PARP inhibition – basic science and clinical challenge

Thomas Helleday, PhD
Poly (ADP-ribose) Polymerase 1 (PARP1)

PARP family of proteins

DNA repair

DNA damage/NAD$^+$ levels dictate responses

PARP1 is critical for efficient SSB repair

DNA single-strand break

PARP1

XRCC1 – Ligase3
PNKP, APTX

Polβ

PCNA, Polδ/ε, Polβ, Ligase1, FEN1

short patch

Polβ

XRCC1

Lig3

long patch

PCNA

Lig3

XRCC1

Lig3

XRCC1

PCNA

Lig1

BRCA2 deficient cells are killed by PARP inhibitors

Specific killing of BRCA2 deficient tumours with PARP inhibitors

Synthetic lethality as an approach for anti-cancer treatments

Cancer cells
- PARP Inhibition
- SSB repair
- Homologous Recombination
- Cell death
- BRCA2-/-

Normal cells
- PARP Inhibition
- SSB repair
- Homologous Recombination
- Survival
- BRCA2+/-

Helbeday T.
PARP inhibitors in monotherapy
PARP inhibitors in treatment for BRCA1/2 cancer

>80 clinical trials with PARP inhibitors in phase I-II

- Progressive disease
- Stable disease
- Partial response
- Complete response

- Ovarian cancer
- Prostate cancer
- Breast cancer

PARP inhibitors in treatment for BRCA1/2 ovarian cancer

Olaparib 400 mg twice daily

Olaparib 100 mg twice daily

Response to PARP inhibitors in triple negative breast cancer is dictated by BRCA mutation

Olaparib 400 mg twice daily

Platinum resistant ovarian cancers and non-BRCA respond to PARP inhibitor

Olaparib maintenance treatment improve progression-free survival in relapsed high-grade serous ovarian cancer

Hazard ratio, 0.35 (95% CI, 0.25-0.49) P<0.001

Ovarian cancers often have silenced Fanconi anemia (FA) pathway, rendering in homologous recombination defect.
Biomarkers for PARP inhibitor sensitivity in monotherapy?

- BRCA1/2 mutation
- Silenced or mutated BRCA related genes
- PARP1 protein levels or PARP activity
- Functional homologous recombination assay (RAD51 foci, FA status)
- RNA/DNA signatures correlating with BRCA status
- BRCA mutational signature
Resistance to PARP inhibitors

Cancer cells

PARP inhibitor  BRCA2 mutation

Cell Death

Rottenberg S et al. Proc Natl Acad Sci USA 2008;105(44):17079-17084;
Complicity of genetic networks – 53BP1 loss as resistance mechanism

Reprinted from Bunting SF et al. Cell 2010;141:243-254. Copyright (2010), with permission from Elsevier
PARP inhibitors in combination therapy
Iniparib plus chemotherapy in metastatic triple-negative breast cancer

Hazard ratio for death with iniparib, 0.57 (95% CI, 0.36-0.90) P=0.01

Iniparib plus chemotherapy in metastatic triple-negative breast cancer

- Reasons for phase III to fail?
  - Phase II design (open label)
  - Combination with gem-carbo?
  - No selection for BRCA mutated patients?
  - Iniparib is not a PARP inhibitor

Rucaparib (PF-01367338, AG014699), with temozolomide in patients with metastatic melanoma

Conclusion: This study show that temozolomide (150–200 mg/m²/day) can safely be given with a PARP inhibitory dose of rucaparib, increasing progression-free survival over historical controls in metastatic melanoma patients.

**Strategies using PARP inhibitors as anti-cancer agents - overview**

- Potentiating chemotherapy
- Synthetic lethality
- Combined with targeted therapies
- Enhance cancer-specific DNA damage
- Context specific synthetic lethality

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Normal cells, no DNA damage</td>
</tr>
<tr>
<td>b</td>
<td>Normal cells, BRCA&lt;sup&gt;mut&lt;/sup&gt;</td>
</tr>
<tr>
<td>c</td>
<td>Normal cells, replication stress</td>
</tr>
<tr>
<td>d</td>
<td>Replication stress, +chemo PARP active</td>
</tr>
<tr>
<td>e</td>
<td>Replication stress, +chemo PARP not active</td>
</tr>
<tr>
<td>f</td>
<td>DNA damage stress, +CDK1 inhibitor</td>
</tr>
<tr>
<td>g</td>
<td>DNA damage stress, hypoxia</td>
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</tbody>
</table>

Hellday T. Curr Opin Oncol 2013;25:609-614
What combination will work in the clinic depends on tumour characteristics and drug mechanism of action

<table>
<thead>
<tr>
<th>Therapy</th>
<th>DNA repair inhibitor</th>
<th>Value</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>PARP inhibitor</td>
<td>+</td>
<td>FA silenced cells exhibit decreased homologous recombination and sensitivity to PARP inhibitors</td>
</tr>
<tr>
<td>Platinum-based chemo</td>
<td>PARP inhibitor</td>
<td>++</td>
<td>FA silenced cells are sensitive to both platinum-based chemo and PARP inhibitors, which cause different DNA lesions, additive effect with both treatments, some normal tissue toxicity.</td>
</tr>
<tr>
<td>Platinum-based chemo</td>
<td>DNA-PK inhibitor</td>
<td>- - -</td>
<td>Sensitivity to crosslinking agents in FA-silenced cells depend on active DNA-PK activity. Cancer cells become selectively resistant to platinum-based chemo.</td>
</tr>
<tr>
<td>Platinum-based chemo</td>
<td>Non-FA crosslink inhibitor</td>
<td>+++</td>
<td>FA silenced cells rely on non-FA mediated repair for survival, which normal cells do not. This pathway not yet identified.</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>PARP inhibitor</td>
<td>-</td>
<td>Temozolomide not standard in ovarian cancer, PARP activity required for normal cell survival. Risk of potentiating side effects.</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>ATR/Chk1 inhibitor</td>
<td>+</td>
<td>ATR/Chk1 inhibitors sensitises to radiotherapy and are especially active in p53 mutated cancer. Furthermore, FA silenced cells exhibit replication lesions requiring ATR/Chk1 for survival</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>PARP inhibitor</td>
<td>+++</td>
<td>DNA-PK lost cells rely on PARP-mediated backup-end joining repair of doxorubicin-induced double-strand breaks. Normal cells have DNA-PK and are not sensitised by PARP inhibitors</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>-</td>
<td>+</td>
<td>Mitosis inhibitor causing uncapping at telomers and DNA damage signalling-mediated cell death.</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Chk1 inhibitor</td>
<td>++</td>
<td>Docetaxel triggers Chk1-mediated mitotic checkpoint required for survival in p53 mutated cells</td>
</tr>
</tbody>
</table>
PARP inhibitor mechanism of action
PARP is involved in SSBR, replication repair, alt-NHEJ, fork protection, NER and BER

Ström CE and Hellday T. Biomolecules 2012;2:635-649
PARP1 trapping is required for PARP inhibitor toxicity

PARP1 + BRCA2 protects replication forks from Mre11 degradation

Reprinted from Ying S et al. Cancer Res 2012;72(11):2814-2821, with permission from AACR
PARP1 + BRCA2 protects replication forks from Mre11 degradation

PARP inhibitors inhibits several PARP family member

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SUMMARY

- Efficacy of PARP inhibitors in monotherapy coupled with HR defect
- Combination strategy complex and in depth mechanistic understanding needed
- PARP inhibitors trap PARP on DNA and has different effect from protein loss
- PARP1 is involved in SSB repair, replication restart, fork protection, B-NHEJ
- Resistance can develop to PARP inhibitors
Thank you!