Method for predicting response to DNA repair pathway inhibitors in diffuse large B-cell lymphoma

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Diffuse large B-cell lymphoma

- ~40% of Non-Hodgkin lymphomas
- ~ 23,000 new diagnoses/year
- ~ 50% cure rate
- ~ 10,000 deaths/year

Molecular heterogeneity

Subtype-specific response to chemotherapy
Patients with high risk are characterized by overexpression of DNA repair genes.

**DNA repair in DLBCL**

**R**ituximab

**C**yclophosphamide

**Alkylating Agent (ICLs)**

**H** doxorubicin hydrochloride

**Intercalating Agent (DSB)**

**O**ncovin (vincristine)

**P**rednisone

*Bret C et al. Oncotarget 2012*

*Bret C. Cell cycle 2013c*
Microarray-based genome-wide screen for high-risk genes involved in DNA repair pathways

- DNA repair pathways → drug resistance
- Identification of high-risk patients that could benefit from inhibitors targeting DNA repair pathways
- FANC, NHEJ and MMR scores displayed independent prognostic information,
- They were combined to create a new DNA repair score

Inhibiting DNA repair appears to be a promising strategy to improve the efficacy of genotoxic drugs and overcome drug resistance in DLBCL

Bret C et al. BJH 2015
Therapeutic interest of DNA repair inhibitors in DLBCL
Identification of high-risk patients that could benefit from inhibitors targeting DNA repair pathways

Screening of DNA repair inhibitors using a panel of 17 DLBCL cell lines

**FANC score**
- R CHOP cohort
  - \( P = 7.8 \times 10^{-8} \)
  - Score \( \leq -5.24 \)
    - \( N = 192 (82.4\%) \)
  - Score \( > -5.24 \)
    - \( N = 41 (17.6\%) \)

Significant higher sensitivity to ATR inhibitors

**HR score**
- R CHOP cohort
  - \( P = 1.8 \times 10^{-8} \)
  - Score \( \leq -8.67 \)
    - \( N = 200 (85.8\%) \)
  - Score \( > -8.67 \)
    - \( N = 33 (14.2\%) \)

Significant higher sensitivity to Topo II inhibitors

**BER score**
- R CHOP cohort
  - \( P = 2.9 \times 10^{-9} \)
  - Score \( \leq -5.10 \)
    - \( N = 163 (70.0\%) \)
  - Score \( > -5.10 \)
    - \( N = 70 (30.0\%) \)

Significant higher sensitivity to Topo II inhibitors

**Identification of high-risk patients that could benefit from inhibitors targeting DNA repair**
Overcome drug resistance using DNA repair inhibitors

Synergistic effect of ATR inhibitor and cyclophosphamide

Improve the efficacy of genotoxic drugs and overcome drug resistance in DLBCL

Synergistic effect of chk1 inhibitor and cyclophosphamide
Conclusions

- DNA repair pathways are deregulated in DLBCL in association with a poor prognosis

- DNA repair scores allow the identification of high risk DLBCL patients that could benefit from treatment by DNA repair inhibitors

- Identification of synergistic combinations with DNA damaging agents used in conventional treatment to develop synthetic lethal approaches

- Overcome resistance to DNA damaging agents in DLBCL
Business opportunity and contact

- Co-development partner for Phase I study validation
- Approach that could be extended to other cancers

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