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HYMN: a trial comparing hyperthermia and mitomycin chemotherapy with a second BCG treatment, or other standard treatment, for bladder cancer that has come back

Submission date
06/03/2009

Recruitment status
Stopped

Registration date
28/05/2009

Overall study status
Stopped

Last Edited
09/07/2020

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/trial-bcg-hyperthermia-transitional-cell-bladder-cancer-hymn

Study website
http://www.hymn.bham.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2008-005428-99

IRAS number

ClinicalTrials.gov number
NCT01094964

Secondary identifying numbers
08/0365

Study information

Scientific Title
A randomised controlled phase III trial comparing hyperthermia plus mitomycin to a second course of Bacillus Calmette-Guerin (BCG) or standard therapy in patients with recurrence of non-muscle invasive bladder cancer following induction or maintenace BCG therapy

Acronym
HYMN

Study objectives
The proposed trial is designed to answer the question whether hyperthermia plus intravesical mitomycin (HM) is effective in patients in whom urothelial cell carcinoma (UCC) has recurred following intravesical BCG induction or maintenance therapy.

Updated 22/02/2011: the anticipated end date for this trial was updated from 01/06/2012 to 30 /04/2015.
Updated 04/11/2013: the trial recruitment has been on temporary halt since 19/07/2013.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Added 04/11/2013: NRES Committee London - Brent, 19/10/2009, REC reference number: 09 /H0717/56

Study design
Phase III open-label multi-centre randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)

Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Non-muscle invasive bladder cancer

Interventions
Current interventions as of 11/02/2013:
Experimental Arm: Patients will receive six weekly induction instillations of hyperthermia plus mitomycin (HM) using the Synergo® System, followed by a 6 week pause and a cystoscopy assessment. If disease free then they will proceed to maintenance HM consisting of one instillation of HM every 6 weeks for the first year and one instillation every 8 weeks for the second year, with further treatment in those disease-free at 24 months at the discretion of the clinician.

Each instillation is divided into two 30 minute cycles each with 20 mg mitomycin dissolved in 50 ml of sterile water. Bladder hyperthermia (42 +/-2°C) will be delivered in combination with each instillation of mitomycin in accordance with the manufacturer's operational guidelines. At the end of the treatment the suspension should be maintained in the bladder for as long as possible up to a maximum of two hours.

Control Arm of patients who failed previous induction BCG: Patients will receive a second course of BCG therapy (BCG2)* (1). This will consist of six consecutive weekly instillations of BCG followed by maintenance therapy. Maintenance consists of three consecutive weekly instillations of BCG at 3, 6, 12, 18 and 24 months following the start of the BCG2 course, with further treatment for those disease-free at 24 months at the discretion of the clinician.

For each instillation:
Bacillus Calmette-Guérin reconstituted with normal saline to a total of 50ml instillation volume. The suspension will be instilled in the bladder and maintained for as long as possible up to two hours.

OR

Control Arm of patients who failed previous maintenance BCG: Patients will receive institutional standard treatment* (1) the best standard therapy for BCG-failure chosen at the discretion of the treating clinician on a case-by-case basis and which have been defined prior to patient randomisation.
Standard treatment can include:
1. Intravesical mitomycin (This may be given via Electromotive Drug Administration)
2. Intravesical epirubicin alone
3. Intravesical Gemcitabine alone - with approval for its use in NMIBC at your centre as it is not currently licensed in this indication
4. Intravesical BCG alone (concentration and schedule may differ from BCG2 treatment)
5. Intravesical BCG plus Interferon alpha (INFa) with prior approval for its use in NMIBC at your centre as it is not currently licensed in this indication
6. Active monitoring with 3-monthly white-light or PDD cystoscopies and urine cytology tests followed by transurethral resection if a bladder tumour is detected

The dosing regime and duration of treatment will be according to local practice and defined prior to patient randomisation.

* BCG is the standard therapy for recurrent NMIBC. However if the patient has already received induction and maintenance BCG prior to entering the trial it may not be beneficial for them to receive further BCG. Therefore if the patient has received BCG maintenance previously and is allocated to the control arm they will receive the standard therapy for BCG failure as defined by their treating centre.
(1) Note: A small proportion of patients experience intolerance to BCG during induction therapy and these patients will not benefit from further BCG treatment. In these cases, patients will be randomised between Hyperthermia plus mitomycin and Institutional Standard.

Previous interventions until 11/02/2013:
Experimental Arm: Patients will receive six weekly induction instillations of hyperthermia plus mitomycin (HM) using the Synergo® System, followed by a 6 week pause and a cystoscopy assessment. If disease free then they will proceed to maintenance HM consisting of one instillation of HM every 6 weeks for the first year and one instillation every 8 weeks for the second year, with further treatment in those disease-free at 24 months at the discretion of the clinician.

Each instillation is divided into two 30 minute cycles each with 20 mg mitomycin dissolved in 50 ml of sterile water. Bladder hyperthermia (42 +/-2°C) will be delivered in combination with each instillation of mitomycin in accordance with the manufacturer's operational guidelines. At the end of the treatment the suspension should be maintained in the bladder for as long as possible up to a maximum of two hours.

Control Arm of patients who failed previous induction BCG: Patients will receive a second course of BCG therapy (BCG2)*. This will consist of six consecutive weekly instillations of BCG followed by maintenance therapy. Maintenance consists of three consecutive weekly instillations of BCG at 3, 6, 12, 18 and 24 months following the start of the BCG2 course, with further treatment for those disease-free at 24 months at the discretion of the clinician.

For each instillation:
81 mg BCG, Connaught strain or Tice strain (12.5 mg per instillation), reconstituted with normal saline to a total of 50 ml instillation volume. The suspension will be instilled in the bladder and maintained for as long as possible up to two hours.

OR

Control Arm of patients who failed previous maintenance BCG: Patients will receive institutional standard treatment* that is currently used by the treating investigators' hospital and which have been defined prior to patient recruitment. Standard treatment can include:
1. Intravesical BCG plus Interferon alpha (INFa)
2. Intravesical mitomycin (This may be given via Electromotive Drug Administration)
3. Intravesical epirubicin

The dosing regime and duration of treatment will be according to local practice and defined prior to patient randomisation.

* BCG is the standard therapy for recurrent NMIBC. However if the patient has already received induction and maintenance BCG prior to entering the trial it may not be beneficial for them to receive further BCG. Therefore if the patient has received BCG maintenance previously and is

allocated to the control arm they will receive the standard therapy for BCG failure as defined by their treating centre.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Bacillus Calmette-Guerin (BCG), mitomycin

Primary outcome measure
Current primary outcome measures as of 11/02/2013:
1. Disease-free survival. For patients without CIS at baseline and those with CIS at baseline but not at the 3-month surveillance visit, this is defined as the interval in whole days between the date of randomisation into the trial and the earliest of date of detection of recurrent disease, or date of death from any cause. For patients with CIS at baseline and at the 3-month surveillance visit, this is defined as the interval in whole days between the date of randomisation and the date of their 3-month surveillance visit. Disease recurrence is defined as the presence of urothelial cell carcinoma or positive cytology. Disease progression is defined as T2 disease or evidence extravesical disease. For those patients who do not have recurrent disease or die during the course of the trial, disease-free survival times will be censored at the last follow-up date. Patients who experience a distant upper-tract recurrence will be censored at the last available assessment. Disease-free survival will be followed-up for 2 years from the first treatment.
2. Complete-response rate at 3 months. For patients with CIS at randomisation, complete response at 3 months is defined as absence of visible tumour recurrence at cystoscopy, negative cytology and no evidence of CIS on random (4 quadrant) biopsy of the bladder.

Previous primary outcome measures until 11/02/2013:
1. Disease-free survival. Defined as the interval in whole days between the date of randomisation into the trial and the earliest of date of detection of recurrent disease, or date of death from any cause. This will also include the interval in whole days between the date proved tumour free (by cystoscopy, negative cytology and biopsy) and the earliest of date of detection of recurrent disease, or date of death from any cause in patients with CIS at randomisation. Disease recurrence is defined as the presence of urothelial cell carcinoma or positive cytology. Disease progression is defined as T2 disease or evidence extravesical disease. For those patients who do not have recurrent disease or die during the course of the trial, disease-free survival times will be censored at the last follow-up date. Patients who experience a distant upper-tract recurrence will be censored at the last available assessment. Disease-free survival will be followed-up for 2 years from the first treatment.
2. Complete-response rate at 3 months. For patients with CIS, complete response at 3 months is defined as absence of visible tumour recurrence at cystoscopy, negative cytology and no evidence of CIS on random (4 quadrant) biopsy of the bladder.

Secondary outcome measures
1. Progression-free survival. Defined as the interval in whole days between the date of randomisation into the trial and the earliest of date of detection of disease progression, or date of death from any cause. Disease progression is defined as stage T2 disease or greater confirmed by histopathology following TUR (>=pT2). For those patients who do not experience

disease progression or die during the course of the trial, progression-free survival times will be censored at the last follow-up date. Patients who experience a distant upper-tract recurrence will be censored at the last available assessment.
2. Overall survival. Defined as the interval in whole days between the date of randomisation into the trial and date of death from any cause; patients who do not die during the course of the trial will be censored at the last follow-up date.
3. Disease-specific survival. Defined as the interval in whole days between the date of randomisation into the trial and date of death due to bladder cancer. Patients who do not die during the course of the trial will be censored at the last follow-up date. Patients who die of other causes will be censored at date of death due to other cause.
4. Recurrence-free survival. Recurrence-free survival will be measured in patients with papillary disease only. It is defined in the same way as disease-free survival, with the important distinction that CIS at the first three-month post-treatment visit will not be included as an event, but rather considered a treatment failure and will be censored. Patients who entered with CIS, became negative at first control, will be also followed up for recurrence free from first control.
5. Safety and tolerability of HM. Safety and tolerability will be reported in terms of the frequency, severity and nature of adverse events, and the treatment received.
6. Quality of life. Quality of life will be assessed at trial entry and every three months using the questionnaires European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer patients (EORTC QLQ-C30), EORTC-QLQ-BLS24 (a 24-item questionnaire for patients with superficial bladder cancer) and Euroqol EQ-5D.
7. Cost effectiveness. Patient costs will be calculated and cost-effectiveness assessed. The economic analysis will be based on both a principal outcome cost-per-survivor (disease-free) at 24 months; and a secondary outcome, cost-per-QALY.

All secondary outcomes will be followed-up for 2 years from first treatment.

Overall study start date
01/06/2009

Completion date
07/10/2016

Reason abandoned (if study stopped)
Recruitment into the trial was temporarily halted on 19th July 2013 and later terminated on 7th October 2013 at the joint request of the independent Data Monitoring (DMC) and Trial Steering Committees (TSC) following concern identified by the DMC that hyperthermia treatment may have led to misinterpretation of the pathology, particularly for participants with carcinoma in situ (CIS) at trial entry. The joint DMC/TSC decided to close the trial following their request for a central pathology review for participants who failed to respond to treatment or recurred on treatment and updated statistical analysis of the trial data. In the intervening period the TSC recommended that all trial participants remain on trial treatment.

Eligibility

Key inclusion criteria
1. Both males and females, age >=18 years
2. Previous BCG induction or maintenance therapy for non-muscle-invasive bladder cancer (NMIBC)
3. Recurrence of disease following induction or maintenance BCG defined as:
3.1. Grade 3 or Grade 2, stage Ta or T1 disease

3.2. Carcinoma in situ (CIS) with Grade 3, Grade 2 or Grade 1 stage Ta or T1 disease
3.3. CIS alone
4. Have undergone a re-resection of all T1 disease to exclude muscle invasive disease
5. World Health Organization (WHO) performance status 0, 1, 2, 3 or 4
6. Normal kidneys and ureters on imaging* study within the past 12 months
7. Pre-treatment haematology and biochemistry values within acceptable limits:
7.1. Haemoglobin >=10 g/dl
7.2. Platelets >=100 x 10^9/l
7.3. White blood cells (WBC) >=3.0 x 10^9/l or absolute neutrophil count (ANC) >=1.5 x 10^9/l
7.4. Serum creatinine <1.5 x Upper Normal Limit (UNL)
8. Negative pregnancy test for women of child-bearing potential
9. Available for long-term follow-up
10. Unfit or unwilling to have a cystectomy
11. Written informed consent

*Imaging of high risk recurrent UCC by computerised tomography (CT) scan is routinely performed in some centres and is recommended as good practice in this trial.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
242

Key exclusion criteria
Current exclusion criteria as of 11/02/2013:
1. Recurrence of Grade 1 UCC following BCG induction
2. Previous intravesical chemotherapy in the past 6 months, other than single instillation post-TUR.
3. UCC involving the prostatic urethra or upper urinary tract
4. >=T2 UCC
5. Known or suspected reduced bladder capacity (<250 ml)
6. Significant bleeding disorder.
7. Pregnant or lactating women or women of childbearing potential unwilling or unable to use adequate non-hormonal contraception. Male patients should also use contraception if sexually active
8. Patients with an immuno-compromised state for any reason except patients on current or long term use of corticosteroids. As good clinical practice it is recommended to notify the consultant who prescribed the corticosteroids of the HYMN treatment the patient will receive.
9. Other malignancy within the past five years, except: non-melanomatous skin cancer cured by excision, adequately treated carcinoma in situ of the cervix or ductal carcinoma in situ (DCIS) /Lobular Carcinoma in Situ (LCIS) of the breast

10. Concurrent chemotherapy or any previous HM
11. Any known allergy or adverse event that would prevent them receiving the Hyperthermia+Mitomycin treatment
12. Active or intractable urinary tract infection (UTI)
13. Urethral stricture, or any situation impending the insertion of a 20F catheter
14. Bladder diverticula >1 cm
15. Significant urinary incontinence
16. History of pelvic irradiation
17. Patients with implanted electronic devices (such as cardiac pacemakers) or metallic implants within the pelvis, lower torso, spine, hip or upper femur
18. Suitable and willing to have or have had a full or partial cystectomy

Previous exclusion criteria until 11/02/2013:
1. Recurrence of Grade 1 UCC following BCG induction
2. Previous intravesical chemotherapy in the past 6 months, other than single instillation post-TUR.
3. UCC involving the prostatic urethra or upper urinary tract
4. >=T2 UCC
5. Known or suspected reduced bladder capacity (<250 ml)
6. Significant bleeding disorder.
7. Pregnant or lactating women or women of childbearing potential unwilling or unable to use adequate non-hormonal contraception*
8. Current or long-term use of corticosteroids or patients with an immuno-compromised state for any reason
9. Other malignancy within the past five years, except: non-melanomatous skin cancer cured by excision, adequately treated carcinoma in situ of the cervix or ductal carcinoma in situ (DCIS) /Lobular Carcinoma in Situ (LCIS) of the breast
10. Concurrent chemotherapy or any previous HM
11. Any known allergy to either mitomycin or BCG, or previously withdrawn from BCG treatment due to a related adverse event (e.g., systemic infection)
12. Active or intractable urinary tract infection (UTI)
13. Urethral stricture, or any situation impending the insertion of a 20F catheter
14. Bladder diverticula >1 cm
15. Significant urinary incontinence
16. History of pelvic irradiation
17. Patients with implanted electronic devices (such as cardiac pacemakers) or metallic implants within the pelvis, lower torso, spine, hip or upper femur
18. Suitable and willing to have or have had a full or partial cystectomy
* Male patients should also use contraception if sexually active

Date of first enrolment
01/06/2009

Date of final enrolment
19/07/2013

Locations

Countries of recruitment
England

United Kingdom

Wales

Study participating centre
University College London Hospital
235 Euston Road
London
United Kingdom
NW1 2BU

Study participating centre
Darent Valley Hospital
Darenth Wood Road
Dartford
United Kingdom
DA2 8DA

Study participating centre
Freeman Hospital
Freeman Road
Newcastle-upon-Tyne
United Kingdom
NE7 7DN

Study participating centre
Leicester General Hospital
Gwendolen Road
Leicester
United Kingdom
LE5 4PW

Study participating centre
Queen Alexandra Hospital
Southwick Hill Road
Porstmouth
United Kingdom
PO6 3LY

Study participating centre
Royal Devon and Exeter Hospital
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
St George's Hospital
Blackshaw Road
London
United Kingdom
SW17 0QT

Study participating centre
The James Cook University Hospital Marton Road
Marton Road
Middlesborough
United Kingdom
TS4 3BW

Study participating centre
The Queen Elizabeth Hospital
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
Basingstoke & North Hampshire Hospital
Aldermaston Road
Basingstoke
United Kingdom
RG24 9NA

Study participating centre
University Hospital of Wales
Heath Park
Cardiff
United Kingdom
CF14 4XW

Study participating centre
Withington Hospital
Nell Lane
Manchester
United Kingdom
M20 2LR

Sponsor information

Organisation
University College London (UK)

Sponsor details
Joint Research Office (part of the Research Support Centre)
1st Floor Maple House
149 Tottenham Court Road
London
England
United Kingdom
W1T 7DN

Sponsor type
University/education

Website
http://www.ucl.ac.uk/joint-rd-unit/

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK (UK) - Clinical Trials Advisory and Awards Committee (CTAAC) grant (ref: C7629/A10008)

Results and Publications

Publication and dissemination plan

Publication and dissemination plan as of 16/11/2018:
End of Trial report submitted to EudraCT on 15th November 2018 (EudraCT ref 2008-005428-99)

Previous publication and dissemination plan:
The primary outcome results of this trial will be submitted for publication in a peer-reviewed journal. Once published, the TMG will disseminate the results to sites, who will further disseminate the results to trial participants on request.
Any secondary publications and presentations must be reviewed by the Trial Management Group and must not occur prior to or less than six months following publication of the main results. Manuscripts must be submitted to the TMG in a timely fashion, in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham and University College London. Intellectual property rights were addressed in agreements between Sponsor and site(s).

Intention to publish date

31/12/2017

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study will be stored in a publically available repository by 7th October 2017.
Respository : European Medicines Agency (EMA)'s European Clinical Trials Database, EudraCT V10.
URL : https://eudract.ema.europa.eu/

IPD sharing plan summary

Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Plain English results				No	Yes
Results article	results	01/01/2019		Yes	No
HRA research summary			28/06/2023	No	No