GnRH Analogs for Preservation of Fertility: A novel use or are we being thrown for a "Leup"

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Case

- 18 year old female presents to hospital ED from doctors office
- Over the previous 3 weeks patient had progressing weakness in her arms and legs and myalgias
- Transient fevers and poor appetite
- Peripheral edema and possible rashes
- SOB on exertion and transient chest pain
- 1 episode of hemoptysis 3 days ago
- Recent blood work had shown pancytopenia

Past medical History

- No significant past medical history
- No known drug allergies
- Family history unremarkable
- Recent travel to Hong Kong for 2 weeks about 2 months prior to presentation
- Non smoker
- No EtOH

Lab Investigations in ED

- Hemoglobin - 95 (Dropped to 77)
- WBC – 1.5
- Neutrophils – 1.2
- Platelets – 101
- Urea – 21
- Serum Creatinine – 106
- AST – 1284
- ALT – 503
- LDH – 1220

Course in Hospital

- Pancreatitis
- Abdominal Compartment Syndrome
  - OR and left with open abdomen
- Septic Shock
- Intubated
- Pulseless arrest post-intubation
  - CPR
- Staph aureus Pneumonia
- Aspergillus on tracheal aspirate
- Abdomen closed and extubated
  - Transferred to ward

Lupus Nephritis

- Manifestation of Systemic Lupus erythematous
  - Up to 60% of SLE patients have kidney complications
- Hypertension, swelling, foamy urine (hematuria and proteinuria)
- 10-30% of patients will develop renal failure and require dialysis or transplant

Treatment Options

- Steroids
  - High doses (prednisone 0.5-1mg/kg/day) for induction
- Immunosuppressants
  - Cyclophosphamide
  - Mycophenolate
  - Azathioprine
  - Biologics
  - Calcineurin Inhibitors

Back to case

- Rheumatology Consult:
  - "For a patient this sick, the first option I would go to is cyclophosphamide. I'm not convinced other agents are as effective for acute treatment of lupus nephritis"

Cyclophosphamide

- Most recent data suggests that efficacy is similar to MMF
- More long term data is available for CYC
- Toxicity
  - Premature Ovarian Failure (POF)

Risk Factors for POF

- Age at initiation of cytotoxic therapy
  - Occurrence of POF ranges from 20-60% in patients under 40y versus 60-80% in women over 40y
  - Around 15% for patients < 18y
- Cumulative dose of therapy
  - Also age dependent
  - 5gm in women >40y
  - 9gm in women 30y-40y
  - 20gm in women 20y-30y

Clinical Question

Population	Women of childbearing age with lupus nephritis
Intervention	GnRH analogues + Cytotoxic chemotherapy (specifically cyclophosphamide)
Comparator	Cytotoxic therapy without GnRH analogues
Outcomes	Premature Ovarian failure (return of regular menses) Pregnancies

Search Strategy

Databases	Medline, Embase, Cochrane, Google Scholar, IPA
Search Terms	Lupus, lupus nephritis, rheumatic disease, cyclophosphamide, cytotoxic, gnrh, leuprolide, fertility, preservation, premature ovarian failure
Limits	Human studies, controlled trials
Results	2 open-label prospective cohort studies 1 Retrospective Chart Review

Options for Fertility Preservation

- Cryopreservation of eggs or tissue
- Embryo cryopreservation following in vitro fertilization
- Ovarian suppression
  - GnRH

Proposed Mechanisms

- Lower hormone levels and prevent ovarian follicle maturation thus decreasing the number of follicles present for damage from CYC
- Decrease in ovarian blood flow
- Up regulation of anti-apoptotic molecules
- Direct GnRH receptor activation may decrease cellular apoptosis

Preservation of fertility and ovarian function and minimizing gonadotoxcity in young women with systemic lupus erythematous treated by chemotherapy

Blumenfeld Z, et al. Lupus.2000;9:401-405

Design

- 8 consenting women receiving alkylating chemotherapy agents
- Given monthly IM depot injections of GnRH (Decapeptyl (triptolrelin)) 3.75mg in parallel to chemotherapy for up to 6 months
- Compared to 9 nine women receiving similar chemotherapy, but without GnRH therapy (retrospective look at controls)

Outcomes

- Premature Ovarian Failure
  - Amenorrhea, estradiol concentrations <100pmol/L, and high gonadotropin levels

Results

	GnRH (mean)	No GnRH (mean)
Age	20-30 (26.3)	20-43 (27.4)
Cumulative Dose	6g – 11g *	4g – 26.5g
POF	0/6	5/9
Follow up Period	2-15 years	4-15 years

•2 patients were still being treated with GnRH and chemotherapy at the end of the study period and not included in the data
•Cumulative dose unknown in 2 patients in GnRH group

Limitations

- Extremely small sample size
- Non-randomized, non-blinded study
- Differences between the groups in both age and cumulative doses
- Unmatched comparisons
- Definition of POF versus true fertility
- No reporting of safety data
- Long term effects?

Conclusions

- Chance can be an explanation of why none of the treated women experienced POF
- There is no data on whether these women were able to become pregnant down the road
- Differing cumulative doses and ages, which are known risk factors for POF
- Hypothesis generating, more studies are required to quantify the true effect of this medication

Use of a Gonadotropin-Releasing Hormone Analog for Protection Against Premature Ovarian Failure During Cyclophosphamide Therapy in Women with Severe Lupus

Somers EC, et al. Arthritis and Rheumatism. 2005:52(9)

Design

- A GnRH protocol nested in a larger Michigan Lupus Cohort with ongoing data collection since 1985
- Consecutive women receiving monthly therapy of cyclophosphamide (CYC) for severe manifestations of lupus (nephritis, cerebritis, or vasculitis)
- GnRH (leuprolide 3.75mg IM monthly) was offered to women undergoing CYC therapy
- GnRH therapy started 10 days prior to initiation of CYC therapy

Population and controls

- Women had to be 35y old or younger at start of CYC therapy
- Had to be scheduled to receive at least 6 months of CYC therapy
- Had to have no signs of ovarian failure prior to study
- Controls were selected from the Michigan Lupus Cohort and met above eligibility criteria, but did not receive GnRH (retrospective)
- Patients were matched with controls who were within 5 years of age and 5grams of cumulative dose using a random sampling procedure

Outcomes

- Ovarian function
  - Presence of menses and/or conception following completion of CYC therapy
  - FSH levels were measured in women with amenorrhea or oligomenorrhea
  - POF was confirmed by amenorrhea for at least 12 months and an FSH level of >40mIU/mL

Results

- A total of 40 women met inclusion criteria (20 treated and 20 controls)
- Mean age was 24 in the treated group and 25 in the control group
- Same mean cumulative dose 12.9g in both groups
- 80% of patients in both groups were diagnosed with nephritis
- 1/20 patients developed POF in the GnRH group compared to 6/20 (OR 0.09, P<0.05)

Limitations

- Unblinded
- Non-randomized
- Controls matched on only 2 variables
- Very small numbers
- Safety/Mortality

Gonadotropin Releasing Hormone Agonists May Minimize Cyclophosphamide Associated Gonadotoxicity in SLE and Autoimmune Diseases

Blumenfeld Z, et al. Semin Arthritis Rheum. 2011;41:346-52

Design

- 44 women treated with CYC for severe connective tissue disease at 2 centres in Israel
- Retrospective chart review
- Decapeptyl 3.75mg IM injection once monthly

Population

- 33/44 women treated with CYC for lupus also received monthly GnRH
- Severe lupus with either nephritis, cerebritis, or vasculitis
- Treatment with CYC for at least 6 months

Outcomes

- Ovarian function evaluated 1-10 years after the end of treatment by existence of spontaneous monthly bleeding, hormone profile (FSH, LH, progesterone), ultrasound of ovaries, and conceptions

Results

- Age ranged from 16-39
- Mean age in GnRH group was 25.6 and 29.4 in the untreated group
- POF in 1/33 patients GnRH treated patients and 5/11 untreated patients

Results

- Second analysis included only patients up to 31y
- Rate of POF remained 40% ($p<0.05$) higher in the untreated group
- Only patients who received up 15g dose – POF was 4% in the treated group and 37.5% in the untreated group ($p<0.05$)
- 8 pregnancies and 7 deliveries in treatment group vs. 3 pregnancies in the control group

Limitations

- Small sample size
- Unblinded, non-randomized
- Retrospective chart review
- Non-standardized treatment regimen

Other Data

- 3 large RCTs in breast cancer all found statistically significant reductions in POF with GnRH treated patients versus untreated
- 4 meta-analyses assessing benefit of GnRH use along with chemotherapy have all demonstrated statistically significant reductions in POF (various disease states and cytotoxic therapies)

Safety Data

- GnRH can induce menopausal symptoms
  - Bone loss, hot flashes, etc
- Potential to reduce efficacy of chemotherapy?
  - Numerous cancer cells express GnRH receptors
- Impact on fetal health
  - In one study where 11/24 patients were attempting pregnancy only 2 delivered healthy children
  - 3 spontaneous abortions and 1 Down syndrome fetus

Conclusion

- There is a lack of well designed randomized controlled trials
- Promising data from uncontrolled prospective and retrospective data in SLE as well as a number of cancers
- Pregnancy versus surrogate outcomes
- There are legitimate safety concerns

My Interpretation

- The risk of POF is highly dependent on patient age and cumulative dose of cytotoxic therapy
- Hard outcome (healthy births) data is lacking with the use GnRH agonists
- Patient age and expected or actual cumulative doses of cytotoxic therapy greatly impact POF outcomes
- Costs and safety concerns can be inhibitory
- If cytotoxic therapy is indicated I would consider offering GnRH therapy