Early switch from intravenous to oral antibiotic therapy in patients with cancer who have low-risk neutropenic sepsis: the EASI-SWITCH RCT

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Disclosure of interests

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Scientific summary

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Scientific summary

Background

Neutropenic sepsis (NS) is a potentially life-threatening complication of treatment with systemic anticancer therapy (SACT). Many consensus guidelines, including the UK National Institute for Health and Care Excellence (NICE) guidance, recommend switching from intravenous (i.v.) to oral antibiotics after 48 hours of therapy, with evidence lacking to support an earlier switch in those patients at low risk of infective complications. The early switch to oral antibiotic therapy in patients with low-risk NS (EASI-SWITCH) trial was developed in response to a commissioned call by National Institute for Health and Care Research (NIHR) to address this evidence gap.

Objectives

To establish the clinical and cost effectiveness of early switch to oral antibiotics (within 12–24 hours of starting antibiotics) in patients with NS at low risk of infective complications. The primary objective was to assess whether early switch was non-inferior to standard care (continuation of i.v. antibiotics for at least 48 hours) in terms of treatment failure at day 14. The secondary objectives were to assess the effects of early oral switch on quality of life, length of hospital admission, re-admission to hospital, changes to subsequent planned SACT and death within 28 days in addition to an assessment of cost-effectiveness and patient preference for these treatment strategies at day 14.

Study design

A pragmatic, randomised, open-label, multicentre non-inferiority trial was designed to compare early oral switch to standard care i.v. antibiotics. Participants were randomised with randomly permuted blocks 1 : 1 to intervention and standard care. Allocation concealment was maintained through use of an automated system with access to the randomisation sequence restricted to the trial statistician. Participants and clinical or research team members were not blinded to allocated treatment due to both the pragmatic nature of the study and patient representatives' advice that outcome assessors would be likely to be made aware by participants of their allocated treatment. An embedded pilot study was included to test the assumptions related to recruitment, adherence and separation between treatment arms underpinning the study design.

The initial sample size was 628 patients based on a stringent approach to trial design in accordance with a typical Phase 3 efficacy study with a line of sight to therapeutic licensing and a non-inferiority margin suggested by consensus guidelines. On review after study initiation, the stringency of this design was felt to be less relevant to a treatment strategy involving agents already routinely used and/or licensed for use in NS and the low-risk nature of this patient population where treatment failure is not associated with serious adverse outcomes such as critical care admission or death. The revised target sample size was 230 patients. This was based on an assumed 15% treatment failure rate in the standard care arm and a 15% non-inferiority margin, at 90% power [one-sided 95% confidence interval (CI)] requiring 98 patients per group. Allowing for a 5% dropout rate and 10% crossover from control to intervention the target was 115 participants per group (230 in total). To conclude non-inferiority of the intervention, the primary analysis was required to demonstrate non-inferiority in both the intention-to-treat (ITT) and per-protocol (PP) analyses.

Methods

Patients aged 16 years and over receiving SACT with fever (≥ 38°C), or symptoms and signs of sepsis, and neutropenia (≤ 1.0 × 10^9/l) within 24 hours of randomisation, with a Multinational Association for Supportive Care in Cancer (MASCC) score of ≥ 21 and receiving i.v. piperacillin/tazobactam or meropenem for < 24 hours were eligible. Patients with acute leukaemia or stem cell transplant were excluded. Participants were recruited from 19 sites across the UK.

Patients were randomised on a 1 : 1 basis to (1) early switch to oral ciprofloxacin (750 mg twice daily) and co-amoxiclav (625 mg three times daily) within 12–24 hours of starting antibiotics and completing 5 days treatment in total or to (2) continuation of i.v. antibiotics for at least 48 hours with ongoing treatment at physician discretion. Patients were discharged by their treating physician in accordance with their routine clinical practice. A patient diary was used to record any further temperatures and oral antibiotic compliance. Follow-up at day 14 determined whether the primary outcome measure of treatment failure was met and health-related quality of life (HRQoL) and patient preference questionnaires were completed. At day 28, survival status and the effect of NS on any subsequent cycle of anticancer treatment were assessed.

Outcome measures

Primary outcome measure

Treatment failure at day 14, defined using a composite measure comprising:

- persistence, recurrence or new onset of fever (temperature ≥ 38°C) after 72 hours of starting i.v. antibiotic treatment
- physician-directed escalation from protocol antibiotic treatment
- re-admission to hospital (related to infection or antibiotic treatment)
- critical care admission
- death.

Secondary outcome measures

- Short-term change in HRQoL, using EuroQoL-5 Dimensions, five-level version (EQ-5D-5L) as the measurement tool, at baseline and 14 days.
- Cost-effectiveness, based on the cost per treatment failure avoided at 14 days and a cost–utility analysis (CUA) estimating the cost per quality-adjusted life-year (QALY) at 14 days.
- Time to resolution of fever from initial i.v. antibiotic administration.
- Adverse events (AEs) related to antibiotics.
- Hospital discharge and total length of hospital stay.
- Re-admission to hospital.
- Death within 28 days.
- Adjustment to the subsequent scheduled cycle of chemotherapy.
- Patient preferences for antibiotic treatment strategy assessed at day 14.

Results

The embedded pilot phase of the study highlighted challenges in recruitment and study delivery but no concerns regarding treatment adherence or separation between treatment arms. Despite revisions to the study design and eligibility criteria, and taking account of the lower than anticipated incidence of NS, recruitment remained challenging and appeared to plateau as the study progressed. While logistical aspects such as the number of potential patients and the short time window for enrolment continued to impact on

recruitment, review of standard care practice in NS management suggested increasing variation in equipoise between trial arms as clinicians shifted towards early or upfront oral antibiotics as the trial progressed.

The study was closed early due to under-recruitment with 129 patients recruited. Sixty-five patients were randomised to the early switch (intervention arm) and 64 to the standard care (control) arm with subsequent ITT and PP analyses including 125 patients (intervention *n* = 61 and control *n* = 64) and 113 (intervention *n* = 53 and control *n* = 60), respectively. In the ITT population, the treatment failure rates were 14.1% in the control and 24.6% in the intervention group, respectively; difference = 10.5% (95% CI 0.11 to 0.22). In the PP population, the treatment failure rates were 13.3% and 17.7% in control and intervention groups, respectively; difference = 3.7% (95% CI 0.04 to 0.148). The criteria for non-inferiority were not met in the ITT analysis but were met in the PP analysis; however, given the under-recruitment, no definitive conclusion regarding non-inferiority can be made and the discordant results between ITT and PP analyses add to the uncertainty in interpreting these data.

The main constituents of the composite primary outcome measure accounting for treatment failure were persistence/recurrence of fever and/or physician-directed escalation from the protocolised antibiotic regimen. None of the treatment failure events recorded in either arm were attributable to the need for critical care support or death before day 14. There were no apparent differences between the two trial arms for time to fever resolution, re-admission to hospital to day 28, survival to day 28 or changes to the originally intended SACT regimen. AEs were as anticipated for the agents used and reported at similar rates between treatment arms.

A within-trial economic evaluation was performed to assess the cost effectiveness of early switch to oral antibiotics. This included a cost-effectiveness analysis (CEA) consistent with the primary outcome measure to estimate the cost per treatment failure avoided at day 14 and a CUA to estimate the cost per QALY at day 14. The primary measure used in these analyses, the QALY, was estimated from the EQ-5D-5L questionnaire. A bespoke Patient Follow-up Questionnaire at day 14 was used to collect information on non-health outcome measures important to patients. Overall, early oral switch appears to be a cost-effective approach within existing NHS care pathways and leads to improvements in global HRQoL. The majority of patients were content with the treatment they received, regardless of the group they were randomised to. Notably, patients had a much higher acceptance of the possibility of treatment failure in order to enable early discharge for their primary admission than might be anticipated by clinicians.

Conclusions

Non-inferiority for early oral switch could not be proven. The findings suggest this may be a an acceptable treatment strategy for some patients who can adhere to such a treatment regimen and would prefer a potentially reduced duration of hospitalisation while accepting a potentially increased risk of treatment failure resulting in re-admission.

Trial registration

This trial is registered as ISRCTN84288963.

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