DONG-A UNIVERSITY HOSPITAL

# Case Report

A 60-year-old woman receiving palliative chemotherapy for unresectable colorectal cancer

[1]Jong Yoon Lee

**Affiliations:**
[1]Divsion of Gastroenterology, Department of Internal Medicine, Dong-A University College of Medicine, Busan 49201, South Korea

# CASE (60 / F)

- **Chief Complaint**
  - Admit for Chemotherapy, 22nd cycle of Cetuximab-FOLFOX

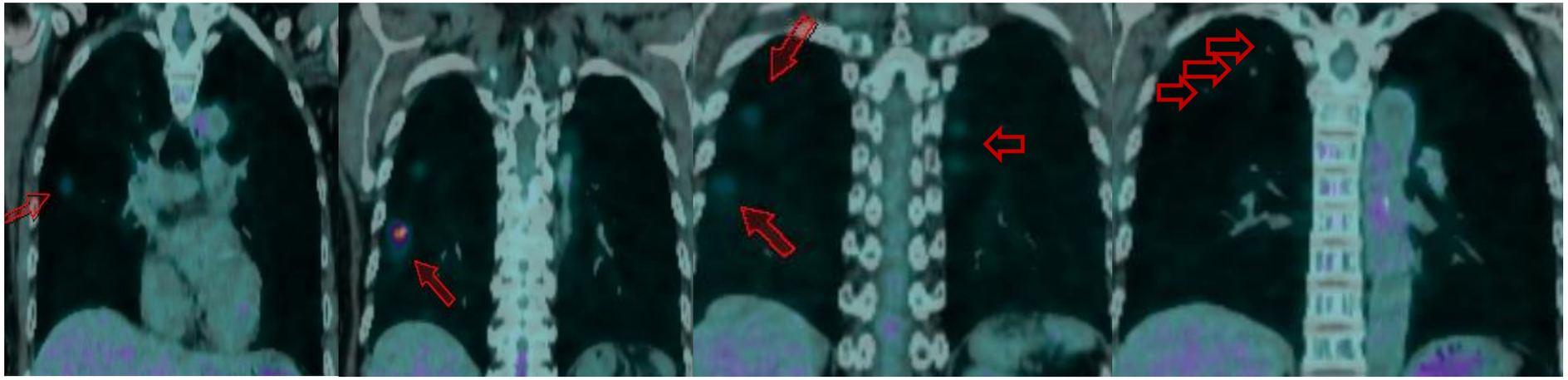
- **Past History**

  2001 Pituitary Gland Tumor, Trans-sphenoid approach resection

# Present illness

- 2020.04.7. Rectosigmoid colon cancer s/p Lapa LAR, pT3N1bM0(IIIB)
- 2020.05.13~10.15 mFOLFOX-6 CTx 11 cycle 후 종료 (d/t Poor General Condition)
- 2021.10.29 PET CT : Multiple lung mets

  * EGFR+/KRAS(wild)/NRAS(wild)/BRAF(wild)/MMR-Proficiency



# Present illness

- 2022.01.03. 4th cycle Cetuximab-FOLFOX
  - Febrile sensation, Whole body itching 발생 → 입원하여 Vital Monitor.
  - 약물과의 관련성 명확하지 않고 비특이적인 반응에 의한 과민반응으로 판단 → 3주 뒤 4차 Chemo 시행하기로 하고 퇴원.
- 2022.01.21.
  - 4th cylcle Cetuximab-FOLFOX CTx. Tolerable.
- 2022.02.11.~10.12.
  - 5~18차 Cetuximab-FOLFOX CTx done & Side Effect (-)
  - F/U CT: Stable Disease.

# 19th cylce of Cetuximab-FOLFOX

- 2022.11.02
  - 19th cycle Cetuximab-FOLFOX
  - Cetuximab 투약 종료 후 Oxaliplatin과 Leucovorin을 투여하기 시작하고 30분 내 Dyspnea, Whole body swelling, Redness 발생.
  - Vital Sign : 90/50 mmHg, HR 101 beats/min, ABGA상 pO2 62 ▼
  - Tryptase 11.4 ▲

# Assessment & Plan

**Oxaliplatin에 의한 Immediate type hypersensitivity reactions**

-> Oxaliplatin Desensitization

# Rechallenge: 19th cycle of Cetuximab-FOLFOX

- 2022.11.14 19th cycle of Cetuximab-FOLFOX 진행 위해 입원

- 2022.11.15 Oxaliplatin Desensitization
  - Oxaliplatin 투여 종료 후 Vital Stable하여 바로 이어 Leucovorin start
  - Leucovorin 투여 30분 후 Facial Redness, Dyspnea 발생.
  - BP 96/60 mmHg, HR 103 beats/min, SpO2 89% → 항암 중단 chlorepheniramine, Epinephrine 투여
  - 이후 Vital stable, Condition tolerable 확인 후 퇴원.

# Progress Note – 20th cycle of Cetuximab-FOLFOX

- 2022.12.19 20th cycle of Cetuximab-FOLFOX 진행 위해 재입원

- 2022.12.21
  - Oxaplatin 탈감작 → Leucovorin 투여 시작.
  - Leucovorin 투여 5분 내 Dyspnea 및 Urticaria 발생
  - BP 100/64 mmHg, HR 90beats/min, SpO2 90% Epinephrine 0.3A 투여
  - 이후 증상 호전 및 Vital stable하여 퇴원.

# Progress Note – 21st cycle of Cetuximab-FOLFOX

- 2023.02.07

  21차 Cetuximab-FOLFOX CTx

  Oxaliplatin 탈감작 진행 및 Leucovorin과 Oxaliplatin 순차적으로 진행

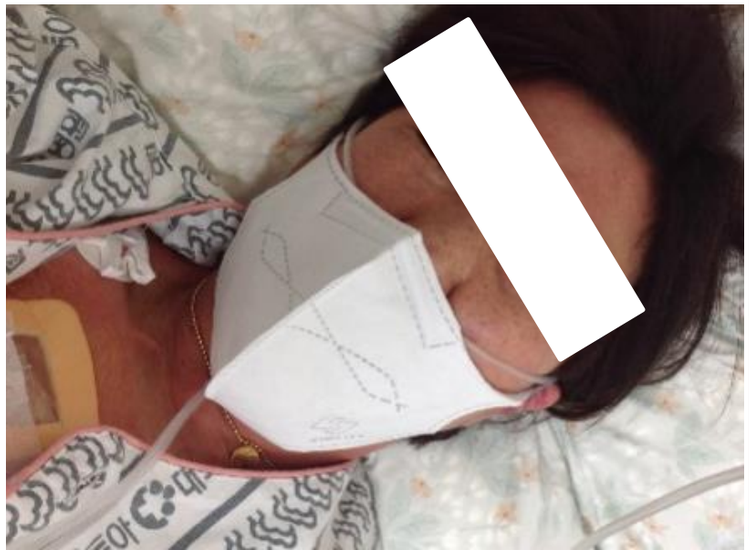
- 2023.02.08

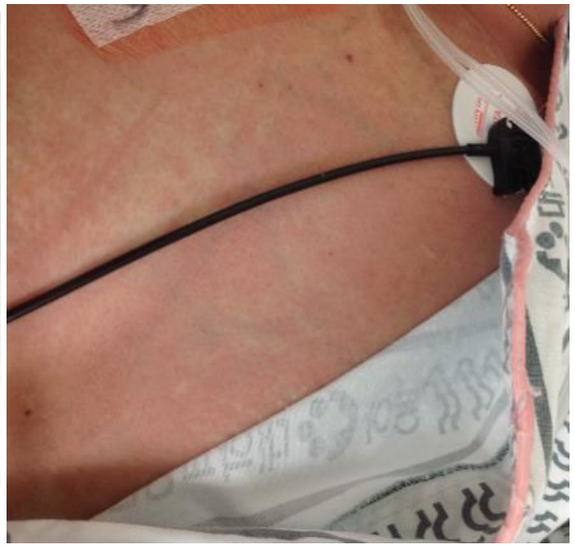
  Cetuximab → Leucovorin → Oxaliplatin 탈감작 → 5-FU 순서로 진행

  Leucovorin 투여 20분 후 Face redness 있었으나 겁이 나서 항암 못받겠다고 했으나 설득 후 Oxaliplatin 탈감작

# 22nd cycle of Cetuximab-FOLFOX

- 2023.02.28
  - Cetuximab 투약 종료 후 이어 Leucovorin 투여시작 30분 후
    몸통부위 발적, SpO2 90% 확인 → 이후 증상 호전 및 Vital stable.
- 2023.03.01
  - V/S 안정 후 퇴원함





# Summary of Hypersensitivity Events after Cetuximab-FOFOLX CTx

| Cycle | Causative Drugs? | CTx & Symptom | Vital Sign |
|---|---|---|---|
| 1~3cycle | - | N-S | Stable |
| 4cycle | Uncertain | Feverile Sensation, Whole body itching | BP 90/50, HR 101, SpO2 98% |
| 5~18cycle | - | N-S | Stable |
| 19cycle(fail) | 30min after Oxaliplatin & *LV infusion | Whole body swelling, Redness → Stopped Chemotherapy | BP 90/50, HR 101, pO2 62 |
| 19cycle (rechallenge) | 30min after Oxaliplatin & *LV infusion | Dyspnea, Whole body swelling, Redness | BP 96/60, HR 103, SpO2 89% |
| 20cycle | 5min after LV infusion (OX desensitization) | Dyspnea, Urticaria | BP 100/64, HR 90, SpO2 90% |
| 21cycle | 20min after LV infusion (LV 먼저 주입 후 OX desensitization) | Facial Redness | Stable |
| 22cycle (fail) | 30min after LV infusion | Upper Chest Redness | BP stable, SpO2 90% |

*LV : Leucovorin **OX : Oxaliplatin

# New Impression & Plan

1. **Leucovorin-induced Hypersensitivity, Most likely**
   - 다음 차수 때 Leucovorin Pre-med 후 탈감작 주입하여 항암 진행.
   - 항암 진행 시 Vital Sign close monitoring.

2. **Oxaliplatin-induced Hypersensitivity, Less likely**

   → 다음 항암 시 Oxaliplatin 탈감작 재시행 후 retry.

   --탈감작하여도 Anaphylactic event 발생 할 수 있어

   Close monitoring.

# Rechallenge 22nd cycle of Cetuximab-FOLFOX

- 2023.03.30
  - Leucovorin 5.2mg + 5% DW 500ml mix
  - Leucovorin 52mg + 5% DW 500ml mix
  - Leucovorin 520mg + 5% DW 500ml mix

| | |
|---|---|
| 1. Premedication | Dexamethasone 5mg IV, Chlorpheniramine 5mg IV |
| 2. Chemotherapeutic agent dilution | A. Leucovorin 5.2mg/5% DW 500ml (1:100 dilution)<br>B. Leucovorin 52mg/5% DW 500ml (1:10 dilution)<br>C. Leucovorin 520mg/5% DW 500ml (target dose) |
| 3. Infusion rate | A. 2 ml/hr → 5 ml/hr → 10 ml/hr → 20 ml/hr<br>B. 5 ml/hr → 10 ml/hr → 20 ml/hr → 40 ml/hr<br>C. 10 ml/hr → 20 ml/hr → 40 ml/hr → 75 ml/hr<br>Infusion rate is increased in 15 minute intervals. |
| 4. When an adverse reaction occurs | Discontinue leucovorin administration, apply fluids, steroids, epinephrine depends on the severity of the symptoms. |

# 23rd cycle of Cetuximab-FOLFOX

- 2023.05.02
  - Plan) Exclude leucovorin, Oxaliplatin desensitization 유지
    (Oxaliplatin cannot be ruled out)
  - Regimen) Premedication → Cetuximab → Oxaliplatin desensitization

# 24th cycle of Cetuximab-FOLFOX

- 2023.05.16
  - Plan) Oxaliplatin desensitization 없이 cetuximab-oxaliplatin
  - Regimen) Premedication → Cetuximab → Oxaliplatin

# Final Diagnosis

- Leucovorin-induced Hypersensitive Reactions

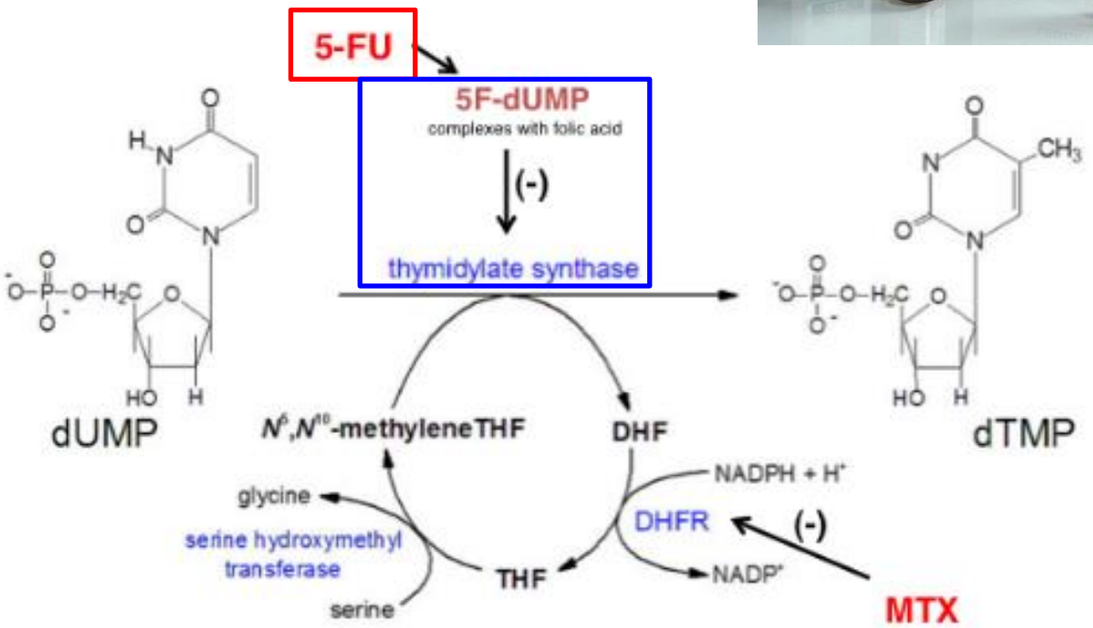
# DISEASE REVIEW

## Leucovorin-induced Hypersensivity Reactions (HRS)

# Leucovorin

- Leucovorin is a reduced form of folic acid & it prolongs the survival in patients when used in combination with 5-FU in colon cancer.


- Mechanism : inhibits folate metabolism
  - Folic acid analog
  - Inhibits dihydrofolate reductase
  - ↓dTMP → ↓DNA and ↓protein synthesis




Hiroshi Tsukihara et al, Folic Acid-MetabolizingEnzymes Regulate the Antitumor Effect of 5-Fluoro-20 Deoxyuridine in Colorectal Cancer Cell Lines, . PLoS ONE 11(9): e0163961

# Leucovorin-induced HSRs

- The pathophysiology and mechanism of HSR remain unclear, but the main mechanism of immediate type HSRs due to oxaliplatin is thought to be IgE-mediated type I hypersensitivity.

- HSRs to leucovorin are considered rare.

Hiroshi Tsukihara et al, Folic Acid-MetabolizingEnzymes Regulate the Antitumor Effect of 5-Fluoro-20 Deoxyuridine in Colorectal Cancer Cell Lines, . PLoS ONE 11(9): e0163961

# Introduction

- There have been very few cases of leucovorin HSRs reported

- Allergic reactions when administered along w/ 5-FU
  - Dermatologic: alopecia, dermatitis
  - Gastrointestinal: nausea, diarrhea, vomiting
  - Central nervous system: fatigue, malaise

Vishwajit S. Hegde, Shivaraj Nagalli, Leucovorin, StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.

# Case of Leucovorin-induced HSRs

- 53-year-old Male, Unresectable Colon Cancer
- Drug allergies (-)
- Present illness
  - **Lung metastasis, K-ras mutant: Bevacizumab + FOLFOX**

Avni Damaske et al, Leucovorin-induced hypersensitivity reaction, Journal of Oncology Pharmacy PracticeVolume 18, Issue 1, March 2012, Pages 136-139

# Case of Leucovorin-induced HSRs

| Cycle | Onset | Duration | Blood pressure (mm/Hg) | Other reactions |
|---|---|---|---|---|
| Cycle 13 | 10 min | 30 min | 142/73 | Flushing, pruritis, wheals. |
| Cycle 15 | 15 min | 5 to 10 min | 159/88 | Hives to upper chest, forehead and scalp, tingling. |
| Cycle 18 | 65 min | Less than 24 h | 167/102, 196/115, 174/104 | Headache, facial flushing, generalized pain all over. |
| Cycle 19 | 20 min | Less than 24 h | 150/93 | Pruritis, tightness in abdomen, chest, hot and diaphoretic. Back pain, generalized discomfort, and headache. |
| Cycle 20 | 15 min | Less than 24 h | 227/104, 220/120, 230/110 | Facial flushing, headache, generalized pain, severe lower back spasms and pain, diaphoretic. |

CTx was stopped

Avni Damaske et al, Leucovorin-induced hypersensitivity reaction, Journal of Oncology Pharmacy PracticeVolume 18, Issue 1, March 2012, Pages 136-139

# Case of Leucovorin-induced HSRs

- Assessment Oxaliplatin-induced HSRs
- Plan 1. Oxaliplatin dose reduction
  2. Skip Bevacizumab at 19th cycle
- 19th cycle Leucovorin, Oxaliplatin admin → Sx onset 7min later

| Cycle | Onset | Duration | Blood pressure (mm/Hg) | Other reactions |
|---|---|---|---|---|
| Cycle 13 | 10 min | 30 min | 142/73 | Flushing, pruritis, wheals. |
| Cycle 15 | 15 min | 5 to 10 min | 159/88 | Hives to upper chest, forehead and scalp, tingling. |
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Avni Damaske et al, Leucovorin-induced hypersensitivity reaction, Journal of Oncology Pharmacy PracticeVolume 18, Issue 1, March 2012, Pages 136-139

# Case of Leucovorin-induced HSRs

- Plan (2) Skip Oxaliplatin, Continue other medications

  Pre-med (Dexamethasone, Palonosetron, Ranitidine, Diphenhydramine)

- 20th cycle Bevacizumab(No S/E)

  → S/E occurred after leucovorin infusion, 15minutes

| Cycle | Onset | Duration | Blood pressure (mm/Hg) | Other reactions |
|---|---|---|---|---|
| Cycle 13 | 10 min | 30 min | 142/73 | Flushing, pruritis, wheals. |
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# Case of Leucovorin-induced HSRs

- New Impression Leucovorin-induced HSRs
- Plan Bevacizumab-oxaliplatin regimen
- Progress Note
  - Admission & Oxaliplatin Monotherapy 230mg was given
  - Pre-med : Dexamethasone, Ondansetron, Diphenhydramine, Famotidin
  - Erythematous spots on the face and chest, Slight pruritis on the scalp
  - But no severe headaches, body aches, or elevated blood pressures.
- F/U : 4 cycles of Bevacizumab and Oxaliplatin w/o Complications

Avni Damaske et al, Leucovorin-induced hypersensitivity reaction, Journal of Oncology Pharmacy PracticeVolume 18, Issue 1, March 2012, Pages 136-139

# Discussion

- So What drug caused this hypersensitivity reaction ??
  1. In each cycle, generic leucovorin was dispensed.
  2. The patient developed a sensitization reaction to leucovorin
     since he did not react to the first round of FOLFOX
  3. Adverse events that the patient experienced from the last five cycles of therapy(which included leucovorin)
     vs. Minimal complications when oxaliplatin was administered

  **-> Probably Leucovorin**

Avni Damaske et al, Leucovorin-induced hypersensitivity reaction, Journal of Oncology Pharmacy PracticeVolume 18, Issue 1, March 2012, Pages 136-139

# Conclusion

- Since the incidence of oxaliplatin-induced HSR is higher than that of leucovorin, it is difficult to suspect that leucovorin is the causative agent.
- Reactions to leucovorin are rare but possible, and physicians should be aware of these possibilities.

Avni Damaske et al, Leucovorin-induced hypersensitivity reaction, Journal of Oncology Pharmacy PracticeVolume 18, Issue 1, March 2012, Pages 136-139

# Reference


1. Nusrat Bano1*, Rahila Najam2, Faaiza Qazi3, Ahmed Mateen4 , Clinical Features of Oxaliplatin Induced Hypersensitivity Reactions and Therapeutic Approaches, Asian Pac J Cancer Prev, 17 (4), 1637-1641
2. Francesca Barbin, Michele Ghidini , Alessandra Panichi, Gianluca Tomasello, Claudia Bareggi, Barbara Galassi, Nerina Denaro , Fiorella Ruatta, Carolina Cauchi, Maria Grazia Rossino and Ornella Garrone, Oxaliplatin-Related Hypersensitivity Reactions: A Single Institution Series and Literature Review, Biomedicines 2022, 10, 3275
3. Bhavana Devanabanda; Anup Kasi, Oxaliplatin, StatPearls
4. Qiuyan Song1*, Yuanxuan Cai2*, Kangyuan Guo3, Min Li4, Zaoqin Yu4, Qirui Tai1, Yuhang Zhao2, Xuan Zhu5, Chengliang Zhang, Risk factors for oxaliplatin-induced hypersensitivity reaction in patients with colorectal cancer, Am J Transl Res 2022;14(4):2461-2468
5. Avni Damaske1, Nichole Ma2, and Reba Williams, Leucovorin-induced hypersensitivity reaction, Journal of Oncology Pharmacy PracticeVolume 18, Issue 1, March 2012, Pages 136-139
6. Hiroshi Tsukihara*, Kenta Tsunekuni, Teiji Takechi, Folic Acid-MetabolizingEnzymes Regulate the Antitumor Effect of 5-Fluoro-20 Deoxyuridine in Colorectal Cancer Cell Lines, . PLoS ONE 11(9): e0163961
7. Vishwajit S. Hegde, Shivaraj Nagalli, Leucovorin, StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.
8. Mishima H, Ikenaga M, Tsujinaka T, Yasui M, Kashiwazaki M, Miyazaki M, Hirao M, Fujitani K, Nakamori S. [FOLFOX]. Gan To Kagaku Ryoho. 2006 Jul;33(7):911-4. [PubMed]
9. Min LI1, Chen JIANG1, Jing-wen YANG1, Zao-qin YU1, Wei LI1, Li ZHAO2, Qiu-yan SONG3, Cheng-liang ZHANG1#, Dong LI U1# Clinical Features of Oxaliplatin-induced Hypersensitivity Reactions in Chinese Patients: A Retrospective Multicenter Analysis*, Current Medical Science, 41(4):827-831,2021.
10. S. Powell*1 , S. Woelich2 , C. Caruthers3 , M. Dykewicz2 , 1. Creve Coeur, MO; 2. St. Louis, MO; 3. Portland,, SUCCESSFUL IV DESENSITIZATION TO RACEMIC LEUCOVORIN, AN UNDERAPPRECIATED CAUSE OF HYPERSENSITIVITY REACTIONS FROM CANCER CHEMOTHERAPY,
11. Oncologist 2004; 9:546-549, Clin Trans Oncol. 2013 Mar;15(3):219-25, Clin Colorectal cancer 2009, Mar;8(2):106-109, Anticancer drugs 2004 Jul;15(6):605-7


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