

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

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Background

- Ectopic pregnancies affect 1-2% of all pregnancies and are a leading cause of maternal death.
- Rarely, ectopic pregnancies implant in non-tubal locations such as the cornua, and typically have poor response to traditional medical management with methotrexate.
- Gefitinib is a tyrosine kinase inhibitor that acts on the epidermal growth factor receptor (EGFR) pathway, is most abundantly expressed in placental tissue, and is crucial for placental development and growth.
- Combination gefitinib and methotrexate has been suggested as a potential treatment for ectopic pregnancy.

Methods

- Retrospective review of all non-tubal ectopic pregnancies treated at Mercy Hospital for Women over a ten year period (2008-2018)
- Data was then compared to a case of extra tubal ectopic pregnancy treated with combination methotrexate and gefitinib.

Case Study

- 35yo primip with single live pregnancy of 6 weeks and 2 days gestation in the right interstitial region with fetal cardiac activity, consistent with cornual ectopic pregnancy. (Figure 1)
- Surgical approach was deemed unfeasible and high risk. Therefore medical therapy with a multidose methotrexate and gefitinib was deemed the safest option
- Inpatient treatment with 75mg Methotrexate alternating days and Gefitinib 250ng daily for 7 days commenced with a starting bHCG of 14,385 IU/L and peak rise to 19,510 IU/L.
- On Day 15 post treatment ultrasound confirmed fetal demise, and by day 20 bHCG had dropped to 1,412 IU/L. Complete resolution was seen by day 42. (Figure 2)

Results

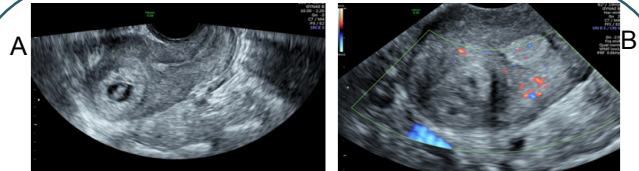


Figure 1. A shows ultrasound image identifying a cornual ectopic pregnancy separate from the endometrium with thin surrounding myometrium. B shows evidence of the resolving ectopic pregnancy mass with absence of vascularity.

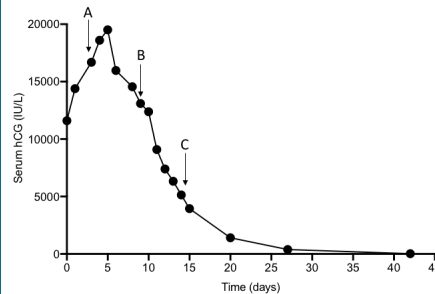


Figure 2. Patient hCG across treatment. A denotes first day of gefitinib treatment (day 3), finishing on B (day 10). C denotes final day of methotrexate treatment (day 15).

Table 1: 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)
Parity	
0 (%)	11 (24)
1 (%)	18 (39)
>=1 (%)	17 (37)
Previous ectopic (%)	3 (6.5)
Gestation at diagnosis (days) Median (IQR) †	50 (45 – 57)
Ultrasound size of mass diagnosis in maximum diameter (mm) Median (IQR)	19 (13 – 24)
Heartbeat (%)	10 (22)
Intrasac methotrexate given (%)	8 (80)
Location	
Cornual (%)	12 (26)
Adnexal (%)	8 (17)
Scar (%)	17 (37)
Cervical (%)	5 (11)
Other (%)	4 (9)
Eventual surgery (%)	8 (17)
Starting bHCG D1 of treatment Median (IQR) ‡	7990 IU/L (1546 – 9994 IU/L)
Time to resolution (days) Median (IQR) ‡	42 (34 – 55)
If fetal heart present	64 (47 – 87)

† Exact gestation at diagnosis missing from 2 women.

‡ Out of those women with data available for a final bHCG of 25 or less.

IQR – Interquartile range

- 46 cases identified
- Median pre-treatment hCG 7990 IU/l.
- **Subgroup analysis of cases with cardiac activity:** median time to resolution of 64 days (22 days longer than our patient).

Conclusion

We have demonstrated successful resolution of a live, interstitial ectopic pregnancy with combination gefitinib and methotrexate. With a time to resolution that is at least equivalent to methotrexate alone.