EBioMedicine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

Gefitinib and Methotrexate to Treat Ectopic Pregnancies with a Pre-Treatment Serum hCG 1000–10,000 IU/L: Phase II Open Label, Single Arm Multi-Centre Trial☆

Monika M. Skubisz [a,b,c,d,1], Stephen Tong [a,b,*,1], Ann Doust [e], Jill Mollison [f], Terrance G. Johns [c], Peter Neil [d], Miranda Robinson [b], Siladitya Bhattacharya [g], Euan Wallace [c,d], Nicole Krzys [b], W. Colin Duncan [e], Andrew W. Horne [e]

[a] Translational Obstetrics Group, Department of Obstetrics and Gynaecology, University of Melbourne, Heidelberg 3084, Victoria, Australia
[b] Mercy Perinatal, Mercy Hospital for Women, Heidelberg 3084, Victoria, Australia
[c] The Hudson Institute, Clayton 3168, Australia
[d] Monash Health, Clayton 3168, Victoria, Australia
[e] MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh EH16 4TJ, United Kingdom
[f] University of Oxford, Nuffield Department of Primary Health Sciences, Oxford OX2 6GG, United Kingdom
[g] Institute of Applied Health Sciences, University of Aberdeen, Aberdeen AB25 2ZD, United Kingdom

ARTICLE INFO

Article history:
Received 23 December 2017
Received in revised form 5 June 2018
Accepted 12 June 2018
Available online xxxx

Keywords:
Gefitinib
Methotrexate
Ectopic pregnancy
Medical treatment
Phase II

ABSTRACT

Background: Ectopic pregnancies are a leading cause of maternal mortality. Most are treated surgically. We evaluated the efficacy and safety of combining oral gefitinib (epidermal growth factor receptor inhibitor) with methotrexate to treat larger ectopic pregnancies.
Methods: We performed a phase II, single arm, open label study across four hospitals in Edinburgh and Melbourne. We recruited women with a stable tubal ectopic pregnancy and a pre-treatment serum hCG between 1000 and 10,000 IU/L. We administered intramuscular methotrexate (50 mg/m^2) once, and oral gefitinib (250 mg) for seven days. The primary outcome was the percentage successfully treated without needing surgery. To show the treatment is at least 70% effective, 28 participants were required, and 24 or more successfully treated without surgery. Secondary outcomes were safety, tolerability, and time to resolution. This study is registered (ACTRN12611001056987).
Findings: 30 participants with stable tubal ectopic pregnancies were recruited but two withdrew, leaving 28 participants. The median (± range) pre-treatment serum hCG was 2039 (1031–8575) IU/L and nine had pre-treatment hCGs levels >3000 IU/L. The treatment successfully resolved 86% (24/28) cases with a median (± range) time to resolution of 32 (18–67) days. The treatment caused transient rash and diarrhoea, but no serious adverse events.
Interpretation: Combination gefitinib and methotrexate is at least 70% effective in resolving ectopic pregnancies with a pre-treatment serum hCG 1000–10,000 IU/L. This may be a new way to treat most stable ectopic pregnancies, but needs to be validated via a randomised clinical trial.

1. Introduction

Ectopic pregnancy complicates 1–2% of pregnancies [1] and is the most common life-threatening condition in early pregnancy. In the United Kingdom, there are 12,000 cases of ectopic pregnancy every year and they contribute to 3–8% of all maternal pregnancy related deaths [2]. 98% are tubal ectopic pregnancies where the pregnancy implants in the Fallopian tube.

Ectopic pregnancies can be treated surgically (mainly by operative laparoscopic excision), or medically (intramuscular injection of the folate antagonist, methotrexate, followed by serial monitoring of serum hCG concentrations) [3]. However, the efficacy of methotrexate treatment is lower with higher pre-treatment serum hCG concentrations [3]. Hence, many cases are still treated surgically [3] and there is a need for a more effective medical therapy to reduce operative intervention (and its inherent risks) in women diagnosed with ectopic pregnancy.

☆ Funding: NHMRC and the Medical Research Council.
* Corresponding author at: Department of Obstetrics and Gynaecology, University of Melbourne, Level 4 Mercy Hospital for Women, 163 Studley Rd., Heidelberg 3084, Victoria, Australia.
E-mail address: stong@unimelb.edu.au (S. Tong).
[1] Equal contribution.

https://doi.org/10.1016/j.ebiom.2018.06.017

In many fields of medicine, notably oncology and rheumatology (where methotrexate is in widespread clinical use), it is clear that outcomes are improved with combination treatments which target different aetiological pathways, compared to single agent treatment. We propose that the addition of oral gefitinib (an epidermal growth factor receptor [EGFR] antagonist) to the current medical management regimen of intramuscular methotrexate could provide an exciting clinical solution to the suboptimal medical therapy currently available for the management of ectopic pregnancy. Gefitinib is a molecularly targeted drug that blocks EGFR signalling, and is licensed to treat non-small-cell lung cancer.

In preclinical studies, we have shown that ectopic pregnancy implantation sites (trophoblast cells) express high levels of EGFR and that gefitinib augments methotrexate-induced regression of pregnancy-like tissue [4]. Importantly, the two agents work additively in trophoblast cells to potently inhibit cell growth, block EGFR signalling pathways, and enhance apoptosis.

We previously reported a Phase I (Gefitinib and Methotrexate Trial 1, or GEM1) single-arm open-label dose-escalation study administering a combination of intramuscular methotrexate (50 mg/m^2, standard care) and 250 mg oral gefitinib (one dose (n = 3), three daily doses (n = 3), seven daily doses (n = 6)) to 12 women with ectopic pregnancy (serum hCG <3000 IU/L) [5]. The combination of methotrexate and gefitinib did not cause any significant toxicities (assessed clinically and by serial biochemical assessment) or serious side effects. We have also reported a case series where we successfully treated eight extra-tubal ectopic pregnancies with gefitinib and methotrexate [6]. While preliminary, the collective data from the preclinical work and the two small early trials suggest combination methotrexate and gefitinib merit further consideration as an effective medical treatment for ectopic pregnancy.

We therefore undertook a phase II clinical trial. Importantly, we wanted to examine whether the treatment is efficacious in treating larger tubal ectopic pregnancies where current medical management is more likely to fail. We set out to recruit tubal ectopic pregnancies with pre-treatment serum hCG concentrations between 1000 and 10,000 IU/L.

2. Materials and Methods

We conducted a phase II single-arm multi-centre open label trial to examine the efficacy and safety of a single dose of intramuscular methotrexate and daily oral gefitinib for seven days to treat tubal ectopic pregnancies (Trial registration number: ACTRN12611001056987). We named this the GEM (Gefitinib and Methotrexate) II study and the protocol has previously been published [7]. This was an investigator led project and the funders had no role in the conduct of the study.

In women with stable tubal ectopic pregnancy with hCG concentrations between 1000 and 10,000 IU/L we expected the success of methotrexate treatment (defined as a decline in serum hCG < 15 IU/L without the need for surgery) to be 70% or less. Using A'Hern's formula for Phase II one-stage designs [8], with 80% power and a 5% level of significance, 28 patients were required to enable us to assess whether the proportion of patients with a successful outcome to treatment was >70%. The reason we selected this figure is that methotrexate in the clinic appears to have a success rate of around 70% [9, 10]. Our power calculation found if 24 or more patients have a successful outcome, we can reject the hypothesis that the true efficacy of combination gefitinib and methotrexate is ≤70%.

We recruited women presenting with tubal ectopic pregnancies with a pre-treatment serum hCG concentration between 1000 and 10,000 IU/L who were considered clinically stable at four hospitals: Royal Infirmary of Edinburgh (Edinburgh, United Kingdom), Mercy Hospital for Women (Victoria, Australia) and two hospitals within the Monash Health Network (Monash Medical Centre and Dandenong District Hospital, both in Victoria, Australia). Ethical approval was obtained from the Scotland A Research Ethics Committee (LREC 12/SS/0005) (UK), the Southern Health Human Research Ethics Committee B (SH HREC 11180B) and the Mercy Health Human Research Ethics Committee (R12/25). We obtained written, informed consent for all participants.

Our inclusion criteria were: women aged between 18 and 45 years; pre-treatment serum hCG of 1000–10,000 IU/L (rising or static); ultrasound diagnosis of definite tubal ectopic pregnancy (extrauterine gestational sac with yolk sac and/or embryo, with or without cardiac activity) or probable (inhomogeneous adnexal mass or extra-uterine sac-like structure) performed by a clinical team of trained, qualified and experienced ultrasonographers; no clinical evidence of intra-abdominal bleeding; no pallor; no guarding/rigidity on abdominal examination; stable blood pressure and heart rate; haemoglobin on full blood examination at day 1 between 100 and 165 g/L.

Our exclusion criteria were: women with a pregnancy of unknown location; evidence of a significant intra-abdominal bleed on ultrasound defined by free fluid above the uterine fundus or surrounding the ovary; women with a history of any significant pulmonary disease; abnormal liver/renal/haematological indices; significant pre-existing dermatological conditions; significant pre-existing gastrointestinal medical illnesses; and Japanese ethnicity (as those of Japanese descent who are administered gefitinib have been reported to be at higher risk of developing interstitial lung disease) [11].

Our intervention was a single dose intramuscular methotrexate (50 mg/m^2) injection with seven daily doses oral gefitinib (250 mg). We started the administration of gefitinib on the same day that the first methotrexate injection was given. To monitor treatment response, we followed protocols to track serial serum hCG concentrations widely used for medical management with methotrexate, and first proposed by Stovall et al. [12]. Serum hCG levels were measured on days 4, 7 and 11, then weekly until hCG levels declined to non-pregnant levels (<15 IU/L). All women were reviewed regularly and subsequent management, and decision for surgery, was based on normal clinical care. Surgery was considered if there was a persistent lack of response to the treatment (evidence of a lack of a fall in serum hCG concentrations) or there was clinical evidence raising suspicions of active bleeding or tubal rupture.

To monitor safety and tolerability, women were assessed clinically (history) and biochemically (haematological, renal and liver function tests) on days 4 and 7 (or if elevated, they were offered repeat testing until any abnormal values returned to normal physiological levels).

Our primary outcome was the resolution of the tubal ectopic pregnancy without the need for surgery. Resolution was defined by serum hCG concentrations (the current clinical marker to monitor treatment response) falling to non-pregnant levels (hCG <15 IU/L, which corresponds to a negative urinary pregnancy test using the most sensitive assays). Failure was therefore defined as women who required salvage surgery.

Our second outcome was to document safety, tolerability and adverse events, as determined by clinical and biochemical assessment. Patients were regularly reviewed clinically and we confirmed normal renal, liver and haematological function tests on day 1 and assessed treatment effects on days 4 and 7. Furthermore, participants were asked to collect information about adverse events in treatment diaries. They were instructed to contact the clinical research team at any time after consenting to join the trial if they have an event that requires hospitalisation or an event that results in persistent or significant disability or incapacity. The protocols and evaluation in place for serious adverse event reporting are described in detail in the published study protocol [9]. After treatment, participants were contacted at least 3 and 6 months post treatment to document return of menstrual cycles and any subsequent pregnancies.

We also compared the numbers who were successfully treated without need for surgery to women not enrolled in the trial, but presented to our clinical services during the period the trial was recruiting participants and treated with methotrexate alone. These were women

Please cite this article as: Skubisz MM, et al, Gefitinib and Methotrexate to Treat Ectopic Pregnancies with a Pre-Treatment Serum hCG 1000–10,000IU/L: Phase II Open Label, Singl..., EBioMedicine (2018), https://doi.org/10.1016/j.ebiom.2018.06.017