Bloom Syndrome: Cancer Diagnosis and Treatment

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Chicago, Illinois
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Agenda for Bloom Syndrome (BS): Cancer Diagnosis and Treatment

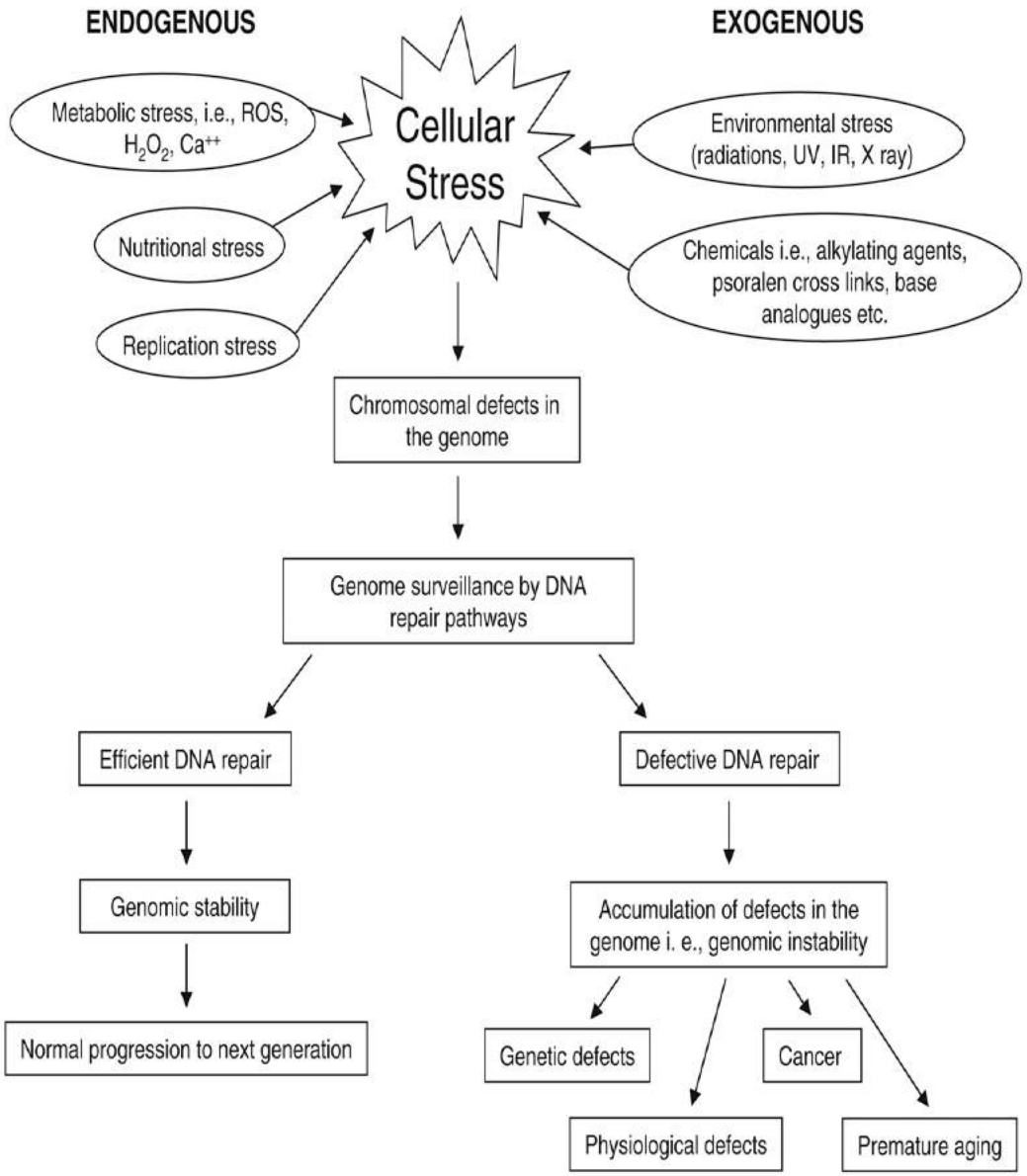
1. Background BS
2. Common ways that cancers are treated in the general population
3. Modification of treatment for people with BS
4. Provide information on which types of chemotherapy are believed to be well tolerated by people with BS
5. Discuss chemotherapy agents that may be associated with problem side effects or long-term risks.
6. Discuss new cancer treatment approaches that are being developed
7. How to use these new treatments may be useful for people with BS

Overview of Bloom Syndrome (BS)

- Rare autosomal recessive disorder
- Characterized by distinctive physical features, growth retardation, sunlight sensitivity
- Individuals with BS develop malignant neoplasms
- Individuals with BS generally have dramatically shortened lifespan with most common cause of death due to cancer
- Pre-existing comorbidities makes treatment challenging
- Significant sensitivity to both chemotherapy and ionizing radiation complicates treatment

DNA Repair

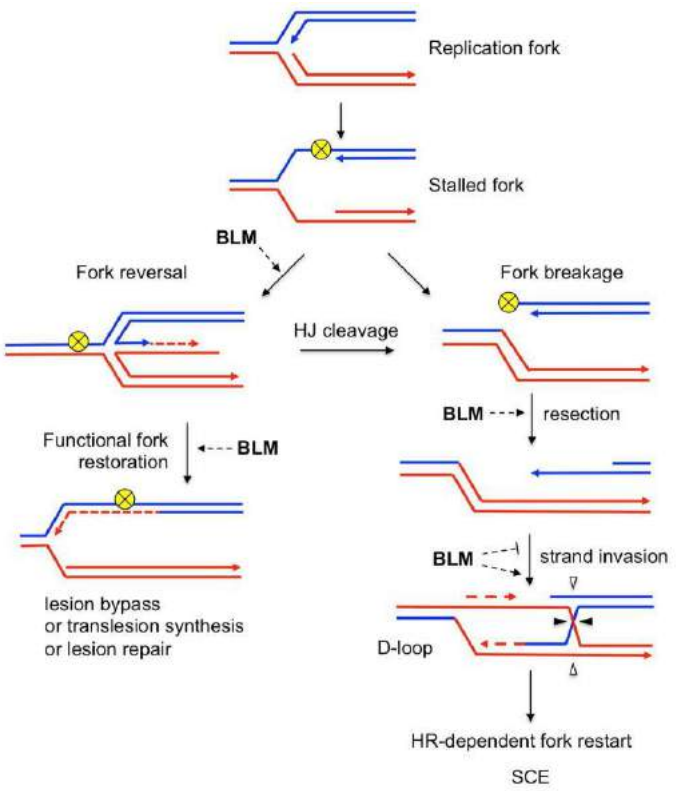
- During an individual lifetime we are exposed to multiple stresses can result in chromosomal defects.
- Counteracted by surveillance and various DNA repair pathways
- DNA repair machinery protects the genome from harmful effects of stress.
- Defective DNA repair machinery would ultimately lead to chromosomal abnormalities
  - genetic defects
  - physiological defects,
  - cancer
  - premature aging



Biogerontology. 2009 Jun; 10(3): 235–252

Role of BLM RecQ Helicase

- Helicases are enzymes that separate the complementary strands of DNA and are essential for all aspects of DNA metabolism
- 5 RecQ Helicases have been identified with 3 of theses giving rise to clinical disorders with cancer predisposition
  - Bloom syndrome, Werner syndrome and Rothmond Thompson syndrome (BLM,WRN, RecQ4)
- BLM gene is located at 15q26.1
- BLM helicase plays an important roles in DNA replication- and recombination-related pathways that maintain chromosome stability
  - BLM gene interacts with other crucial DNA-repair proteins including BRCA1, ATM, and RAD51
- Errors during replication process → chromosomal rearrangements and breakages→ increased incidence of cancer



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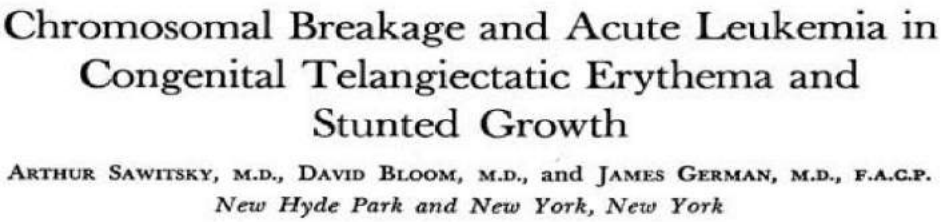
Ageing Res Rev. 2017 Jan; 33: 36–51.

Predisposition to Malignancies



Chromosomal Breakage and Acute Leukemia in Congenital Telangiectatic Erythema and Stunted Growth

ARTHUR SAWITSKY, M.D., DAVID BLOOM, M.D., and JAMES GERMAN, M.D., F.A.C.P.

New Hyde Park and New York, New York

3 cases of leukemia in BS registry out of 23 patients in the registry in 1960s

In 1997 Dr. German published "The First 100 Cancers"

- Reported 100 cancers in 71 out of 168 registered individuals
- Increased risk of malignancy compared with the general population
- Wide variety of cancers reported
- Earlier age of onset than the general population

Sawitsky et al, Annals of Internal Medicine, 1966
German 1997 "Bloom Syndrome. XX. The First 100 Cancers

Cancer Frequency From BS Registry

Anatomic Site/Types	Mean age at dx (Range)	Frequency
Leukemia	**18 (2-40)**	**40**
AML	19(6-32)	17
ALL	17 (4-40)	11
Other/Biphenotypic	19 (2-40)	12
Lymphoma	**21 (4-49)**	**37**
Oro-Pharyngeal	**37 (26-48)**	**23**
Tongue	40 (26-48)	9
Pharynx	34.8 (31-45)	5
Tonsil	38 (25-46)	4
Other	N/A	5
Upper GI	**22 (15-48)**	**13**
Esophageal	37 (25-48)	5
Gastric	29 (24-33)	4
Other	N/A	4

Anatomic Site/Types	Mean age at dx (Range)	Frequency
Colorectal	**35 (16-49)**	**28**
Genitourinary	**29 (10-47)**	**14**
Cervical	21 (19-23)	5
Other	N/A	9
Breast	**35 (21-52)**	**23**
Skin	**31 (18-42)**	**21**
Basal Cell	28 (18-38)	13
Squamous cell	35 (35-36)	4
Pharynx	34.8 (31-45)	5
Other	N/A	4
Wilms Tumor	**3 (1-8)**	**8**
Lung	**36 (32-40)**	**4**
All other	**N/A**	**12**

- **277 individuals in BS registry**
- **223 cancers in 144 individuals**
  - **Multiple cancers in same patients**

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Cunniff et al, American Journal of Genetics, 2018

What is cancer?

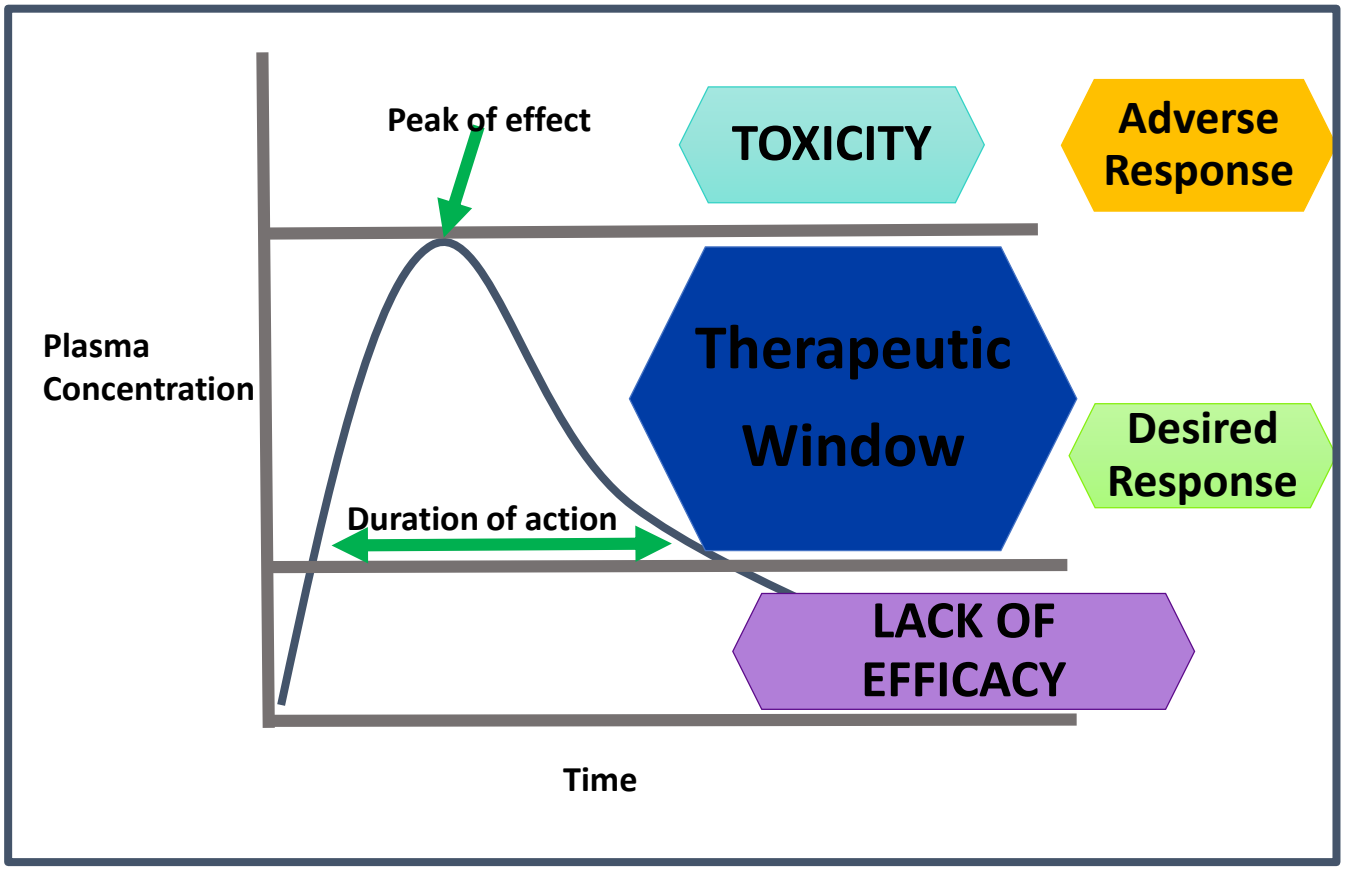
- Cancer is a result of uncontrolled growth and loss of apoptosis
- Alterations in three groups of genes → deregulated control mechanisms

Oncogenes	Tumor Suppressor Genes	DNA stability Genes
constitutively active	inactive	inactive
Drive tumorigenesis	Loss of function permits unregulated cell cycle progressions	Not necessarily directly involved in or rate limiting for neoplastic transformation
One allele inactivated	Both alleles inactivated	Both alleles inactivated
		Particularly potent when inherited
		Not selective simply increase the probability that oncogenes/TS genes will be hit

Treatment Modalities

- Surgery
- Radiation Therapy
- Chemotherapy
  - Cytotoxicity is non-specific
  - Adjuvant
    - Chemotherapy given to patients without evidence of residual disease (after surgery or radiation)
    - Goal is to eliminate micrometastases
  - Neoadjuvant/Primary Chemotherapy
    - Prior to surgery or radiation to decrease tumor bulk
- Biotherapy/ Immunotherapy

How much chemotherapy to give?



Goals of Chemotherapy

Cure
- Complete response

Control
- Extend the length of life when a cure is not realistic

Palliative
- Provide comfort when cure or control is not possible

- Use agents which are known to be individually active
- To enable cytotoxicity of resting and dividing cells
  - Cell cycle non specific agents can recruit cells into specific phase of the cell cycle to increase cell kill
- Hit sanctuary sites
- Rescue-from the toxic side effect of another agent (ie: Leucovorin)

- Combination chemotherapy can overcome or avoid tumor resistance
- Have different, non-antagonistic and preferably additive or synergistic mechanisms of action
- Non-Cross resistant (different mechanisms of resistance)
- Non-Overlapping toxicities so that each can be delivered at the dose and schedule that optimizes efficacy

Chemotherapy challenges in BS

- Patients affected by BS are more susceptible to the toxicity of chemotherapies
  - Due to pre-existing comorbidities
  - Due to underlying immunodeficiency
  - Due to inherent cellular oversensitivity caused by the direct DNA damage of normal proliferating cells

  →Even narrower therapeutic index
- Lack of guidelines for treatment and guidance on dose adjustments
- How do we figure out how to modify chemotherapy dosing and regimen due to BS?

Burkitt lymphoma in a child with BS

5 yo Tunisian M with BS from consanguineous family with an abdominal Burkitt lymphoma stage IV (liver mets)

- Treated based on standard protocol: Cyclophosphamide/VCR/Prednisone/Doxo/Methotrexate x 2
  - Developed grade IV myelosuppression and severe mucositis
- Treated with ara-c and Mtx
- Found to have residual disease in liver
- Due to previous toxicity did NOT intensify treatment, continued with same therapy
- Presented with local relapse while on therapy:
  - 2nd line chemo: Ifosfamide, carboplatin, etoposide at 2/3 dose but had severe toxicity and failure of remission
  - Died due to metastatic tumor progression 14 months after diagnosis

Fedhila-Ben Ayed F et al. Arch Pediatr. 2016 Apr;23(4):382-4

Successful treatment of B-cell lymphoma in BS: Rituximab-based chemotherapy

11 yo Saudi male with BS with mature B cell lymphoma of larynx and mediastinum (No CNS or BM involvement)

- Reduction/Induction cycle with severe complications
  - cyclophosphamide/vincristine/prednisone/doxorubicin/and methotrexate
  - Delayed methotrexate clearance resulted in severe skin, liver and mucus membrane toxicity
  - Prolonged febrile neutropenia with typhlitis, bacterial endocarditis, cholestasis, emotional instability and depression
  - Grade IV myelotoxicity bone marrow with aplasia but no evidence of malignancy
  - Remained transfusion dependent for one year post treatment→ bone marrow recovered
- Modified chemotherapy with Rituximab, vincristine and prednisone followed by 5 cycles of Rituximab only
- 4 years later presented with pancytopenia with no evidence of lymphoma but bone marrow aplasia →diagnosed with second malignancy Acute myeloid leukemia (AML)

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Jastaniah W. Pediatr Blood Cancer. 2017 Jul;64(7).

Pediatric Lymphoma in BS successfully treated in Colorado with dose adjusted chemotherapy

7 yo with BS diagnosed with Stage 3 Group B abdominal DLBCL

- treated with chemotherapy following the Children's Oncology Group protocol for lymphoma (ANHL01P1 with rituximab)
- Doxorubicin and cyclophosphamide were dose reduced by 50%
- MRI was substituted for PET/CT for interval scans.
- Supplemented IVIg for IgG levels <500 throughout therapy
- Post-cycle 3 he had a small amount of residual disease on his MRI
- Biopsy revealed 80-90% necrosis
- Gave 2 doses of rituximab off protocol as maintenance

- Remains in complete remission at 4 years off therapy
- No evidence of cardiac issues or secondary malignancy at this time
- Low IgG levels but no longer receiving supplementation

Personal Communication August 2018, Dr Eisenman at Children's Colorado

Toxicity of chemotherapy in BS: gastric cancer

21 yo F with BS diagnosed with stage IV gastric adenocarcinoma after prolonged complaint of postprandial epigastric pain

- At the time of total gastrectomy--peritoneal carcinomatosis
- Planned to treated with capecitabine and oxaliplatin
- After oxaliplatin only
  - Severe bronchospasm and hyperglycemia
  - Severe diarrhea
  - Pancytopenia
  - 3 weeks of febrile neutropenia
  - Chemotherapy suspended
- Died 2 months later of progressive disease

Priscila et al. Journal of Pharmacy and Pharmacology 7 (2017) 430-433

Adenocarcinoma of Right colon in BS

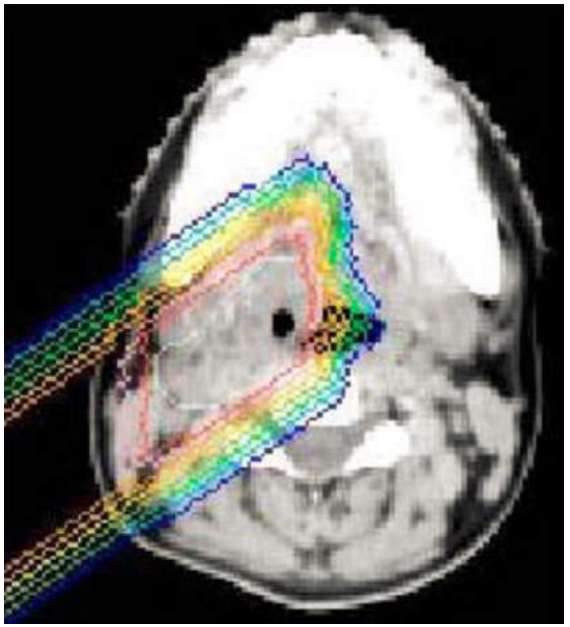
34 yo M with BS presented with palpable abdominal mass (RLQ)

- s./p right colectomy without nodal involvement (Stage IIA)
- 5 years from diagnosis without recurrence
- Simultaneous diagnosis of Basal cell carcinoma of the forehead
  - 12% of BS patients develop colon cancer with mean age dx 35
  - Role of surveillance colonoscopy
  - Surgery for early stage disease to avoid chemotherapy

Martinez et al. Case Rep Surg. 2016

Proton beam therapy for malignancy in BS

32 yo F BS oropharyngeal squamous cell carcinoma



- Right base of tongue extended to right lateral pharyngeal wall
- lymph node involvement(T2N2bM0)
- Unresectable
- Avoid chemotherapy due to risk of toxicity
- Proton RT to decrease dose to non-cancerous tissue
  - Reduce clinical target volume with only 8mm margin
  - Avoided irradiation of oral cavity, contralateral pharynx and
- Radiation was interrupted due to severe mucositis
  - requiring opioid pain medication and hyperalimentation
- Resumed to a total dose of 59.4 in 33 fractions over 71 days
- Unfortunately patient developed multiple lung metastasis as well as a left breast cancer invasive ductal carcinoma (T1N0M0)
- Despite the dose of RT being considered *sub-therapeutic* the primary oropharyngeal lesion remained stable at the time of death from lung metastasis 9 months after proton therapy

Mizumoto et al. Strahlenther Onkol 2013, 189:335-338.

AML after treatment for ALL in girl with BS

9 yo girl who was small and dysmorphic presented with pancytopenia and bruising diagnosed with B cell ALL

- During induction developed painful photosensitive rash

  →BS testing and diagnosis
- Morphological remission but with +MRD so changed to high risk therapy
- VCR, dex doses reduced to 50% due to GI sensitivity and HTN
- Intensification with 25% cyclophosphamide, 66% cytarabine doses, No anthracyclines
- Completed 2 years of chemo with maintenance that had frequent modification
- 16 months post-ALL therapy developed pancytopenia-No evidence of ALL but developed **MDS**
  - Treated with low dose cytarabine to try to delay progression to AML
- Progressed to **secondary AML** with short latency
  - Despite low doses fludarabine/ARAC developed severe myelotoxicity and severe mucositis
  - Died 3 weeks later

Adams et al. J Genet Syndr Gene Ther. 2014; 4(8):

Our Experience: High Risk ALL in girl with BS

13 year old F with BS with High Risk pre-B cell ALL

- Comorbidities at the time of diagnosis included:
  - Hypogammaglobulinemia on monthly IVIg
  - GERD on protonix
  - Type II Diabetes on metformin
  - Hypothyroidism on synthroid
  - Frequent sinus infections
  - History of frequent pulmonary infections on singular and albuterol as needed
  - Constipation on stool softeners as needed
- Planned modifications of therapy:
  - Avoid alkylators and anthracyclines
  - Use standard risk induction despite high risk disease
  - Reduction in individual doses due to concerns for toxicities
  - Reduction in number of doses of several agents
  - Use neupogen to decrease periods of neutropenia
  - Supplemental IVIg to keep IgG level > 700

Despite dose reductions and modifications: Toxicities out of proportion to doses

- Even with significant reductions experienced multiple toxicities
  - Severe vincristine neuropathy with bronchospasm, urinary obstruction, hearing loss as well as severe pain that required morphine/methadone
  - Intractable nausea (no vomiting do to h/o Nissan fundoplication)--????PAIN
  - Severe hyperglycemia despite metformin needing insulin
  - Severe hyperlipidemia with asparaginase
  - Early neutropenia and profound neutropenia to 6TG and 6MP
  - Prolonged periods of neutropenia complicated with pneumonia
  - Due to toxicity she skipped second half of consolidation, delayed intensification
- Maintenance complicated by infections and early and protracted cytopenias
    - Septic shock with Acinetobacter during maintenance 1
    - Klebsiella bacteremia
    - Recurrent UTIs despite daily prophylaxis
    - Thrush from the steroids and severe mucositis even with low dose oral MTX and leucovorin
  - Required significant modifications to maintenance cycles with short pulse doses of 6MP, dosing changed and neupogen to prevent infectious complications

Our experience: High Risk ALL in remission but….:

HR-ALL in remission with residual severe vincristine neuropathy

At age 17 she presented with mass in her right breast

- Diagnosed as a sarcoma phylloides tumor
- Underwent right mastectomy and reconstruction
- Now 22 with no evidence of Breast cancer 4 years from diagnosis and **ALL in remission for 9 years**

What is the risk to BLM carriers? Are there modifier genes that increase cancer risk that can be identified?

- **66 yo F AJ known BLM CARRIER with Breast cancer at 54 (tx with Sx+RT), mucoepidermoid carcinoma of the parotid at 64, and now with endometrial cancer**
  - No evidence of Lynch syndrome
  - Identified APCI1307K
  - History of polyps

- Identified APCI1307K in 2 out 3 Grandchildren
- **22 yo F with BS**
  - history of ALL and Breast cancer
  - Polyp
- **12 yo M with BS**
  - history of testicular tumor
  - No polyps on colonoscopy
- **20 yo F with BS** No APC mutation seen in
  - No personal history of cancer

-Is there a risk of cancer for BLM carriers?

-What is the risk of colon cancer with APCI1307K?

-What is the risk of other cancers with APCI1307K?

-Can we identify genes that will help us identify which BS patients will get cancer?

Summary of our experience

Individuals with BS have significant risk for developing cancer as well as sensitivity to the therapies necessary to treat them

- Remission induced with a fraction of normal doses
- In ALL we were able to complete modified therapy and sustain a long term remission

Molecular alteration of genomic instability leads to hypersensitivity to the treatment leading to greater side effects

- Like Down syndrome (DS) patients the cancer cells retain the susceptibility to chemotherapy and make the cancers inheritantly more sensitive to therapy
  - It is known that children with DS have a better outcome utilizing less intensive chemotherapy regimens
  - DS tolerate the more intensive regimens less well

??? Molecular alteration of genomic instability results in hypersensitivity of the normal and tumor cells to the treatment which translates into lower doses can be used in BS to treat cancer

Gamms et al, PBC 2005,44(1):13-20.

Treatment Recommendations:

Avoid anthracyclines or alkylators

- Due to risk of secondary malignancy and cardiac damage
- If using start low (<50%) and give with cardioprotective agents

Dose modifications

- Start lower and escalate as tolerated
- 40-60% doses of other agents including vincristine, mercaptopurine and methotrexate
- Clinician must monitor closely for toxicity with increased vigilance as further dose modifications may be required to complete therapy

Supportive care

- Vigilant mouth care
- Immunoglobulin support to keep level above 700 start when lower than 400
- Consdier glutamine to prevent mouth sores and allow for higher doses of vincristine

Avoid radiation

- Minimize ct scan, xray and pet/ct
- Use MRI, ultrasound, or Pet/MRI when absolutely necessary

PARP inhibitors in DNA repair disorders

- PARP1 (poly ADP ribose polymerase) repairing single-strand breaks
  - unrepaired single strands during replication→ds breaks
  - BRCA1, BRCA2 and PALB2 are proteins that are important for the repair of dsDNA breaks
- Mutations→errors in DNA repair → cancer.
- PARP1 inhibitors cause multiple double strand breaks to form →interferes with replication, causing cell death in cancer cells while normal cells can recover
  - Tumors with BRCA1, BRCA2 or PALB2 mutations cannot repair ds breaks →leading to the death of the cancer cells.
  - Normal cells can survive PARP inhibition
  - don't replicate their DNA as often as cancer cells
  - don't have the mutated BRCA1/2→ still have homologous repair operating
- How would a BS patient handle a PARP inhibitors??
- Is there a role for pre-emptive therapy for BS patients?

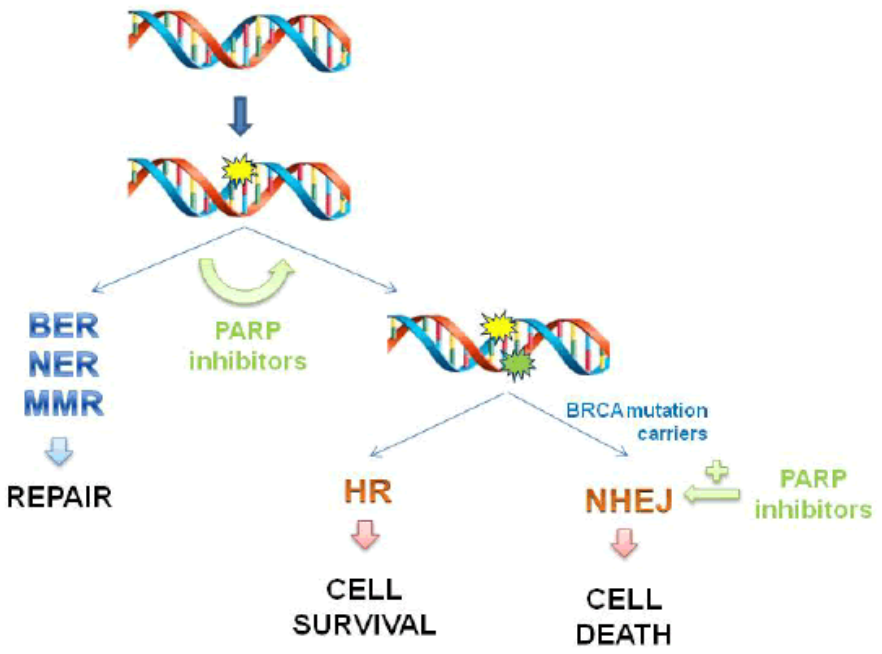


Figure 6: PARP inhibitors functions and DNA repair mechanisms. When a SSB occurs, the repair is accomplished by BER, NER and MMR. If BER is impaired, through the inhibition of PARP, single strand breaks become double strand breaks. In patients with HR defects, such as a *BRCA* mutation carrier, this damage causes the cancer cell death since PARP inhibitors induce aberrant activation of NHEJ.

Cancer. J Cancer Sci Ther 2013, 5:409-416.
Haematologica 2008; 93:1886-1889.

Thank you to the incredible families who have allowed me to care for their children.

They taught me everything I know about Bloom syndrome and gave me the gift of the most valuable lesson--how to approach life with a positive attitude.