.
- Response to antimyeloma therapy at 16 weeks.
- Quality of life (QoL).
- Health economics.
- Overall survival.

Trial design and methodology

Multicentre, randomised, double-blind, placebo-controlled trial.

Patients were randomised to receive levofloxacin or placebo tablets for 12 weeks at the start of antimyeloma treatment. Treatment allocation was blinded and balanced by centre, estimated glomerular filtration rate (eGFR) and intention to give high-dose chemotherapy with autologous stem cell transplant. A central randomisation telephone service used a minimisation algorithm to generate a trial number and a drug pack number for each patient and allocate treatments in a 1 : 1 ratio. All investigators, patients and trial co-ordination staff were blinded to the treatment allocation. The levofloxacin and placebo tablets were packaged in coded, but otherwise identical, blister packs. Neither the patient nor the clinical team responsible for the patient's care could break the treatment code. The treatment code could be broken only by the Emergency Scientific and Medical Services team at Guy's and St Thomas' Hospital.

Treatment and investigations

In the experimental arm, patients were given 500 mg of levofloxacin orally, once daily, for 12 weeks (dose reduced in patients with renal impairment).

In the control arm, patients were given placebo orally, once daily, for 12 weeks (dose reduced in patients with renal impairment).

All patients received antimyeloma treatment and supportive care including bisphosphonates as per standard practice. If it was intended to give patients high-dose chemotherapy with autologous stem cell transplant, this information was collected at randomisation and taken into account during stratification. When patients were within 14 days either side of starting a programme of antimyeloma treatment, they received two levofloxacin (dose of 250 mg) or placebo tablets daily for 12 weeks. The start of the antimyeloma treatment was determined as the start of high-dose steroids or chemotherapy, whichever came first.

Estimated glomerular filtration rate provided locally, where possible, was assessed at baseline and reassessed at each scheduled trial visit to identify changes in renal function that would necessitate a change in dose of levofloxacin. It is recommended that eGFR was assessed within the 7- to 14-day period

prior to randomisation. Those patients with an eGFR of > 50 ml/minute/1.73 m^2 took two tablets once per day (dose of 500 mg), patients with an eGFR of 20–50 ml/minute/1.73 m^2 took one tablet daily (dose of 250 mg) and patients with an eGFR of < 20 ml/minute/1.73 m^2 took half a tablet daily (dose of 125 mg). Both the active and placebo tablets were identical in breakable form. Dose reductions were recorded on the front of the patient diary, which was provided at each trial visit in conjunction with a review of eGFR. At entry and at 4, 8, 12 and 16 weeks, central laboratory analysis of stool samples and nasal swabs for microbiology, blood and urine for paraprotein response and immune function were collected. QoL [is assessed via the EuroQoL-5 Dimensions (EQ-5D), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 and the Hospital Anxiety and Depression Scale] and health economics data were collected via the patient diaries.

Sample size determination

The final number of patients recruited was 977 (randomised to levofloxacin, $n = 489$; randomised to placebo, $n = 488$). The primary outcome measure was time to first febrile episode or death from all causes, using a Kaplan–Meier survival curve and log-rank analysis. Assuming that the proportion of patients experiencing a febrile episode or death is 30% in the first 3 months and that prophylactic antibacterials would reduce that rate to 20%, then recruiting 800 patients into the trial (400 patients in each arm) would allow differences in excess of 10% to be detected with 90% power using a two-sided test at the 5% level of significance. Recruiting 1000 patients into the trial (500 in each arm) would allow differences in excess of 8% to be detected with a 90% power using a two-sided test at the 5% level of significance. Recruiting 1000 patients would also allow detection of a levofloxacin-induced threefold increase in the rate of *C. difficile*-positive stools from 5% to 15% from entry to the trial to 12 weeks, with a 95% power and a 5% level of significance (two-sided test).

Other analyses included the incidence of suspected infections by site, severity and therapy; response to antimyeloma therapy and its relationship to infection; patient characteristics and indices of immunocompetence (blood leucocyte subset enumeration and antibacterial antibody titres) as prognostic markers for colonisation and invasive infection by antibiotic-resistant organisms; health economics; and QoL (by daily diary card and 4-weekly EQ-5D up to 16 weeks). With 1000 patients, reliable estimates can be reported for these secondary outcomes.

Follow-up

Patients were followed up at 4-weekly intervals up to 16 weeks, with a further follow-up at 1 year. Long-term follow-up will be collected for patients until the end of the trial by flagging with the Office for National Statistics and requesting copies of death certificates.

Key inclusion criteria

Patients were eligible for this trial if:

- they were aged ≥ 21 years and able to give informed consent
- they had newly diagnosed symptomatic myeloma based on internationally agreed criteria
- there was an intention to treat their myeloma actively
- they were within 14 days of starting, and no more than 14 days into, a programme of antimyeloma treatment
- they were able to provide written informed consent.

Key exclusion criteria

Patients were ineligible for this trial if they:

- had a contraindication to levofloxacin
- were women of childbearing age who were not willing to use appropriate methods of contraception to prevent pregnancy or women who were breastfeeding
- were thought to have a mandatory requirement for antibacterial prophylaxis.

- had received previous treatment for myeloma, except for the following –
    - local radiotherapy to relieve bone pain or spinal cord compression
    - prior bisphosphonate treatment
    - previous (< 5 years since diagnosis) or concurrent active malignancies except surgically removed basal or squamous cell carcinoma of the skin, treated carcinoma in situ of the breast or cervix, or incidental histological finding of prostate cancer (tumour, node, metastasis stage of T1a or T1b) [patients with remote histories (> 5 years) of other cured malignancies could be entered].

Results

Tackling Early Morbidity and Mortality in Myeloma (TEAMM) recruited 977 patients between August 2012 and April 2016 from 93 centres in the UK. The median age of participants was 67 years, 63% were male, 76% had an eGFR of > 50 ml/minute/1.73 m^2, 54% had planned high-dose chemotherapy with autologous stem cell transplantation, 76% had ECOG performance status 0 or 1 and 71% presented with bone disease. In total, 977 patients were randomised (levofloxacin, $n = 489$; placebo, $n = 488$); 24 patients withdrew before their first assessment and were censored at their date of withdrawal for the primary outcome.

A total of 134 (27%) events (febrile episode alone, $n = 112$; febrile episodes plus death, $n = 7$; deaths alone, $n = 15$) occurred in the placebo arm and 95 (19%) events (febrile episode alone, $n = 87$; febrile episodes plus death, $n = 4$; deaths alone, $n = 4$) occurred in the levofloxacin arm. The hazard ratio (HR) for time to first event (febrile episode or death) within the first 12 weeks was 0.66 [95% confidence interval (CI) 0.51 to 0.86; $p = 0.002$]. Cox regression models adjusting for slight imbalances between baseline factors did not identify any significant independent prognostic factors in the presence of treatment (adjusted HR 0.73, 95% CI 0.53 to 0.99; $p = 0.04$) in favour of levofloxacin.

Levofloxacin also reduced other infections (144 infections from 116 patients) compared with placebo (179 infections from 133 patients) (p-trend of 0.06). There was no difference in new acquisitions of *C. difficile*, methicillin-resistant *S. aureus* and ESBL Gram-negative organisms when assessed up to 16 weeks. Levofloxacin produced slightly higher quality-adjusted life-year gains over 16 weeks compared to placebo but had associated higher costs for health resource use. With a median follow-up of 52 weeks, there was no significant difference in overall survival ($p = 0.94$).

Conclusions

During the 12 weeks from new diagnosis, the addition of prophylactic levofloxacin to active myeloma treatment significantly reduced febrile episodes and deaths without increasing HCAIs or carriage.

Trial registration

This trial is registered as ISRCTN51731976.

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This report

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