# Acute Pancreatitis from Treatment with BRAF-inhibitors in patients with Erdheim-Chester Disease

Gordon Ruan, MD, Gaurav Goyal, MD, Mithun Shah, MD/PhD, Ronald Go, MD

6th Annual International ECD Medical Symposium
Ruan.gordon@mayo.edu

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# Background – BRAF-inhibitors

- Vemurafenib and Dabrafenib
  - Selectively inhibits mutated B-raf protein kinase with the V600E mutation
  - Prevents tumor cell growth

- 50-60% of patients with Erdheim-Chester Disease (ECD) harbor the *BRAF-V600E* mutation

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# Background – BRAF-inhibitors

- Vemurafenib
  - FDA approval in 2017 to treat ECD with *BRAF-V600E* mutation[1]
- Dabrafenib
  - Case reports of dabrafenib successfully treating *BRAF-V600E* ECD[2]
  - No FDA approval

1. Diamond et al: JAMA Onc 4(3): 384, 2018
2. Bhatia et al: Haematologica 103(4): e177, 2018

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# Background – BRAF-inhibitor Adverse Effects

- Adverse effects (AE) of BRAF-inhibitors are established from treatment of V600E metastatic melanoma patients[1,2]
  - Rash, hyperkeratosis, photosensitivity
  - Arthralgias, fatigue, headache

- VE-BASKET Trial:
  - Arthralgias, rash, fatigue, skin papilloma[3]


1. Larkin et al: Lancet Oncol 15(4): 436, 2014
2. Hauschild et al: Lancet 380(9839): 358, 2012
3. Diamond et al: JAMA Onc 4(3): 384, 2018


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# Background – Vemurafenib induced Pancreatitis

## Vemurafenib

- Frequency: 0.2% (7 out of 3603 patients) among three clinical trials for the treatment of metastatic melanoma.
  - 1920mg/day[1-2]
  - 240–1120 mg/day or 1920 mg/day[3]
- Frequency: 5.6% (3 out of 54) patients for the treatment of refractory hairy cell leukemia
  - 1920 mg/day[4]


1. Chapman et al: Ann Oncol 28(10):2581, 2017
2. Blank et al: Eur J Cancer 79:176, 2017
3. Puzanov et al: Eur J Cancer 51(11):1435, 2015
4. Tiacci et al: NEJM 373(18):1733, 2015


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# Background – Dabrafenib induced Pancreatitis

## Dabrafenib monotherapy

- Only reported in post-marketing studies[1].

## Dabrafenib and Trametinib

- Frequency of 0.8% (1 out of 125 patients) among 1 clinical trial for treatment of metastatic melanoma to the brain[2]
  - Dabrafenib 300mg/day and Trametinib 2mg/day

1. Davies, et al: Lancet Onc 18(7):1863, 2017
2. Dabrafenib. In Life-Sciences-Europe.com from Tafinlar. EU Summary of Product Characteristics. 30 August 2013.

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# No reports of vemurafenib or dabrafenib induced pancreatitis in ECD patients

Diamond et al: JAMA Oncol 4(3):384, 2018
Cohen et al: Blood 130(11): 1377, 2017

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# Patients and Methods

- Retrospective Study
- ECD patients evaluated at Mayo Clinic from January 1998 to November 2018 who received vemurafenib or dabrafenib.
- Diagnosis of ECD made by using clinical criteria in conjunction with histopathologic findings.
- Diagnosis of acute pancreatitis was made by using 2012 revised Atlanta criteria.
  - Severity grading: Common Terminology Criteria for Adverse Events v 5.0

Banks et al: Gut 62(1):102, 2013

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# Results

| | |
|---|---|
| Total ECD patients (1998-2018) | 89 |
| # Patients tested for BRAF-V600E | 44 |
| *BRAF-V600E* mutation | 25/44 (57%) |
| **Treated with BRAF-I** | **21** |
| Median age | 57 years (range, 32-76) |
| Male | 57% (12/21) |
| Site of Organ Involvement | |
| Bone | 71% |
| Central Nervous System (CNS) | 67% |
| Kidney | 62% |
| Retroperitoneum | 48% |
| Kidney and Retroperitoneum | 33% |

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# Results

| Treated with BRAF-I | 21 |
|---|---|
| First BRAF-I (with MEK-I) | |
| Vemurafenib | 18 (86%) |
| Dabrafenib | 2 |
| Dabrafenib and Trametinib | 1 |
| Second BRAF-I (with MEK-I) | |
| Vemurafenib | 2 |
| Dabrafenib | 2 |
| Dabrafenib and Trametinib | 1 |
| Adverse Effects | |
| Dermatologic* | 6 (29%) |
| Fatigue | 6 (29%) |
| Acute Pancreatitis | 3 (14%) |

*Dermatologic side effects: Skin papillomas, photosensitivity, or rash.

# Results: Cohort with Pancreatitis

| | Age | Sex | Prior Therapy | BRAF-I (dose mg/d) | *Time (days) | CTCAE Grade Severity | Interim non-BRAF therapy | Second line BRAF-I (dose mg/d) | Outcome (months to last known follow up) |
|---|---|---|---|---|---|---|---|---|---|
| Pt 1 | 33 | F | M, I | V (960) | 4 | 3 | M, I | D, T (75, 2) | N (12) |
| Pt 2 | 58 | M | P, M, I | V (1920) | 28 | 2 | None | V (960) | N (20) |
| Pt 3 | 54 | M | P, M | D (150) | 1 | 3 | A | V (240-(720) | N (38) |

P=prednisone
M=methotrexate
I=infliximab

V=vemurafenib)
D=dabrafenib
T=trametinib

*Time in days from start of initial therapy to diagnosis of acute pancreatitis

N= No recurrence of pancreatitis

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# Results: Cohort with Pancreatitis

- After discontinuing initial BRAF-inhibitor…
  - All had clinical and radiologic progression of disease

- After re-starting second BRAF-inhibitor…
  - All ultimately had clinical and radiologic response to therapy
  - Time to re-starting second BRAF-inhibitor
    - 32, 27, and 5 months respectively for patient 1, 2, 3.

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# Discussion - Medication-induced Pancreatitis

- Pancreatitis due to medications is rare (<5 percent)
- Mechanism is unknown
- Often reversible and prognosis is good

- Our patients likely had pancreatitis due to BRAF-inhibitor therapy based on:
  - BRAF-inhibitor exposure and the onset of acute pancreatitis
  - Resolution of symptoms after discontinuing BRAF-inhibitor therapy

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# Key Points

- Clinicians need to be aware of acute pancreatitis
- Acute pancreatitis as a side effect of BRAF-inhibitors appears to be more common in hematologic diseases (ECD, hairy cell leukemia) compared to melanoma
  - Mechanism remains unclear
- May start another BRAF-inhibitor or restart at a lower dose.

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# Questions?

Ruan.Gordon@mayo.edu

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