Generic Oncology Drug Label Updates: Implications for Patient Care

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EMORY WINSHIP CANCER INSTITUTE

National Cancer Institute-Designated Comprehensive Cancer Center

FDA-Housed Data and Value to the Clinician

- FDA is an impartial, respected source of drug information
- Data provided in labels is freely available to the practicing clinician
  - Subscription clinical information services useful but costly
  - Primary literature often behind firewalls
- Evolution of increasing data transparency and availability
  - Drugs@FDA
  - Drug Information Soundcasts in Clinical Oncology

FDA-Housed Data and Value to the Clinician

- What do clinicians need from a label?
- With vetted data, in order of (my) preference:
  - Best dosing and scheduling strategy(ies)
  - Information in specific populations
  - Updated safety information
  - Updated pharmaceutical/admixture data
  - Updated pharmacology information

Case Example – Capecitabine

DOSAGE AND ADMINISTRATION

- Take XELODA with water within 30 min after a meal (2)
- Monotherapy: 1250 mg/m^2 twice daily orally for 2 weeks followed by a one week rest period in 3-week cycles (2.1)
- Adjuvant treatment is recommended for a total of 6 months (8 cycles) (2.1)
- In combination with docetaxel, the recommended dose of XELODA is 1250 mg/m^2 twice daily for 2 weeks followed by a 7-day rest period, combined with docetaxel at 75 mg/m^2 as a 1-hour IV infusion every 3 weeks (2.1)
- XELODA dosage may need to be individualized to optimize patient management (2.2)
- Reduce the dose of XELODA by 25% in patients with moderate renal impairment (2.3)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020896s037lbl.pdf

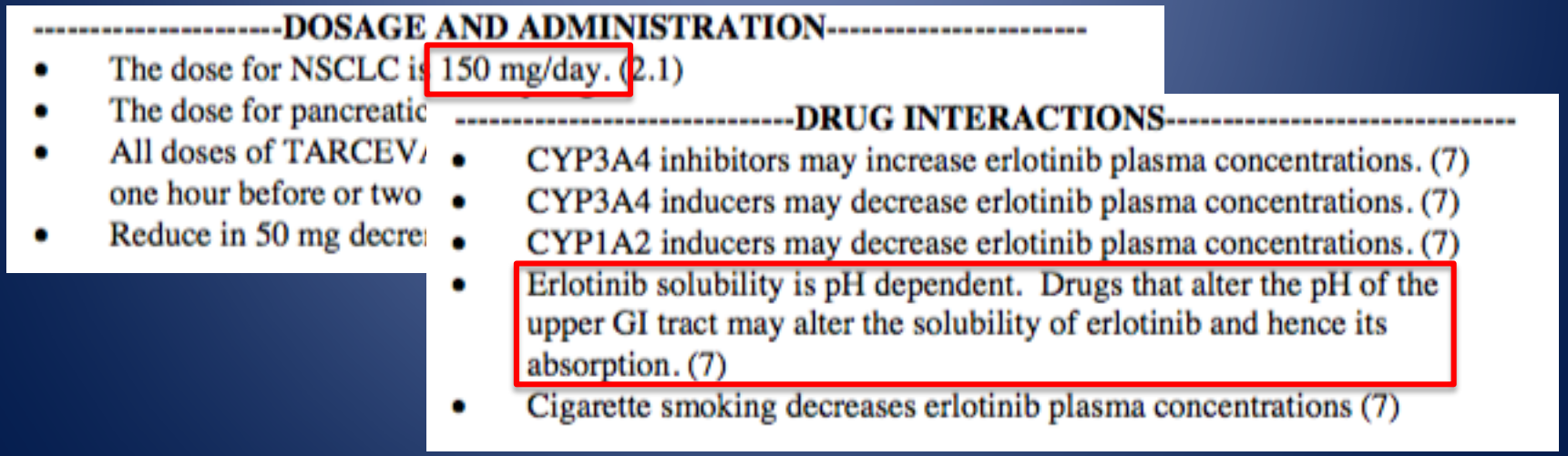
Case Example – Capecitabine

- Non-label data as maintenance in adjuvant triple negative breast cancer[a]
  - Terminated early due to benefit
  - 1250 mg/m^2 PO BID days 1-14 every 21 days
  - Overall survival hazard ratio 0.59 (0.39 – 0.9, p = 0.01)
- With docetaxel[b]
  - Optimal dose = 950 mg/m^2 (rather than 1250)

[a]Masuda N, et al. N Engl J Med 2017;376:2147-2156.
[b]Mavroudis D, et al. Ann Oncol 2010;21:48-54

Case Example – Erlotinib

- Approved prior to understanding role of *EGFR* mutations
- Dose derived from phase I escalation studies
  - Dose limiting toxicities: diarrhea, rash



----------DOSAGE AND ADMINISTRATION----------

- The dose for NSCLC is 150 mg/day. (2.1)
- The dose for pancreatic
- All doses of TARCEV
  one hour before or two
- Reduce in 50 mg decre

----------DRUG INTERACTIONS----------

- CYP3A4 inhibitors may increase erlotinib plasma concentrations. (7)
- CYP3A4 inducers may decrease erlotinib plasma concentrations. (7)
- CYP1A2 inducers may decrease erlotinib plasma concentrations. (7)
- Erlotinib solubility is pH dependent. Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its absorption. (7)
- Cigarette smoking decreases erlotinib plasma concentrations (7)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021743s14s16lbl.pdf

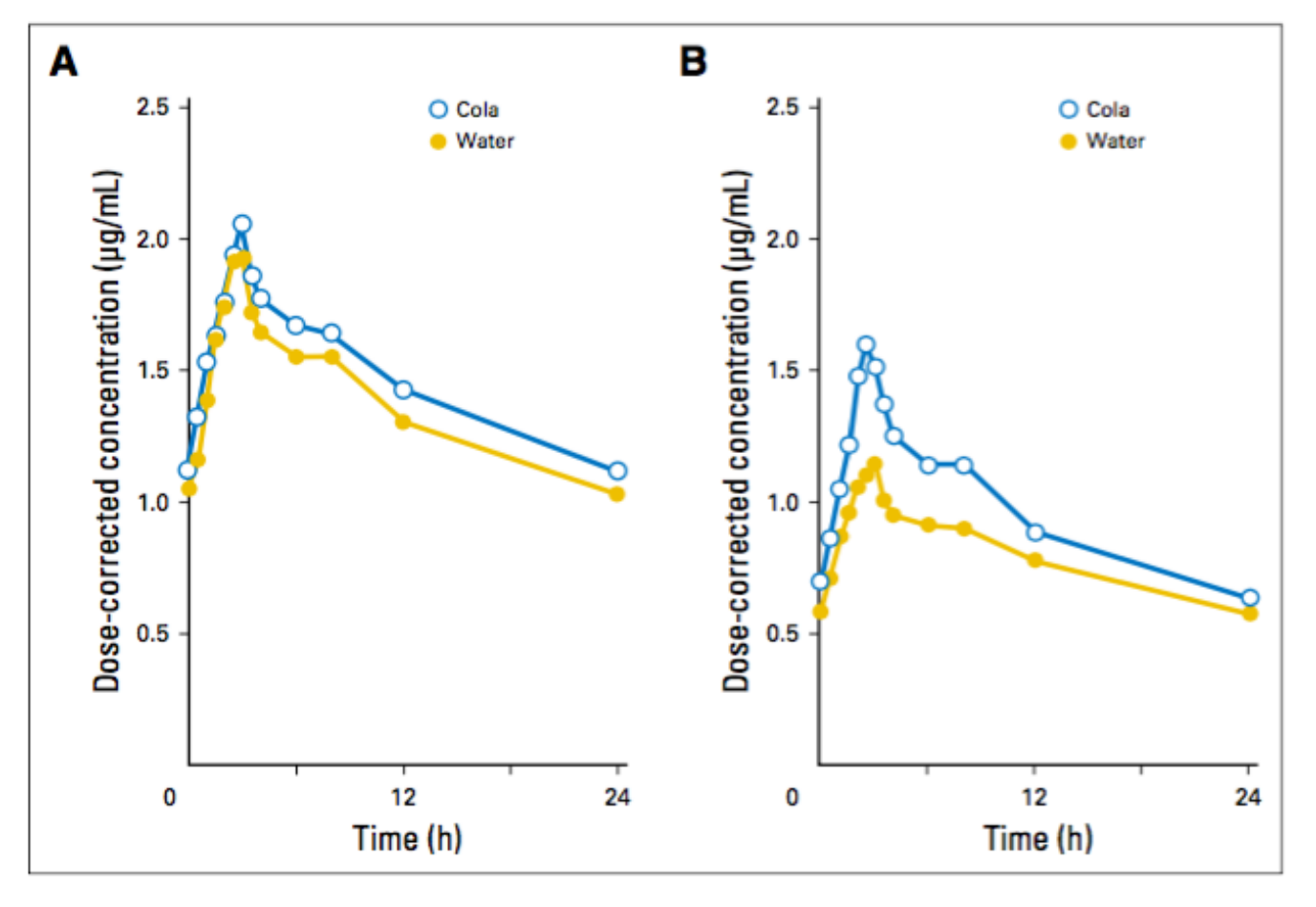
Hidalgo M, et al. J Clin Oncol 2001;19:3267-3279.

Case Example – Erlotinib

- Acid suppression used in up to 55% of cancer patients[a]
- Proton pump inhibitors reduce erlotinib absorption by 55%[a]
- Median maximum concentration (C_{max}) in licensing data = 1.28 micrograms/mL
- Clinical trial of erlotinib (n=28) +/- esomeprazole +/- cola (Coca-Cola classic)

[a]Planchard D. J Clin Oncol 2016;34:1292-1294.
[b]Van Leeuwen RWF, et al. J Clin Oncol 2016;34:1309-1314.

Case Example – Erlotinib



Van Leeuwen RWF, et al. J Clin Oncol 2016;34:1309-1314.

Case Example – Lenalidomide

- Trial performed in subjects without cancer and with renal impairment
- Single dose, PK collection and comparison
  - Recommendation
    - 60% dose reduction if creatinine clearance (CrCL) 30-60 mL/min

Table 1: Starting Dose Adjustments for Patients with Renal Impairment in MM, MDS or MCL

Category	Renal Function (Cockcroft-Gault)	Dose in MM or MCL	Dose in MDS
Moderate Renal Impairment	CLcr 30-60 mL/min	10 mg Every 24 hours	5 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 mL/min (not requiring dialysis)	15 mg Every 48 hours	2.5 mg Every 24 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	5 mg Once daily. On dialysis days, administer the dose following dialysis.	2.5 mg Once daily. On dialysis days, administer the dose following dialysis.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020896s037lbl.pdf

Chen N, et al. J Clin Pharmacol 2007;47:1466-1475.

Case Example – Lenalidomide

- Follow up study in relapsed myeloma patients with varying degrees of renal function (30-60, < 30, <30 mL/min on dialysis)
  - Median 2 (1-6) prior lines
  - Performance status 0-2, ANC $\geq$ 1000/mm^3, platelets $\geq$ 75,000/mm^3

Mikhael J, et al. Blood Cancer J 2018; 8(9):86. doi: 10.1038/s41408-018-0110-7.

Case Example – Lenalidomide

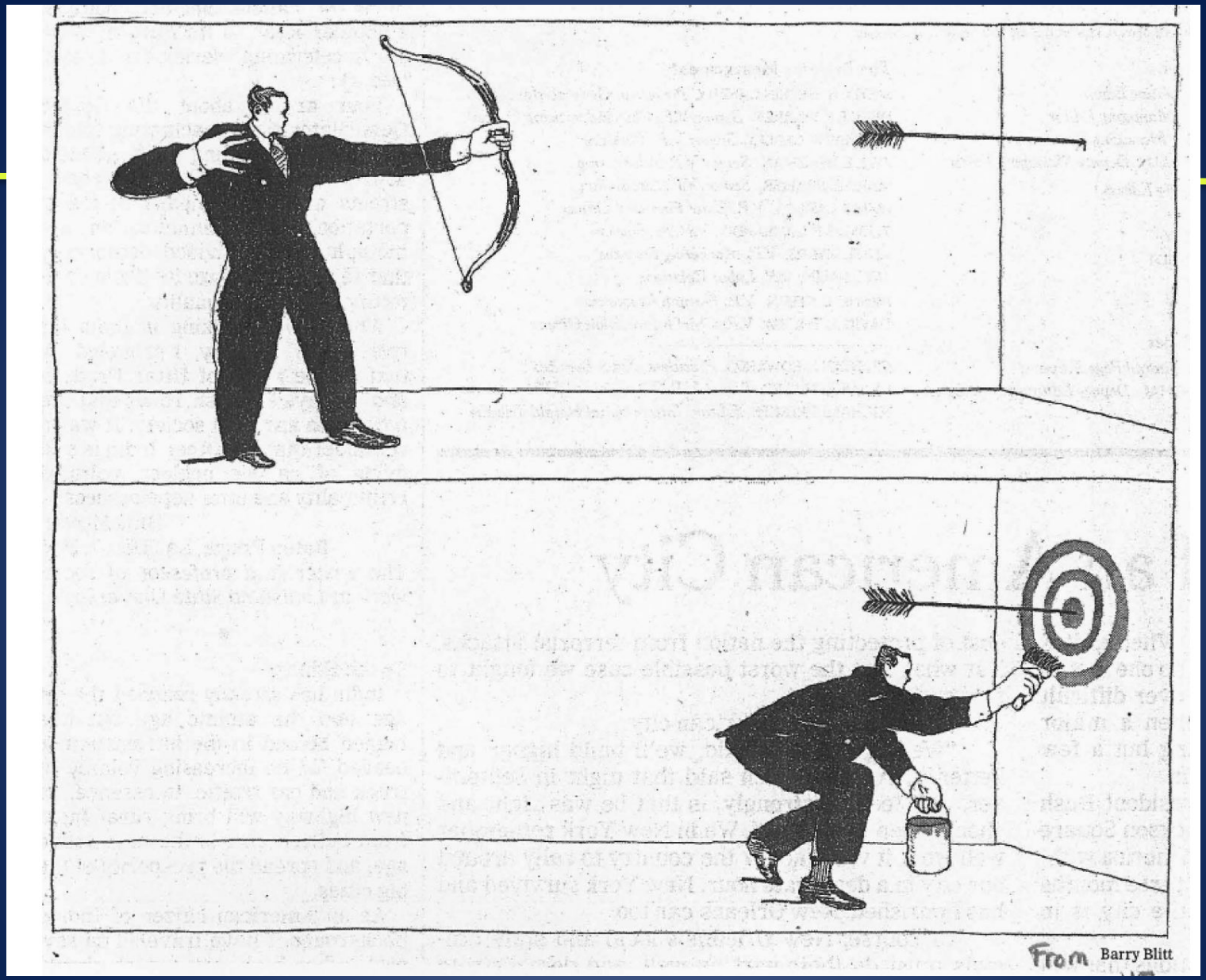
- Design
  - n = 62
  - 29/19/14 dose escalation cohorts in each group
- Conclusions
  - Full dose (25 mg) may be given if CrCL > 30 mL/min
  - CrCL < 30 mL/min - recommended dose 15 mg daily

Mikhael J, et al. Blood Cancer J 2018; 8(9):86. doi: 10.1038/s41408-018-0110-7.

Case Example – Oxaliplatin

- Infusion time per label = 120 minutes
- When infused at 1 mg/m^2/min (e.g., 85 mg/m^2 given over 85 minutes):
  - Hypersensitivity reaction rate 8% (n=667) versus 11% with historical cohort (n=1936 at 85 mg/m^2)

Cercek A, et al. J Oncol Pract 2016;12:548-553.



Slide courtesy of Merrill Egorin, MD