Treatments and Their Effects

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Types of treatment effects

- Early effects (during treatment generally)
- Late effects (occurring as a result of the treatment, but years later)

- I will focus on specific treatments used and highlight particular commonly used drugs in our lymphoma and CLL regimens

- Won’t be comprehensive, and I won’t be speaking about side effects of supportive medications

Low blood counts

- Some regimens are more likely than others to cause myelosuppression
- Myelosuppression is bone marrow suppression resulting in low white blood cell, red blood cell and platelet counts
- Higher risk with more intensive regimens
- Higher risk if one is starting off with low blood counts or bone marrow involvement with lymphoma
- Higher risk if you have had chemotherapy before

Low blood counts : neutropenia

- Neutropenia = low neutrophil count
- Important in fighting infections, particularly bacterial
- Most treatments require your neutrophil count to be >1.0 before a subsequent treatment is given
- Can be boosted up with growth factor injections such as Lapelga or grastofil
- Exception is ABVD – can treat even with low count

Low blood counts: anemia

- Anemia occurs when your hemoglobin is low
- When chemo-related, it is not helped by taking iron or vitamin B12
- Sometimes we use blood transfusions if the hemoglobin is quite low and/or there are symptoms from it
- Can also use growth factor injections for red blood cells
- Improves once treatment stops and bone marrow can recover

Low blood counts: thrombocytopenia

- Occurs when your platelet count is low
- Platelets help to prevent bleeding
- This is usually caused by chemotherapy
- Can also be low due to bone marrow involvement with lymphoma, or due to an enlarged spleen
- Rarely may lead us to delay a chemo treatment to allow it to rise up
- There is no growth factor to boost platelets
- We can give transfusions if they are very low and avoid blood thinners if they are too low

Anthracycline effects eg RC**H**OP and **A**BVD

- Sometimes referred to as the “red devil” chemo
- Developed in the 1960’s, utilized for many cancers
- Same drug, different names: Adriamycin=Doxorubicin=Hydroxydaunomycin
- Can cause heart muscle weakness detected on an echocardiogram, usually years after treatment but sometimes sooner
- We do baseline echo testing in everyone > 55 yrs even if no cardiac history
- Cardiac toxicity is dose-related, 3-5% if dose is under 400mg/m2 (for reference, 6 cycles of RCHOP or ABVD is 300mg/m2)
- Other side effects: hair loss, nausea, low blood counts

Peripheral Neuropathy

- Nerve ending damage that can result in the feeling of numbness or tingling in fingers or toes
- Can be painful and occasionally lead to weakness – decreased hand grip, foot drop, issues with balance
- Very common to result in chemo dose reduction or drug discontinuation
- Not always reversible
- There exists no clear prevention. Higher risk if one already has neuropathy (eg, from diabetes or otherwise) or if one has an inherited form of neuropathy
- Associated with many cancer drugs: Vincristine (Oncovin, in RCHOP), Vinblastine in ABVD, Brentuximab, Platinum-based drugs (in DHAP or GDP), Etoposide, Pembrolizumab. (does not occur with Bendamustine /Rituxan)
- An important contributor to impaired quality of life in cancer survivors

Constipation

- A side effect from various treatments most notably vincristine and vinblastine – usually for the first few days to week after the chemo
- Also can be caused by antinauseant ondansetron (zofran)
- All narcotics cause constipation (codeine, dilaudid/hydromorphone, morphine, tramadol)
- Various prescription and over the counter treatments and prevention exist – talk to your medical team for advice
- During chemo, generally enemas and suppositories are not recommended

Rituxan side effects

- Infusion reactions with first IV infusion in up to 50%. Less with subsequent subcutaneous injections. Most of the time we can manage these and continue with Rituxan
- Can cause low neutrophils (neutropenia), though usually we assume it is the chemo causing it (eg in BR, RCVR or RCHOP regimens)
- When used by itself as maintenance for some low grade lymphomas, sometimes the neutropenia can be severe and prolonged – even a year
- Increased risk of infections, potential to reactivate dormant infections like Hepatitis B or TB for example. Very rare risk of PML (progressive multifocal encephalitis from JC virus reactivation)
- Maintenance Rituxan results in prolonged immune suppression due to B –cell depleting effects – increased risk of infections, potentially increased severity of infections, and impaired vaccine response for up to 6-9 months afterwards

Bendamustine and rashes

- Rash can be a relatively common side effect (up to 25%)
- Can look like insect bites (hives) or can cause diffuse skin redness and rash
- If mild, managed with antihistamines and steroid cream
- Sometimes requires oral steroid like prednisone
- At its worst, can cause a severe blistering rash and fevers to the point that we discontinue giving Bendamustine

- *note that a blistering rash on one part of your body could be shingles*

Lung toxicity

- Can be associated with Bleomycin (ABVD), Pembrolizumab, chest radiation
- Rarely from Rituxan
- Presently, much less Bleomycin is used overall as we are either using Brentuximab-AVD instead of ABVD, or we only use it in the first two cycles of ABVD instead of in all 6.
- Risk factors for lung toxicity are higher age, smoking and prior lung disease
- In patients at higher risk we may do baseline lung function tests before starting ABVD

Side effects of oral therapies eg BTK inhibitors Ibrutinib, Acalabrutinib, Zanubrutinib

- Daily oral continuous therapies used in CLL and in some lymphomas
- In CLL, often used as first line therapy today
- In some low grade lymphomas (Waldenstrom, marginal zone) used mostly in second line
- Combination studies underway combining them with frontline chemoimmunotherapy eg Bendamustine+Rituxan+BTKi
- Potentially taken for years on end

BTKI side effects: spotlight on cardiac and bleeding effects

- Increased risk of high blood pressure
- Increased risk of heart rhythm abnormalities, mainly atrial fibrillation
- Potentially may affect cardiac muscle function
- The newer versions of BTKi seem to have less cardiac side effects

- Increased risk of bleeding and bruising
- Particularly an issue when needs to be combined with certain blood thinners

Brain Fog/Chemo Brain

- Very common
- Probably the most troubling side effect of all
- Similar to brain fog experienced by long COVID sufferers
- Affects concentration, focus, short term memory
- Does not turn into dementia
- Usually improves with time
- Getting a good sleep, proper nutrition, physical activity and social interactions are important
- Exercise your brain (crossword, Sudoku, reading)
- Set reminders, keep notes, make lists

Late Effects

- Sometimes chemotherapy or radiation can cause damage that only shows up months or years (even decades) after the treatment
- This results in the development of a new (secondary) medical condition or issue that can be related to the treatment that was given
- Some of these risks are very treatment-specific while others can be more generalizable
- Sometimes, individual risk factors can weigh in on the likelihood of a late effect occurring

Fertility

- With lymphoma treatments, high dose therapy (such as doses used when undergoing stem cell transplantation) generally results in permanent male and female infertility
- Standard-dose treatments (RCHOP, ABVD, BR) generally don't, but consideration of fertility preservation and a consultation with the fertility clinic is often offered when time permits prior to chemo
- Temporary cessation of menstrual periods during chemo is common. Early menopause in women is rare (5%) with RCHOP, but occurs more frequently in those >40 years of age
- Sperm, egg or embryo freezing can be considered as an "insurance" in case chemotherapy dose-escalation is required mid-way, or if a relapse occurs and high dose therapy is considered

Heart disease following radiotherapy to the chest (mediastinal radiation)

- Can result in higher risk of coronary artery disease/CAD (can lead to angina or heart attack) due to effects of radiation on the arteries of the heart
- Usually takes 10+ years to be apparent
- Called “premature coronary artery disease” because it occurs earlier than one would expect (late CAD is diagnosed at >55 years of age in men and >65 yrs in women)

Premature CAD and chest radiation AKA Radiation-Induced Coronary Artery Disease (RICAD)

- Most commonly seen after breast cancer radiation due to the frequency of breast cancer
- In lymphoma, radiation is used in some Hodgkin lymphoma regimens and less commonly in NHL
- RICAD takes 10-15 years to develop
- The risk is increased if prior risk factors, younger age at treatment and higher radiation dose/volumes
- Individual risk factors that increase risk of CAD are smoking, diabetes, high blood pressure, elevated cholesterol, elevated body mass index, sedentary lifestyle
- Nonmodifiable risk factors are age, gender, ethnicity and family history of heart disease

How should you be monitored for heart disease after radiation?

- There is no validated guideline for follow-up
- Recommendations are to continually monitor cardiac risk factors, optimize and/or treat risk factors
- Take any potential cardiac symptoms seriously
- Consider some kind of cardiac stress testing at 10-15 years post radiation and perhaps every 5 years thereafter
- * consider neck/carotid artery ultrasound* as some chest radiation protocols include lower neck, as a screening test for carotid artery blockage and stroke risk

Radiation-induced second cancers
Example: breast cancer after chest radiation for lymphoma

- Breast cancer is increased in women who are treated with chest radiation before menopause
- Higher risk is when radiation occurs under age 30, highest in children
- Depends on dose given; likely any type of radiation increases risk
- Screening recommendations exist for adults treated with chest radiation: begin breast imaging 8 years following radiation, or at age 40, whichever occurs first. Combination of breast MRI and mammogram used for screening
- In Ontario, your doctor can register you on the high risk breast cancer screening program if you meet criteria

Other radiation-induced cancers

- In smokers, chest radiation increases the risk of lung cancer
- The risk in nonsmokers is less clear

- The type of radiation-induced cancer depends on where the radiation is aimed, eg if it involves neck, can increase risk of thyroid cancer

- Lung cancer screening is not universally recommended.
- Can consider annual chest X rays in smokers
- (Having chest radiation doesn’t qualify one for the Ontario high risk lung cancer screening program – that is aimed at smokers)

Chemotherapy-induced cancers

- Main issue can be higher risk of myelodysplasia
- Cyclophosphamide can increase the risk of bladder cancer
- Patients with CLL have a higher risk of second cancers in general, likely primarily due to immune dysregulation as well as therapies used

Therapy-related myelodysplasia and leukemia

- Chemotherapy and radiation treatment can cause bone marrow damage
- This can result in a new condition called myelodysplasia, which can sometimes turn into acute leukemia
- Myelodysplasia can occur in 1-5%, higher rates occur after transplant than after conventional doses of chemotherapy
- It is diagnosed with a bone marrow biopsy
- Treatment can include transfusions, other types of chemo or targeted therapies and stem cell transplantation using a donor

What can I do to stay healthy years after treatment?

- Ideally, have a family doctor who can organize an annual CBC blood count, and keep you on track with routine cancer screening as you age and check you for cardiac risk factors as needed
- The exception to routine cancer screening is the high risk breast cancer screening recommended for women particularly if chest radiation was given under age 30-40
- Smoking cessation is imperative
- Use sun block
- Follow a healthy diet, minimize alcohol consumption
- Exercise regularly