

Combination methotrexate and gefitinib: A potential medical treatment for inoperable non-tubal ectopic pregnancy.

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Abstract

Non-tubal ectopic pregnancies present as a therapeutic challenge. A 35-year-old primigravida at seven weeks gestation had a live interstitial ectopic pregnancy and contraindications to surgery. The patient was treated with a multidose methotrexate regimen combined with oral gefitinib (250mg daily for seven days). The peak human chorionic gonadotropin (hCG) of the patient was recorded at 19,510 IU/L and began declining from day 4 of combination therapy (day 6 of initial treatment). Successful resolution of the ectopic was demonstrated by cessation of the fetal heart by day 15 and hCG falling to 23 IU/L by day 42. A ten-year review of all non-tubal ectopic pregnancies treated with methotrexate identified 46 cases, which had a comparable time to resolution to combination therapy. However, for cases where cardiac activity was present, the median time to resolution following methotrexate treatment was 64 days (47-87 days), 22 days longer than combination therapy. Combination therapy may provide a safe medical treatment for inoperable non-tubal ectopic pregnancy.

Keywords: Gefitinib, Interstitial ectopic pregnancy, Methotrexate, Non-tubal ectopic pregnancy

Introduction

Ectopic pregnancies arise when the conceptus implants outside of the uterus and affect 1-2% of all pregnancies, with most (>90%) implanting within the Fallopian tubes ¹. Rarely, ectopic pregnancies implant in non-tubal locations such as the cornua, cervix or caesarean section scar. This subgroup of ectopic pregnancies present a therapeutic challenge due to surgical access and poor response to traditional medical management with methotrexate ¹. In cases where surgical access is compromised and definitive treatment unavailable, a more effective medical treatment is required.

Gefitinib is a tyrosine kinase inhibitor that acts on the epidermal growth factor receptor (EGFR) pathway and is used most commonly to treat non-small cell lung cancer. Importantly, EGFR is most abundantly expressed in placental tissue compared to all other non-malignant human tissue ². Additionally, EGFR is crucial for placental development and growth ³. Due to its placental expression and role in survival, combination gefitinib and methotrexate has been suggested as a potential treatment for ectopic pregnancy.

This combination therapy has been progressed from preclinical findings through to a phase III clinical trial which is currently underway. During the early phase I trial, combination gefitinib and methotrexate showed a 34% reduction in median resolution time compared to methotrexate therapy alone for tubal ectopic pregnancies ⁴. Additionally, during the phase II study, an 86% success rate was found for tubal ectopic pregnancies with a pretreatment hCG between 1000-10,000 IU/l ⁵. Furthermore, a case series of 8 women with non-tubal ectopic pregnancies and pretreatment hCG between 2,485-48,550 IU/L showed successful treatment with combination

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gefitinib and methotrexate without surgical intervention ⁶. Together, these studies demonstrate the potential of combination gefitinib and methotrexate to treat ectopic pregnancy.

Here, we describe a case of a live, non-tubal ectopic pregnancy in a patient with poor surgical prognosis and high starting hCG which was successfully treated with combination gefitinib and multidose methotrexate. This case was compared with a 10-year case series of non-tubal ectopic pregnancies treated with methotrexate alone at the same tertiary centre.

We also conducted a retrospective review of all non-tubal ectopic pregnancies treated with methotrexate at a tertiary centre in Melbourne Australia, over a ten-year period (2008-2018). Cases were identified as those coded with treatment of methotrexate and non-tubal ectopic pregnancy, which were confirmed through review of individual patient files. Maternal characteristics were collected, as well as mode of conception, gestation at diagnosis, size of mass on ultrasound, presence or absence of a heartbeat, location of the ectopic pregnancy, starting serum hCG and time to resolution.

Specific ethics approval to use gefitinib off label for this case (due to the fact she was a poor operative candidate with serum hCG rising rapidly, and that there was some evidence of its possible efficacy) was sought and granted from the Mercy Hospital for Women Human Research Ethics Board. We had written informed consent from the patient.

Ethics approval for this study was also subsequently obtained from the Mercy Health Human Research Ethics Committee for a retrospective case series study of non-tubal ectopic pregnancies (Approval number 2018-065). Given this was a retrospective study deemed to be of low risk, we were not required to obtain consent from women studied in this case series.

Case Report

A 35-year-old primigravida presented to a tertiary hospital emergency department after routine dating ultrasound showed a single live pregnancy of 6 weeks and 6 days gestation in a position suspicious for a proximal tubal ectopic pregnancy or intramural ectopic pregnancy. This pregnancy was the result of in vitro fertilization (IVF), with transfer of a day 5 donor embryo thirty days prior.

The patient had an extensive gynecological history of Stage IV deep infiltrating endometriosis, with bowel involvement, rectal nodules, adenomyosis, and recurrent endometriomas. She had had three laparoscopies. Initial operative findings included widespread peritoneal endometriosis to the level of the diaphragm, and “kissing ovaries” with bilateral endometriomas, and dilated and distorted Fallopian tubes. The procedure was abandoned after removal of the endometriomas to discuss further removal of bilateral severe hydrosalpinges, which were later removed. Subsequently, her first stimulated cycle of IVF was complicated by a large pelvic abscess post oocyte collection which required laparoscopic drainage. At the time of drainage, the abscess was widespread throughout the abdomen and pelvis, and neither the Pouch of Douglas nor ovaries were visible due to severity of intra-abdominal adhesions.

Upon presentation, the patient was haemodynamically stable and asymptomatic. On examination her abdomen was soft and non-tender, with no adnexal tenderness. Blood tests confirmed pregnancy, with a hCG of 11,603 IU/l, and a haemoglobin of 128×10^9 g/L.

Ultrasound revealed a heterogenous mass 26 x 24 x 21mm in the right interstitial region posterior to the uterus and distinct from the endometrial cavity. It contained a gestational sac

(mean sac diameter (MSD) 11mm, yolk sac 3.8mm), an embryo with crown-rump length (CRL) of 6.4mm (equivalent to 6 weeks and 2 days gestation) and cardiac activity at 137 beats per minute. These findings were consistent with a live interstitial ectopic pregnancy (Figure 1 - Identification and resolution of a live interstitial ectopic pregnancy. Panel A shows ultrasound image identifying of a cornual ectopic pregnancy separate from the endometrium with thin surrounding myometrium. Panel B shows evidence of the the resolving ectopic pregnancy mass with absence of vascularity.).

Additionally, evidence of deep infiltrating endometriosis was seen, with left pouch of Douglas obliteration, the right ovary adherent to the posterior uterus adjacent to the ectopic mass, and the left ovary adherent to the pouch of Douglas, left uterosacral ligament and bowel. Given these findings, the patient was admitted as an inpatient for further management.

Based on her most recent ultrasound and previous gynecological history, with no visibility or laparoscopic access to the pelvis, a surgical approach was deemed unfeasible due to significant risk to the patient. Additionally, ultrasound showed the ectopic pregnancy was not accessible transabdominally or transvaginally without risk to the bowel, thus preventing direct injection into trophoblastic tissue. Injection via a hysteroscopic approach was considered, however was deemed not possible due to the potential for significant bleeding and inability to perform emergency abdominal surgery if required.

Due to the potential significant risk of surgery for this patient and based on previous reports of successful treatment, a multidose methotrexate and gefitinib therapy was deemed the safest

option. The patient consented to treatment, provided with the results of previous trials and informed about the possible side effects related to gefitinib use including acne, skin rash, hair loss, diarrhoea and interstitial lung disease ⁷.

Outcome

Medical treatment commenced after confirmation of normal renal and liver function, and a normal full blood examination to exclude contraindications to therapy. Intramuscular methotrexate was administered based on the dosage of 1mg/kg (rounded to 75mg to the closest available formulation) every second day alternating with folinic acid at 7.5mg. On the first day of treatment, serum hCG was 14,385 IU/L (Figure 2 – Patient hCG across treatment. A denotes first day of gefitinib treatment (day 3), finishing on B (day 10). C denotes final day of methotrexate treatment (day 15)). Daily oral gefitinib (250mg) was commenced 2 days after the first dose of methotrexate for 7 days, with serum hCG 16,685 IU/L on this day.

The patient was observed closely for side effects, with ongoing serum hCG and ultrasound monitoring. Treatment was generally well tolerated, with mild lower abdominal pain and vaginal spotting on the second day of combined therapy (day 4) and diarrhoea on day 5. A facial acne rash developed on the final day of gefitinib treatment (day 9).

After a week of treatment, while the serum hCG had dropped from a peak of 19,510 to 15,970 IU/L (Figure 2), a repeat ultrasound found the trophoblastic mass had enlarged (31 x 26 x 26 mm), with a CRL of 9 mm and cardiac activity of 146 bpm. Despite this finding, the hCG continued to fall, and by day 15, an ultrasound confirmed embryonic demise, with a CRL of 11mm, no cardiac activity and a combined mass size of 33 x 29 x 31mm. At this point,

methotrexate was ceased, with the patient receiving a total of 8 doses of methotrexate and 7 doses of gefitinib. The patient was discharged for outpatient follow up.

Follow up

Six days later (day 20), serum hCG had fallen to 1,412 IU/L, an ultrasound demonstrated a similar sized trophoblastic mass (36 x 35 x 31mm) and a 7 mm embryonic pole and no sign of bleeding within the mass. The patient was asymptomatic. By day 42, serum hCG had dropped to 23IU/L, with a stable trophoblastic mass (35 x 32 x 28mm) and no associated haematoma or discrete embryonic pole.

At routine follow up, 1 month later, complete resolution was confirmed with a hCG of <0.6 IU/L, and a trophoblastic mass (19 x 16 x 17mm).

To provide comparison with methotrexate treatment alone, we conducted a retrospective review of non-tubal ectopic pregnancies treated with methotrexate from 2008 - 2018. As shown in Table 1, 46 cases were identified. These were a heterogenous group, with a relatively late median gestation at diagnosis (50 days), large median size at presentation (19 mm), and high pre-treatment hCG (7990 IU/L). Ten (22%) of these cases, had cardiac activity present, and of these, 8 (80%) received intrasac methotrexate, which our patient did not receive. For all 46 cases, the median time to resolution following initial treatment was 42 days. Subgroup analysis of cases with cardiac activity revealed a median time to resolution of 64 days (22 days longer than our patient), with a lower quartile of 47 days, despite intrasac methotrexate therapy. A total of 8 cases failed medical management and required surgery.

Discussion

We present a case of successful treatment with combination methotrexate and gefitinib in an of a live, interstitial ectopic pregnancy with an increasing hCG peaking at nearly 20,000 IU/L, in an inoperable candidate. Soon after treatment, fetal cardiac activity ceased and the resolution of the ectopic pregnancy appeared to be quite rapid. To provide a comparison for this case, we conducted a retrospective case series of all non-tubal ectopic pregnancies treated with methotrexate alone at the same tertiary centre over a 10-year period. This review highlights the advanced stage at presentation and lengthy time to resolution for these women.

The median pre-treatment hCG among the 46 identified cases was almost half that of our patient (14,385 IU/l vs 7990 IU/l), yet we were able to demonstrate a comparable time to resolution (both 42 days). Additionally, our patient posed a particular therapeutic challenge, presenting with an advanced ectopic pregnancy with cardiac activity. Within the case series, 80% of the non-tubal ectopic pregnancies with cardiac activity received intrasac methotrexate, which was not a feasible option for our patient. Subgroup analysis of cases with cardiac activity revealed a median time to resolution of 64 days (22 days longer than our patient), with a lower quartile of 47 days, despite intrasac methotrexate therapy. This provides further evidence for the use of combination gefitinib and methotrexate to treat complex ectopic pregnancies, particularly those that are poor surgical candidates.

Although there is no clear consensus on the management of non-tubal ectopic pregnancies, it has been suggested that for certain non-tubal ectopic pregnancies, such as interstitial

pregnancies, methotrexate (even a multidose protocol), is often not effective, and that surgery is commonly required, or even recommended ⁸. Furthermore, laparoscopic surgery is thought to be the gold standard for the management of interstitial pregnancies ⁹. Although medical management, including local administration of methotrexate into the trophoblastic tissue, is an option in select cases, it is not recommended for large interstitial pregnancies with fetal cardiac activity ⁹. A retrospective case series of 60 non-tubal ectopic pregnancies with a median hCG of 13,659 IU/l, revealed primary surgical management was required in over one third of patients and in almost 60% of interstitial cases, with one in five medically treated cases requiring salvage surgery ¹⁰. A more effective medical treatment is clearly needed for cases such as the one presented here, where surgical management would put the patient at high risk of significant morbidity.

To date, early human trials of combination gefitinib and methotrexate to treat non-tubal ectopic pregnancy have been promising (4, 5, 6). However, the pre-treatment and peak hCG of these interstitial ectopic cases were lower than our patient and only one had fetal cardiac activity. Thus, we have demonstrated successful treatment of a more advanced interstitial ectopic pregnancy than previously described in the literature with combination therapy.

Non-tubal ectopic pregnancies represent a significant clinical challenge, given they often present late, with high serum hCG. We have demonstrated successful resolution of a live, interstitial ectopic pregnancy with combination gefitinib and multidose methotrexate. Importantly, we have demonstrated a time to resolution that is at least equivalent to methotrexate alone. This suggests this treatment is a novel and potentially effective treatment

approach for complex ectopic pregnancies and could be considered in situations where the patient is a poor surgical candidate.

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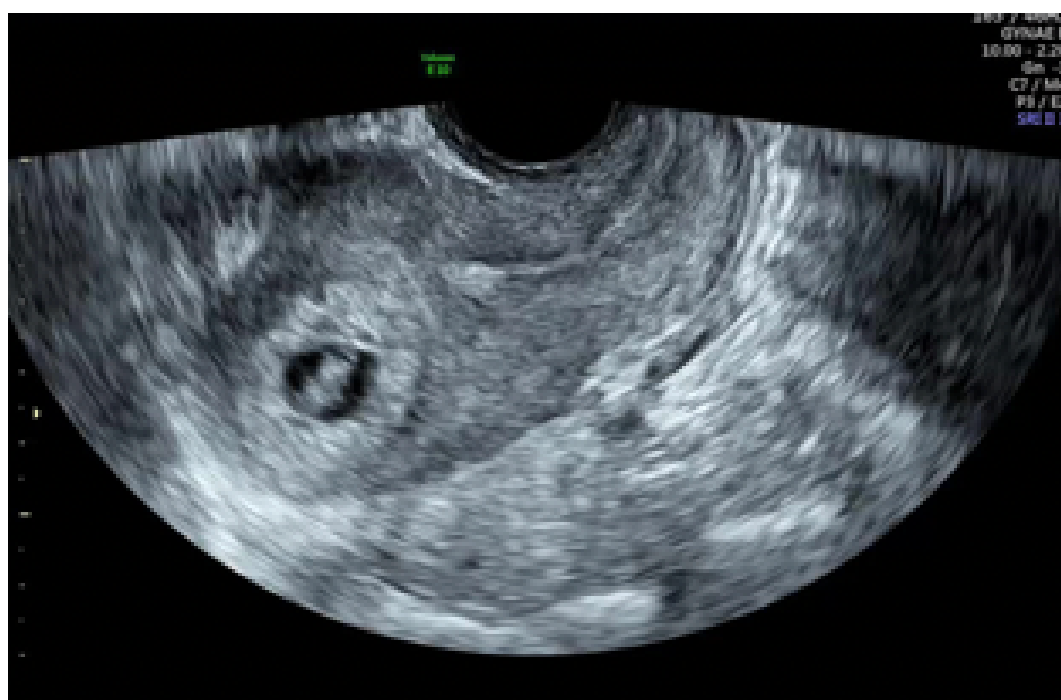
Figure Legends

Figure 1: Identification and resolution of a live interstitial ectopic pregnancy. Panel A shows an ultrasound image identifying a cornual ectopic pregnancy separate from the endometrium with thin surrounding myometrium. Panel B shows evidence of the resolving ectopic pregnancy mass with absence of vascularity.

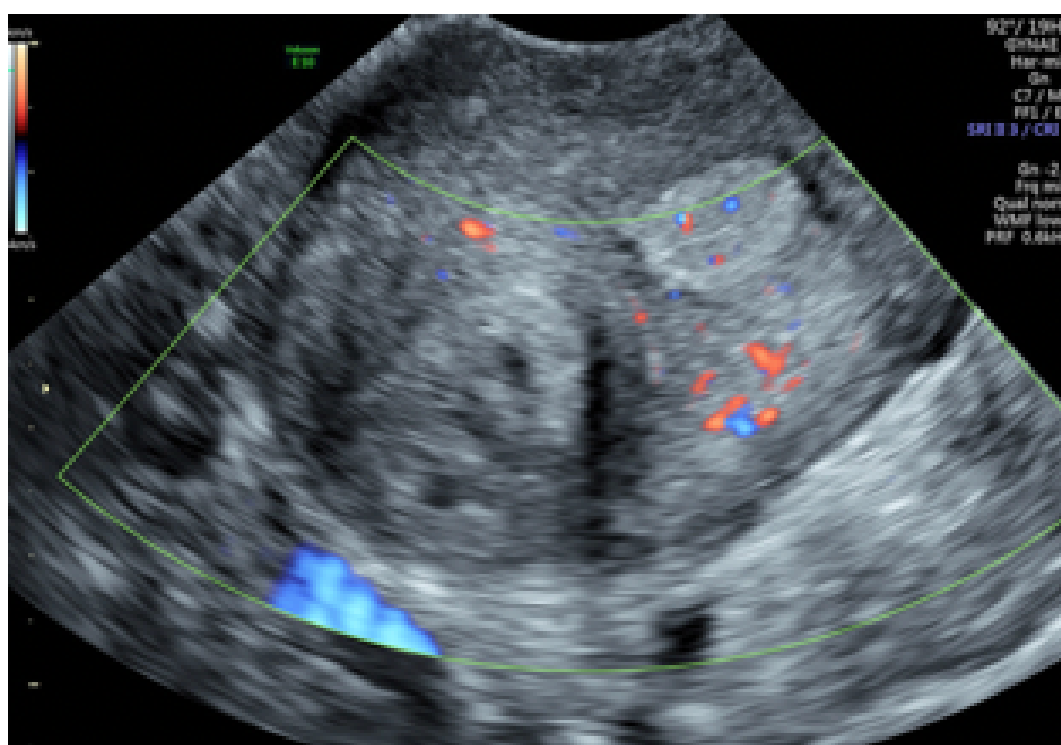
Figure 2: Patieng hCG across treatment. A denotes first day of gefitinib treatment (day 3), finishing on B (day 10). C denotes final day of methotrexate treatment (day 15).

Table 1: Characterstics of 46 extra-tubal pregnancies from 2008-2018 at a single tertiary centre.

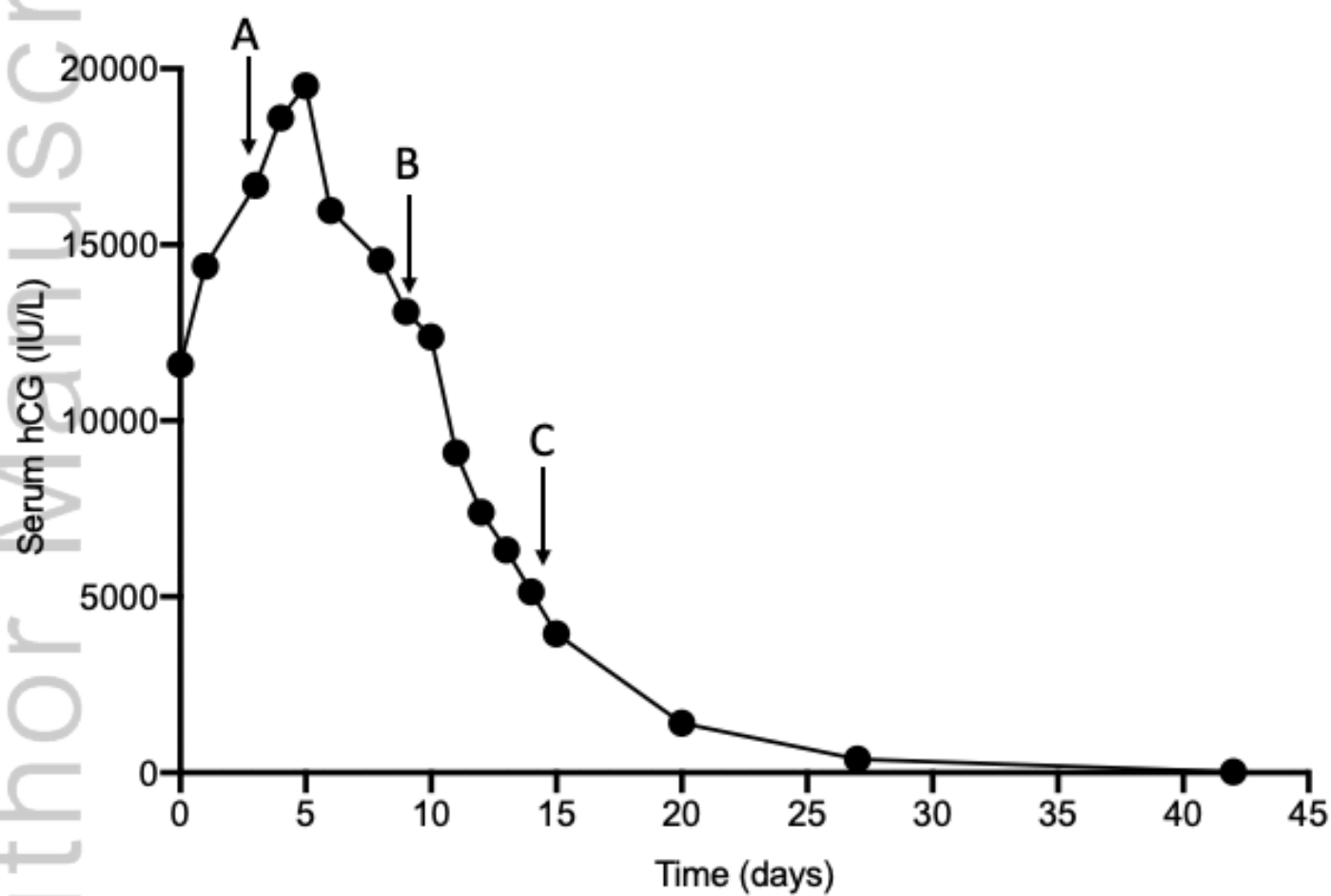
A



B



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Table1: Characteristics of 46 extra-tubal pregnancies from 2008-2018 at a single tertiary centre.

Characteristics	Outcome
Age (years) Median (IQR)	35.2 (32.1 – 38.5)
Body Mass Index (BMI) (kg/m ²) Median (IQR) *	25.9 (23.2 – 30.8)
Gravidity Median (IQR)	3 (2-3)
Parity 0 (%) 1 (%) ≥1 (%)	11 (24) 18 (39) 17 (37)
Previous ectopic (%)	3 (6.5)
Mode of conception Spontaneous (%) IVF (%) Ovulation induction (%)	39 (85) 5 (11) 2 (4)
Gestation at diagnosis (days) Median (IQR) †	50 (45 – 57)
Ultrasound size of mass diagnosis in maximum diameter (mm) Median (IQR)	19 (13 – 24)
Heartbeat (%) Intrasac methotrexate given (%)	10 (22) 8 (80)
Location Cornual (%) Adnexal (%) Scar (%) Cervical (%) Other (%)	12 (26) 8 (17) 17 (37) 5 (11) 4 (9)
Eventual surgery (%)	8 (17)
Starting βHCG D1 of treatment Median (IQR) ‡	7990 (1546 – 9994)
Time to resolution (days) Median (IQR) ‡ If fetal heart present	42 (34 – 55) 64 (47 – 87)

*BMI data missing for 5 women. †Exact gestation at diagnosis missing from 2 women. ‡ Out of those women with data available for a final βHCG of 25 or less.