Unique Toxicities with PARP Inhibitors…and What to do

Robert L. Coleman, MD

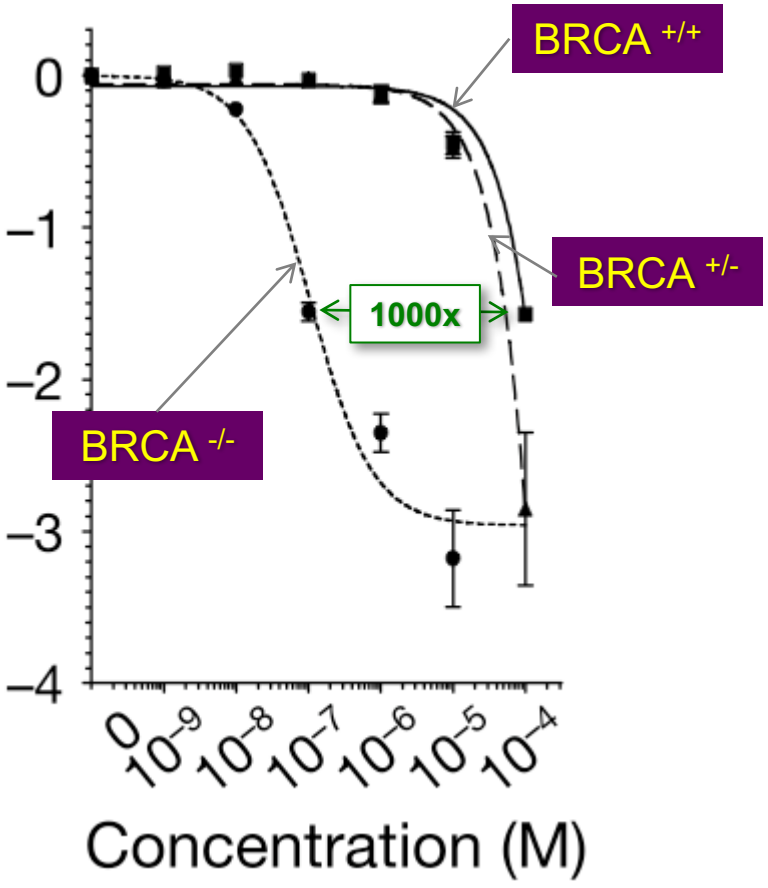
Professor & Deputy Chair
Department of Gynecologic Oncology & Reproductive Medicine
University of Texas, M.D. Anderson Cancer Center

Disclosures Related to This Presentation

- Institutional Research Funding:
  - AbbVie, AstraZeneca, Clovis
- Clinical Trial Scientific Steering Committee (uncompensated):
  - AbbVie, AstraZeneca, Tesaro, Clovis

rcoleman@mdanderson.org

PARPi and "Synthetic Lethality"



Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase

Helen E. Bryant[1], Niklas Schultz[2], Huw D. Thomas[3], Kayan M. Parker[1], Dan Flower[1] Nicola J. Cu

[1]The Institute Beech Hill Ro
[2]Department Stockholm Un
[3]Northern Ins Medical Scho

Poly(ADP-r binding to site of dam

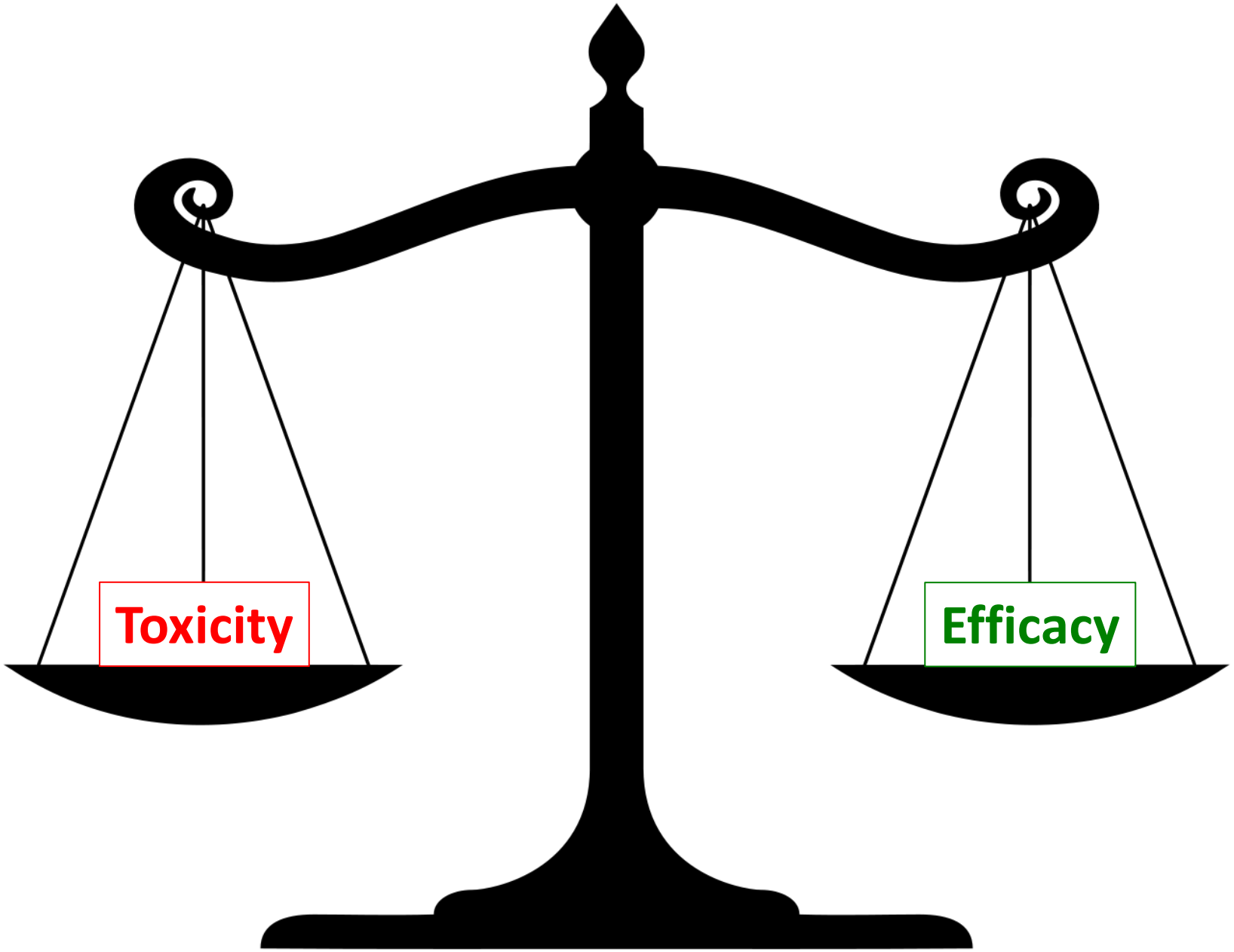
Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy

Hannah Farmer[1,2]*, Nuala McCabe[1,2]*, Christopher J. Lord[2]*, Andrew N. J. Tutt[2,3], Damian A. Johnson[2], Tobias B. Richardson[2], Manuela Santarosa[2]†, Krystyna J. Dillon[4], Ian Hickson[4], Charlotte Knights[4], Niall M. B. Martin[4], Stephen P. Jackson[4,5], Graeme C. M. Smith[4] & Alan Ashworth[1,2]

[1]*Cancer Research UK Gene Function and Regulation Group and* [2]*The Breakthrough Breast Cancer Research Centre Institute of Cancer Research, Fulham Road, London SW3 6JB, UK*
[3]*Guy's Hospital, St Thomas' Street, London SE1 9RT, UK*
[4]*KuDOS Pharmaceuticals Ltd, Cambridge Science Park, Cambridge CB4 0WG, UK*
[5]*Wellcome Trust and Cancer Research UK, Gurdon Institute of Cancer and Developmental Biology, and Department of Zoology, University of Cambridge, Tennis Court Road, Cambr*

Nature 2005

rcoleman@mdanderson.org


Toxicity
Efficacy

Take Home Point

- PARP inhibitors, despite being “just a pill”, have adverse events and toxicities that require attention to optimize treatment exposure
- Fortunately, most toxicities are manageable
- Monitoring should be at least once a month during the first few cycles of therapy
- Dose reductions and delay should be utilized to ensure compliance

Hematologic Toxicity

Toxicity	Grade	Olaparib[1]	Rucaparib[2]	Niraparib[3]
Anemia (%)	All Grades	90	67	50
	Grade 3 and 4	15	23	25
Thrombocytopenia (%)	All	30	39	61
	Grades 3 and 4	3	6	34
Neutropenia (%)	All	25	35	30
	Grades 3 and 4	7	10	20

[1]FDA package insert, [2]FDA package insert, [3]NOVA NEJM 2016

Gastrointestinal Toxicity

Toxicity	Grade	Olaparib [1]	Rucaparib[2]	Niraparib[3]
Nausea (%)	All Grades	64	77	74
	Grade 3 and 4	3	5	3
Constipation (%)	All	21[5]	40	40
	Grades 3 and 4	0	2	0.5
Vomiting (%)	All	43	46	34
	Grades 3 and 4	4	4	2
Decreased appetite (%)	All	22	39	25
	Grades 3 and 4	1	3	0.3
Abdominal pain (%)	All	43	32	23
	Grades 3 and 4	8	3	1
Diarrhea (%)	All	31	34	19
	Grades 3 and 4	1	2	0.3
Dyspepsia (%)	All	25	9[4]	11
	Grades 3 and 4	0	<1%	0

[1]FDA insert, [2]FDA insert, [3]NOVA NEJM 2016, [4]Swisher Lancet Onc 2016, [5]Ledermann Lancet Oncology 2014

GI Toxicity Management

- Early response to symptoms
  - Agent timing, empty stomach
- Supportive care measures
  - Anti-emetics – be aggressive here (pre-empt the AE)
  - Bowel regimens
  - Anti-diarrheals
  - Appetite stimulants

Generalized Toxicity

Toxicities	Grade	Olaparib [1]	Rucaparib[2]	Niraparib[3]
Fatigue (%)	All Grades	66	77	59
	Grade 3 and 4	8	11	8
Insomnia (%)	All	NR	12	24
	Grades 3 and 4	NR	0	0.3
Headaches (%)	All Grades	25[5]	17[4]	26
	Grades 3 and 4	0	0[4]	0.3

[1]FDA insert, [2]FDA insert, [3]NOVA NEJM 2016, [4]Swisher Lancet Onc 2016, [5]Ledermann Lancet Oncology 2014

Additional Toxicities That Differ Between Agents

Toxicities	Grade	Olaparib[1]	Rucaparib[2]	Niraparib[3]
Increased Creatinine (%)	All	30	92	-
	Grades 3 and 4	2	1	-
Elevated ALT (%)	All	-	74	-
	Grades 3 and 4	-	13	-
Elevated AST (%)	All	-	73	-
	Grades 3 and 4	-	5	-
Hypertension (%)	All	-	-	19
	Grades 3 and 4	-	-	8
Dyspnea (%)	All	-	21	19
	Grades 3 and 4	-	0.5	1

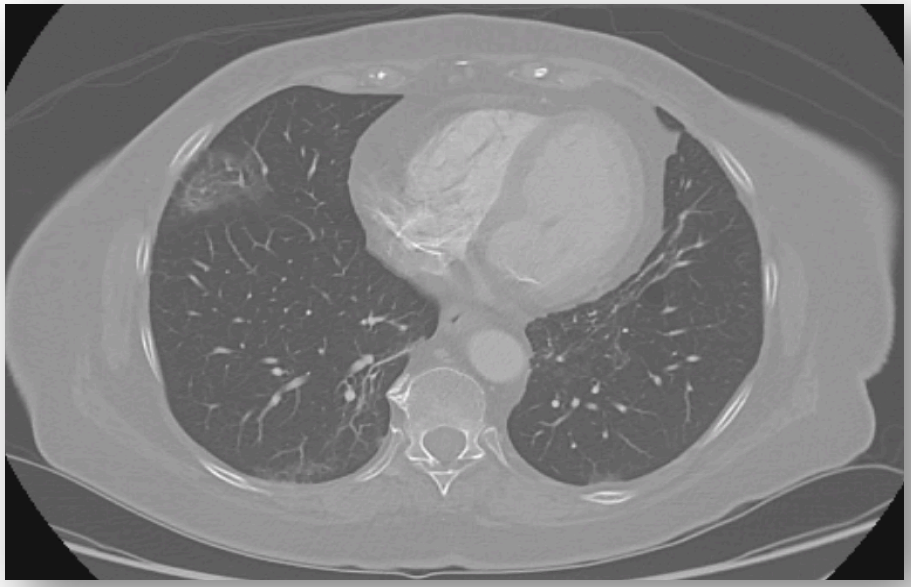
[1]FDA insert, [2]FDA insert, [3]NOVA NEJM 2016,

Elevation in Creatinine

- Related to effect of PARP inhibitor on renal transporter proteins MATE1 and MATE2-K
  - Increase in creatinine without corresponding kidney dysfunction
- Utilize nuclear medicine testing to determine the true GFR
  - Avoid dose reduction or drug interruption if the GFR is appropriate

Other AE's of Interest

- Pneumonitis
  Olaparib: <1%
- AML/MDS
  Olaparib 0.8% (22/2618)[1]
  Rucaparib 0.5% (2/377)[2]
  Niraparib 1.4% (5/367)[3]
- Increase in cholesterol
  Rucaparib[2]: 40%/2%
- Rash/photosensitivity reaction
  Rucaparib: 15%/10%
  Olaparib: 25%/0%



[1]FDA insert, [2]FDA insert, [3]NOVA NEJM 2016,

General Toxicity Management

- G1:
  - Monitor
- G2:
  - Monitor
  - Thrombocytopenia – hold agent, dose reduction
- G3/4:
  - Hold agent
  - Dose reduction
  - Consider transfusion, growth factors

PARP Inhibitor Toxicity

- Typically, easily managed with supportive care and dose reduction
- Patients should be monitored closely during the first cycles of therapy
  - Off protocol, I frequently ramp up dose after 2 weeks (start at dose level -1)
- It is important to manage expectations of patients and caregivers to alleviate key symptoms so that therapy can continue uninterrupted