Management of adverse effects of the chemotherapy used for treating lymphoma/CLL

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“Potential” conflicts of interest (over the last 36 months)

- Lectures
  - Pharmaceutical companies involved in oncology
    - Lundbeck, Celgene, Novartis, Seattle Genetic (CANCER evenings)
    - Janssen, Pfizer (ONCible), Alexion, Amgen, Abbvie, Apobiologix
  - Professional organizations
    - APES, Familiprix, APPSQ

- Advisory Committee: Gilead, Roche, Takeda, Abbvie, Janssen

No conflict of interest associated with today’s presentation
Objectives

#1 Discuss various adverse effects in the classes of agents used in treating lymphoma/CLL
   - “traditional” chemotherapy, targeted therapies, Immunotherapy, corticotherapy

#2 Discuss the management of the main adverse effects encountered in chemotherapy
   - Nausea/vomiting, neutropenia/infections
   - Ulcers, hair loss, fatigue

#3 Know reliable documentary sources
Plan

- Introduction and basic principles
- Conventional chemotherapy
  - Mechanism of action/Classes
  - Main side effects
  - Management
- Targeted therapies
- Immunotherapy and corticotherapy
- Toolbox
  - Handling oral therapies
  - Sources of information
- Conclusion
Introduction and Basic Principles

BEFORE GETTING INTO THE REAL ISSUES!
Introduction
Treatment modalities

CANCER

Chirurgie
(pas pour les cancers hématologiques)

PATIENT

Anti-cancer drugs
(option most often used for treating lymphomas/CLL)

Radiotherapy
(for localized stages)
Introduction
How it all started

- 1919: US MD serving in France during World War I evaluated the effects of mustard gas
  - Effects on the lymphatic system
  - ↓ GB in surviving soldiers
  - Death from immunosuppression

- 1942: Goodman and Gilman administered nitrogen mustard to patients with lymphoma
  - After the autopsy of dead soldiers exposed to sulphurous mustard

Liberty Ship SS John Harvey
Bari Raid, Italy 1943

E.B. and H.D. Krumbhaar, ca. 1918.
**Introduction**

**Rapid growth of research**

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<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen mustards</td>
<td>MTX</td>
<td>6-MP</td>
<td>Busulfan</td>
<td>CBL</td>
<td>VCR</td>
<td>Cyclophosphamide</td>
<td>5-FU</td>
</tr>
</tbody>
</table>

Thousands of molecules investigated but very few with clinical applications

Discovery of new therapeutic targets = New mechanisms of action
Introduction
Basic Principle #1

It is **impossible** to put all the anti-cancer drugs in the same basket (efficacy/adverse effects)

- Adverse effects are **generally** related to the drug’s mechanism of action
  - Differences between the agents of the same class

- Cytotoxic agents
- Corticotherapy
- Targeted therapies
- Immunotherapy

- Chemotherapy
Introduction

Basic Principle #2

Everyone reacts differently to chemotherapy

- Every drug can cause one or more side effects, **but that does not mean that they will continue**
  - When teaching, a pharmacist talks about adverse effects
    - The most frequent are ≥ 10% (1 patient out of 10) and/or
    - The most severe that are generally very rare < 1% (1 patient in 100)

- Certain factors can ↑ or ↓ the risk of undesirable effects
  - Patient: age, sex, etc.
  - Protocol: Number of agents, doses, frequency, cycle number

Introduction
Basic Principle #3

Intensity of adverse effects varies from patient to patient

- Health professionals track their intensity
- Grade I to IV with the CTCAE scale (v4.03)
  - Grade I = no intervention (low intensity)
  - Grade IV = hospitalization necessary (high intensity)

<table>
<thead>
<tr>
<th>Grade</th>
<th>1 (low)</th>
<th>2 (moderate)</th>
<th>3 (severe)</th>
<th>4 (very severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of neutrophil count (in the blood) sang</td>
<td>LLN – 1.5 × 10⁹/L</td>
<td>1.49-1.0 × 10⁹/L</td>
<td>0.99-0.5 × 10⁹/L</td>
<td>&lt; 0.5 × 10⁹/L</td>
</tr>
<tr>
<td>Mucositis (mouth ulcers)</td>
<td>Asymptomatic, Mild symptoms</td>
<td>Moderate pain while eating, Modification of diet</td>
<td>Severe pain, difficulty eating</td>
<td>Very severe, Unable to eat</td>
</tr>
</tbody>
</table>
Adverse effect management varies from situation to situation

1. **Modify the current treatment**
   - Reduce the chemotherapy dose (e.g. neuropathies 2nd vincristine)
   - Stop or change treatment (if adverse effects very severe)
   - Delay the next cycle (allow the body time to recover)

2. **Add support drugs or treatments**
   - ↓ Duration of symptoms and/or severity (e.g.: loperamide vs diarrhea)
   - Prevent recurrence of an undesirable effect (e.g. G-CSF if fever)

3. **Closer follow-up** (medical appointment or blood test)
## Basic Principle #5

**Presentation of adverse effects varies over time**

### Cytotoxic chemotherapy

<table>
<thead>
<tr>
<th>0</th>
<th>7-10 d</th>
<th>14-21 d</th>
<th>m</th>
<th>y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Diarrhea, Ulcers</td>
<td>Hair loss</td>
<td>Neurotoxicity</td>
<td>Cardiac toxicity</td>
</tr>
<tr>
<td>Vomiting</td>
<td>↓ Immune system ↓ Platelets</td>
<td></td>
<td>Fatigue Anemia</td>
<td>Infertility</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>Urine coloration (anthracyclines)</td>
<td></td>
<td></td>
<td>Secondary cancers</td>
</tr>
</tbody>
</table>
Introduction
Basic Principle #5 (cont’d)

Immunotherapy (anti-CTLA-4)

- Rash, pruritis
- Liver toxicity
- Diarrhea, colitis
- Hypophysitis

What do patients consider the most feared adverse effects?

Larruso D et al., Eur J Cancer Care (Engl). 2017 Mar;26(2)
Introduction
Patient’s perception

- Questionnaire completed by 761 Italian cancer patients receiving a treatment

<table>
<thead>
<tr>
<th>Before starting chemotherapy, what were the adverse effects you were most afraid of?</th>
<th>During chemotherapy, what were the adverse effects that were the most unbearable?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting (≈ 60%)</td>
<td>Nausea/vomiting (≈ 45%)</td>
</tr>
<tr>
<td>Hair loss (≈ 52%)</td>
<td>Fatigue (≈ 40%)</td>
</tr>
<tr>
<td>Fatigue (≈ 25%)</td>
<td>Hair loss (≈ 33%)</td>
</tr>
<tr>
<td>Taste/Infections (≈ 10%)</td>
<td>Taste (21%)</td>
</tr>
<tr>
<td>Diarrhea/other (&lt; 10%)</td>
<td>Constipation (12%)/Other (&lt; 10%)</td>
</tr>
</tbody>
</table>
Conventional Chemotherapy

MECHANISM OF ACTION/CLASSES
MAIN ADVERSE EFFECTS
MANAGEMENT
Conventional chemotherapy
Mechanism of action

**Goal:** Disrupt cell division
- Affects all cells that divide (non-specific)
- Action differs by therapeutic class
- Tumor cells are most affected because they divide more quickly than the body’s “good” cells
  - Normal cells: toxicity/Tumor cells: efficacy

Allows combining agents with a different effect on cell division

Ex: CHOP in treating aggressive lymphoma
Conventional chemotherapy
Agents by class

- Principal cytotoxic agents used in treating lymphomas/CLL
  - Arranged by class (for information purposes)
  - Allows a better understanding of the adverse effects

<table>
<thead>
<tr>
<th>Alkylation agents</th>
<th>Topoisomerase 2 inhibitors</th>
<th>Anti-metabolites</th>
<th>Anti-microtubules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine/Melphalan</td>
<td>Etoposide</td>
<td>Cytarabine</td>
<td>Vincristine</td>
</tr>
<tr>
<td>Dacarbazine/Chlorambucil</td>
<td>Doxorubicin</td>
<td>Fludarabine</td>
<td>Vinblastine</td>
</tr>
<tr>
<td>Cyclophosphamide/Ifosfamide</td>
<td></td>
<td>Gemcitabine</td>
<td></td>
</tr>
<tr>
<td>Carboplatin/Cisplatin</td>
<td></td>
<td>Methotrexate</td>
<td></td>
</tr>
</tbody>
</table>
Conventional chemotherapy
Adverse effects by class

<table>
<thead>
<tr>
<th>Adverse effects (&gt; 10%)</th>
<th>Alkylating agents</th>
<th>Topoisomerase Inhibitors</th>
<th>Anti-metabolites</th>
<th>Anti-microtubules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>Moderate/High</td>
<td>Moderate</td>
<td>Low</td>
<td>-</td>
</tr>
<tr>
<td>↓ Immune system</td>
<td>Low to Moderate*</td>
<td></td>
<td></td>
<td>Very low</td>
</tr>
<tr>
<td>hair loss</td>
<td>Partial</td>
<td>Partial/Total</td>
<td>Little</td>
<td>-</td>
</tr>
<tr>
<td>Mucositis/ulcers</td>
<td>Low to Moderate*</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>-</td>
</tr>
<tr>
<td>Constipation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Moderate</td>
</tr>
<tr>
<td>Neuropathies</td>
<td>Cisplatin/carboplatin</td>
<td>-</td>
<td>-</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

**Non-exhaustive list**
- Cardiac toxicity (doxorubicin)
- Secondary cancer > 10 years (very rare)
- Infertility (variable depending on agents/doses)

*Variable depending on agents and doses

↓ Magnesium (carboplatin/cisplatin)
↓ Hearing (cisplatin)
Red urine (doxorubicin)
NVIC management
Why is there N/V?

Administration of chemotherapy
- Release of neurotransmitters ($M_1$, 5-HT, DA, NK)
- Stimulates the trigger zone in the brain
- Sends a signal to the vomiting centre
- Body reacts by vomiting

Several targets to for stopping the N/V signals

Important to know the type of Nausea/Vomiting Induced by the Chemotherapy (NVIC) because the treatment varies.

- Importance of the questionnaire administered by the nurse/pharmacist/MD

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Target to block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>&lt; 24h after chemotherapy</td>
<td>NK, 5-HT</td>
</tr>
<tr>
<td>Delayed</td>
<td>24 to 120h after chemotherapy</td>
<td>D₂, NK, M₁</td>
</tr>
<tr>
<td>Anticipatory</td>
<td><strong>BEFORE</strong> chemotherapy (conditioned by the stress or anxiety after a bad experience)</td>
<td>Stress/ anxiety</td>
</tr>
<tr>
<td>Resistant</td>
<td>Occurs in spite of the therapy given</td>
<td>Other targets</td>
</tr>
</tbody>
</table>

AN OUNCE OF PREVENTION IS WORTH A POUND OF CURE

Nowadays, it is **UNACCEPTABLE** to target anything other than the **COMPLETE** absence of nausea and vomiting

- Drug adjustment to reach this target
NVIC management

Agents used

NVIC treatment and prevention

5-HT₃ antagonists
- Granisetron (Kytril MD) po/IV
- Ondansetron (Zofran MD) po/IV
- Palonosetron (Aloxi MD) po/IV

Corticosteroids
- Dexamethasone po/IV

NK₁ antagonists
- Aprepitant (Emend MD) po
- Fosaprepitant (Emend IV MD) IV

Dopamine (D₂) antagonists
- Metoclopramide po/IV
- Prochlorperazine (Stemetil) po/IR
- Olanzapine (Zyprexa MD) po

Histamine (H₁) antagonists
- Dimenhydrinate (Gravol MD) po/IV/IR

Benzodiazepines
- Lorazepam (Ativan MD) po/IV

Cannabinoids
- Nabilone (Cesamet MD) po

Non-exhaustive List
# NVIC Management

## NVIC – IV chemotherapy

### Sévère > 90 %
- Cyclophosphamide > 1.5 g/m²
- Doxorubicine
- Etoposide
- Ifosfamide > 10 g/m²
- Melphalan
- Méthotrexate (≥ 1 g/m²)
- Streptozocine

### Modéré 30-90 %
- Cytarabine > 1 g/m²
- Dacarbazine (DTIC)
- Daunorubicine
- Irinotécan
- Mitotane
- Oxaliplatin
- Temozolomide
- Trabectedine

### Léger 10-29 %
- 5-Fluouracil bolus
- Irinotécan
- Lapatinib
- Nab-paclitaxel
- Pemetrexed
- Perlesun
- Trastuzumab-emtansine (Kadcyla)

### Faible < 10 %
- Fludarabine
- Gemcitabine
- Genetixumab ozogamicin
- Infusion de doxorubicine
- L-Asparaginase
- Mitostat
- Mitoxantrone
- Pegaspargase
- Peginterferon
- Pemtrexed
- Pertuzumab
- Ramucirumab
- Rituximab
- Tensirolimus
- Trastuzumab (Herceptin)
- Vinblastine
- Vincristine
- Vinorelbine

### Algorithme # 1

<table>
<thead>
<tr>
<th>Chimiothérapie à potentiel hautement émettisant (&gt; 90 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protocoles</strong></td>
</tr>
<tr>
<td><strong>A : Cisplatine &gt; 40 mg/m²</strong></td>
</tr>
<tr>
<td>• Aprépitant 125 mg po</td>
</tr>
<tr>
<td>• Ondansétron 24 mg po o</td>
</tr>
<tr>
<td>• Dexaméthasone 12 mg po o</td>
</tr>
<tr>
<td>• *Olanzapine 10 mg o</td>
</tr>
<tr>
<td>• Lorazépam 1 mg po prn</td>
</tr>
<tr>
<td><strong>B : Cisplatine ≤ 40 mg/m² et AC et FEC-100 en cancer du sein</strong></td>
</tr>
<tr>
<td>• Aprépitant 125 mg po</td>
</tr>
<tr>
<td>• Ondansétron 24 mg po o</td>
</tr>
<tr>
<td>• Dexaméthasone 8 mg po o</td>
</tr>
<tr>
<td>• *Olanzapine 10 mg o</td>
</tr>
<tr>
<td>• Lorazépam 1 mg po prn</td>
</tr>
<tr>
<td><strong>C : SANS cisplatine</strong></td>
</tr>
<tr>
<td>• Ondansétron 24 mg po o</td>
</tr>
<tr>
<td>• Dexaméthasone 16 mg po o</td>
</tr>
<tr>
<td>• Lorazépam 1 mg po prn</td>
</tr>
</tbody>
</table>

### Si échec à la thérapie standard

- Considérer l’ajout d’une dose d’ondansétron 8 mg po sous séquence 12 heures post-chimiothérapie ou modifier l’ondansétron en pré-chimiothérapie pour le granisetron 1 mg IV
- Considérer l’ajout de métoploclamamide 30 mg (ou 0.5 mg/kg) + diphydramine 25 à 50 mg IV post-chimiothérapie

### Algorithmes 1C :
- Considérer l’ajout d’aprépitan qui indiqué

### Après 24 heures
- S’assurer de la prise adéquate des antiémétiques
- Prise régulière de prochloréprazine ou métoploclamamide si indiqué
- Considérer l’ajout d’apprépitan ou de l’olanzapine (2.5 à 5 mg po pré-chimio, 2.5 à 5 mg po le soir de la chimio puis 5 à 10 mg po par jour x 3 jours) ou autre thérapie selon le cas

*Exceptions :
- GP : Utiliser l’algorithme 1C et OMETTRE la dexaméthasone PRÉ et POST chimiothérapie (déjà incluse dans le protocole). Considérer l’ajout d’emblée de l’olanzapine (ex : si nausées par le paquet).*

Algorithm 2, 3 and 4 available on the GEOQ site (support care section)
Since each agent (or protocol) has a different NVIC potential, the preventive therapy will be adapted accordingly.

- Take the prescribed drugs **as needed** if nausea/vomiting.
- Otherwise, the longer you wait, the harder it is to treat!

Anti-NVIC drug management is usually the job of the pharmacist (varies from hospital to hospital).

1st chemotherapy cycle is a good indicator:

- If no N/V: Keep the same therapy (it’s working!)
- If N/V: Change the preventive therapy (it’s not working!)
Infection risk
Definition of neutropenia

- Neutropenia = low point 7-10 days post-chemo (dose-dependent effect)
  - CSF tracking is variable, depending on the protocol

- ↑ Risk of clinically **significant** infection when neutrophils < 0.5 x 10^9/L for a period ≥ 7 days
  - According to groups of experts, the neutropenia threshold may vary

- This is the **principal criterion** predicting the risk of NF
  - Justifies or not the use of G-CSF

Growth factor or white cell food
Risk of infection
Febrile neutropenia

Possible complication of chemotherapy
- Presence of fever in a patient with neutropenia (n < 0.5)
  - Fever = ≥ 38.3 °C x 1 OR between 38 and 38.2 x 2 (1 hour interval)
- Most due to bacteria from the human body
- Variable risk depending on the chemotherapy (e.g. R-CHOP ≥ 65 years)

It is a medical emergency (15-20 min. wait)!
- Rapid management by initiating a broad-spectrum antibiotic to avoid complications (sepsis, death, etc.)
- ≈ 50-60% in blood bacteria/no suspected sources

Mortality of 2 to 21% (depending on the studies)
Risk of infection
Use of G-CSF

1st step: Evaluate the risk of febrile neutropenia (FN) from chemotherapy

Risk of FN must be routinely evaluated before each cycle

Low risk (< 10% of FN)
- Prophylactic G-CSF not recommended

Moderate risk (10-19% of FN)

2nd step: Identify and evaluate the FN risk factors

- Age ≥ 65 years and anthracycline + alkylating combination (e.g.: AC, CHOP)
- Persistent neutropenia (2nd or other chemotherapy)
- Significant cytopenia caused by bone marrow damage
- Prior bone marrow radiotherapy
- Open wounds, active infection or serious risk of infection
- Significant comorbidities*, poor functional index or nutritional assessment

Moderate overall risk (10-19% of FN)

High risk (≥ 20% of FN)
- Prophylactic G-CSF RECOMMENDED

* Pulmonary, cardiovascular, liver, kidney disease (CICr < 50 mL/min), uncontrolled diabetes

Eur J Cancer 2006;42:2433-53
Risk of infection
Use of G-CSF

- **Secondary prophylaxis**
  - Patients with neutropenia in a prior cycle (with or without FN)

- **Variable clinical conduct depending on the clinical context**
  - Curable disease: Add G-CSF immediately (avoid later delay or complications)
  - Palliative disease: Consider ↓ doses or delay x 1 week

- G-CSF should not be used x 1-2 doses pour ↑ neutrophils pre-chemotherapy
  - No evidence to recommend this conduct
  - Chemotherapy should be given with G-CSF post-chemo **OR** be delayed x 7 days and then re-evaluated
Hair loss
What to know?

- Variable loss 2 to 3 weeks after 1st chemo cycle
  - Doxorubicin (R-CHOP)/autograft = Total hair loss
  - Other agents = No loss to partial loss

- Hair grows back 4 weeks after treatments end

- Avoid all elements that could precipitate hair loss
  - Use a mild shampoo
  - Avoid vigorous brushing
  - Avoid hair dyes (especially those with an alcohol base)

- Many patients use wigs/head scarves
Hair loss
Scalp Cooler

- Role of the scalp cooler or “scalp hypothermia”
  - ↓ Blood circulation = ↓ circulation of chemotherapy to the scalp
  - Old studies in the 80’s
    - Effective in 20 to 40% of patients
    - However: Few patients + doses lower v. today
    - For the others = delay in hair loss (according to the studies)

- Controversy on ↑ possibility of metastases in the brain
  - Could compromise the efficacy of the treatment

- For these reasons, used little or not at all in Québec

Dean J.C. et al., N Engl J Med 1979; 301:1427-1429
Ulcers/mucositis
Prevention and management

- Ulcers may appear 7 to 10 days after the chemotherapy

- Preventive: maintain good oral hygiene
  - Brush teeth gently and regularly
  - Brush manually with a soft brush
  - Gargle 4 times per day with a rinse
  - Gargle 4 times per day with a water and salt plus bicarbonate of soda mouthwash

- If you have an ulcer, notify your medical team
  - Goal: effectively relieve pain in order to avoid ↓ nutrition
Fatigue can have a major impact on your quality of life and depends on several factors:
- Blood-borne cancer, anemia
- Chemotherapy treatment, stress, lack of sleep
- Travel (medical, radiotherapy appointments)

Maintain a good level of activity but rest when you feel the need.
- Just don’t stay home all the time doing nothing!

Studies suggest that yoga (2 x 75 min/week) can be beneficial in reducing the fatigue associated with cancer in women with breast cancer.

Targeted therapies

MECHANISM OF ACTION/CLASSES
PRINCIPAL ADVERSE EFFECTS
MANAGEMENT
Targeted therapies
What’s that?

Monoclonal antibodies
- Large molecules targeting a receptor on the surface of the cancer cells
- Intravenous
  - MAB

Tyrosine kinase inhibitors
- Small molecules that block function inside the cancer cell
- Oral
  - NIB

Guide ONCible 2015
Over the last 20 years, the cancer therapy landscape has changed
- ⬆⬆ number of drugs that specifically target the mutated receptors involved in the growth of certain cancers
- Different toxicity profile depending on the targeted receptor
  - Impossible to speak of in detail in a 45-minute presentation
Targeted therapies
Number of targeted therapies

2001

Imatinib (Gleevec)
## Targeted therapies

### Number of targeted therapies

<table>
<thead>
<tr>
<th>Year</th>
<th>Oral</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Imatinib (Gleevec)</td>
<td></td>
</tr>
</tbody>
</table>
### Monoclonal antibodies

**Frequent adverse effects**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Frequent adverse effects &gt; 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab (Rituxan MD)</td>
<td>CD20</td>
<td>Reactions related to the perfusion (fever, chills, rashes, itching, difficulty in breathing, dizziness, hot flashes, etc.)</td>
</tr>
<tr>
<td>Obinutuzumab (Gazyva MD)</td>
<td></td>
<td>- ↓ Neutrophils/↓ Platelets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Numbness or prickling sensations in fingers and toes</td>
</tr>
<tr>
<td>Brentuximab (AdceterisMD)</td>
<td>CD30</td>
<td>- Diarrhea</td>
</tr>
</tbody>
</table>

**Brentuximab: Antibody is associated with 5 units of monomethyl auristatin E (MMAE)**

See Appendix II for a more exhaustive list of the antibodies used in cancer treatment.
Monoclonal antibodies
Reactions associated with the perfusion

Reactions associated with murine components

Rituximab

Reactions mainly with LLC because of rapid lysis

Obinutuzumab
Brentuximab
Ex: Panitumumab
Monoclonal antibodies
Reactions associated with the perfusion

- Reaction to the perfusion **very variable**, depends on the agent used
  - 2nd Molecular structure (e.g. murine v. humanized)
  - 2nd Mechanism of action (e.g. : Obinutuzumab = rapid and large lysis and major cause of the release of inflammatory cytokines)

- Monitoring of vital signs important (according to the protocol)
  - IV or PO pre-medication (e.g. benadryl, tylenol, prednisone)
  - Generally, slower administration of the 1st dose
  - Mandatory observation period for certain drugs

**RituxanMD**: hypotension and reactions associated with the perfusion (ad bronchospasm)
  - premedication (acetaminophen+diphenhydramine+prednisone)
  - very slow perfusion (#1) → if no reaction → accelerated (#2+)
  - vital signs: closely monitored
Tyrosine kinase inhibitors
Frequent adverse effects

- 40 molecules targeting > 20 different sites (see Appendix III)
- Identification of mutations sometimes necessary (CLL del17p)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Frequent adverse effects &gt; 5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idelalisib (Zydelig MD)</td>
<td>PI3Kdelta</td>
<td>- Nausea/vomiting, diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ↓ Neutrophils, ↓ Platelets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ↑ Liver enzymes, ↑ TG</td>
</tr>
<tr>
<td>Venetoclax (Venclexta MD)</td>
<td>BCL-2</td>
<td>- Nausea/vomiting, diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ↓ Neutrophils, ↓ Platelets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Tumor lysis syndrome, headaches</td>
</tr>
<tr>
<td>Ibrutinib (Imbruvica MD)</td>
<td>Bruton</td>
<td>- Atrial fibrillation, blurred vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ↓ Neutrophils, lymphocytosis, infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ↓ Platelets, minor bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Rashes, diarrhea</td>
</tr>
</tbody>
</table>

See Appendix III for a more exhaustive list of the tyrosine kinases used in cancer treatment
Examples of other adverse effects specific to targeted therapies (not in hematology)

- Cardiotoxicity (Trastuzumab, lapatinib)
- Hypomagnesemia (Cetuximab, panitumumab)
- Hypothyroidism (Sunitinib)
- Acne (Cetuximab, panitumumab, erlotinib, gefitinib)
- Swollen eyelids + legs (Imatinib)
- Hypertension, proteins in urine (Sunitinib)
- Change of hair colour
Immunotherapy and corticotherapy

MECHANISM OF ACTION
PRINCIPAL ADVERSE EFFECTS
MANAGEMENT
Immunotherapy
An overview!

- Mechanism of action: activation of the immune system “numbed” by the cancer cells
  - 2 molecules used (nivolumab/pembrolizumab)
  - Effect in a number of solid tumors

- Research underway in the treatment of NHL/leukemia
  - Used in some cases of refractory Hodgkin in several lines

- Adverse immune effects
  - 2nd immune system activation against our cells
  - Diarrhea, hepatitis, rashes, etc.
  - Treatment with cortisone necessary
    - Except if thyroid gland involved
Corticotherapy
An overview!

- Several uses in lymphoma/LLC
  - Stops lymphocytosis (chemo regimen)
  - Prevents/treats nausea and vomiting
  - Prevent reactions to the perfusion (e.g.: rituximab)
  - ↓ Pain, ↓ swelling 2nd cancer if brain affected

- Several adverse effects
  - Short term: increased appetite, heartburn, nervousness and difficulty sleeping, ↑ glucose in the blood
  - Long term: Cataracts, osteoporosis

- Helped by morning dose with food
Tool box

HANDLING ORAL THERAPIES
INFORMATION SOURCES
Information Sources

Reliable references

- GEOQ (www.geoq.com) - FR
  - Patient access = clinical tests underway in Québec
  - Patient advice not accessible to patients

- Cancer Care Ontario (www.cancercare.on.ca) - EN/FR

- BC Cancer Agency (www.bccancer.bc.ca) - EN
  - Very complete drug information records
  - Very fast update of new therapies

- Canadian Cancer Society (www.cancer.ca)
- Lymphoma Canada (www.lymphoma.ca)
- Cancer.net (www.cancer.net)
Information sources

Patient advice

- GEOQ
  - Advice in French and English
  - Adverse and frequent effects (> 10%)

- CCO
  - Advice in French and English
  - Adverse effects + exhaustive (sometimes too much)

- BCCA
  - Advice in English
  - Some leaflets in Mandarin/Punjabi

- Chemocare
  - Basic information on chemotherapy
  - Translation into several languages using Google Translate
Handling oral therapies
Precautions

- Oral therapies = Dangerous drugs (NIOSH 2016)
- Accidental contact if no precautions taken
  - Skin directly or indirectly (contact with biological liquids)
  - Ingestion or inhalation (crushing or cutting tablets)
- See Appendix IV: Precautions to apply
- See Appendix V: To avoid
Oral therapy handling
Precautions (cont’d)

- A number of tools available on line to help you
- If advice not given by the hospital pharmacist

See Appendix VI

Paper information sheet/PDF

Video available on line (4 sections)

#1 Manipulation sécuritaire/gestion déchets (7:15)
https://www.youtube.com/watch?v=5PwrvDPqQdM

#2 Assiduité au traitement (5:15)
www.youtube.com/watch?v=JQBQLo25iRY

#3 Gestion des effets secondaires (13:22)
https://www.youtube.com/watch?v=nBgQFxI3HzI

#4 Professionnels pour vous appuyer (5:52)
https://www.youtube.com/watch?v=gsaGQawzoog
Conclusion
What you should remember!

- There are a number of anti-cancer agent families
  - Cytotoxic agents, targeted therapies, immunotherapy, corticotherapy

- These can cause adverse effects in some patients
  - Variable intensity, presentation varies over time

- Management of adverse effects varies from one situation to another

- For more information, your oncology pharmacist and your team is there for you!
Appendix I

NVIC – IV Chemotherapy

Algorithm 2, 3 and 4 available on the GEOQ site (support care section)

OC PHARM 003 CHUM: Prévention et traitement des nausée et vomitting induits par la chemotherapy, 2016
Appendix I (cont’d)

NVIC – Oral chemotherapy

<table>
<thead>
<tr>
<th>Sévère &gt; 90 %</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexaméthylmélamine (Altrétamine)</td>
<td>Procarbazine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modéré 30-90 %</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Busulfan ≥ 4 mg/jour</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Grzitinib</td>
<td>Lenvatinib</td>
</tr>
<tr>
<td>Cyclophosphamide ≥ 100 mg/m²</td>
<td>Olaparib</td>
</tr>
<tr>
<td>Estramustine</td>
<td>Témozolomide</td>
</tr>
<tr>
<td></td>
<td>Vismodegib</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Léger 10-29 %</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>Étoposide</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>Évérolimus</td>
</tr>
<tr>
<td>Busulfan &lt; 4 mg/jour</td>
<td>Fludarabine</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>Lapatinib</td>
</tr>
<tr>
<td>Capécitabine</td>
<td>Lénalidomide</td>
</tr>
<tr>
<td>Cyclophosphamide &lt; 100 mg/m²</td>
<td>Palbociclib</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>Pomalidomide</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Faible &lt; 10 %</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>Melphalan</td>
</tr>
<tr>
<td>Chiorambucil</td>
<td>Mercaptopurine</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Méthotrexate</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Osimertinib</td>
</tr>
<tr>
<td>Géftinib</td>
<td>Pazopanib</td>
</tr>
<tr>
<td>Hydroxyurée</td>
<td>Ponatinib</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Régorafenib</td>
</tr>
<tr>
<td></td>
<td>Ruxolitinib</td>
</tr>
<tr>
<td></td>
<td>Sorafenib</td>
</tr>
<tr>
<td></td>
<td>Thalidomide</td>
</tr>
<tr>
<td></td>
<td>Thioguanine</td>
</tr>
<tr>
<td></td>
<td>Tramétinib</td>
</tr>
<tr>
<td></td>
<td>Vorfostat</td>
</tr>
</tbody>
</table>

**Algorithm #1**

Chimiothérapie à potentiel modéré à hautement émétisant *

* Utiliser cet algorithme d’emblée seulement pour : Témozolomide et Lomustine

<table>
<thead>
<tr>
<th>Pré-chimio</th>
<th>Post-chimio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansétron 8 mg po bid ou tid x 24 h ou granisétron 1 à 2 mg po</td>
<td>Prochlorpérazone 10 mg po/IR q 6 h prn ou métoclopramide 10 mg po q 6 h prn</td>
</tr>
</tbody>
</table>

**Si échec à la thérapie standard**

Dans les premières 24 heures

- S’assurer de la prise adéquate d’antiémétiques au besoin.
- Ajouter un agent d’une classe pharmacologique différente.

**Algorithm #2**

Chimiothérapie à potentiel léger ou faiblement émétisant

<table>
<thead>
<tr>
<th>Pré-chimio</th>
<th>Post-chimio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aucune</td>
<td>Prochlorpérazone 10 mg po/IR q 6 h prn ou métoclopramide 10 mg po q 6 h prn</td>
</tr>
</tbody>
</table>

**Si échec à la thérapie standard**

Dans les premières 24 heures

- S’assurer de la prise adéquate d’antiémétiques au besoin
- Utiliser algorithme 1 ou donner une dose de prochlorpérazone ou métoclopramide avant la chimiothérapie.
### Appendix II
Monoclonal antibodies

<table>
<thead>
<tr>
<th>Common name</th>
<th>Trade name</th>
<th>Target</th>
<th>Usual indications (examples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>Herceptin MD</td>
<td>HER2</td>
<td>Breast, stomach cancer (HER2+)</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>Perjeta MD</td>
<td>HER2</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Bévacizumab</td>
<td>Avastin MD</td>
<td>VEGF</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>Cyramza MD</td>
<td>VEGF</td>
<td>Esophageal cancer</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Rituxan MD</td>
<td>CD20</td>
<td>NHL, LLC</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>Gazyva MD</td>
<td>CD20</td>
<td>LLC</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>Arzerra MD</td>
<td>CD20</td>
<td>LLC</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Erbitux MD</td>
<td>EGFR</td>
<td>Colorectal, head and neck cancer</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Vectibix MD</td>
<td>EGFR</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>Empliciti MD</td>
<td>SLAMF7</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>Darzalex MD</td>
<td>CD38</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Blinatumomab</td>
<td>Blincyto MD</td>
<td>CD19/3</td>
<td>Refractory ALL</td>
</tr>
<tr>
<td>TDM1</td>
<td>Kadcyla MD</td>
<td>HER2</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>Adcetris MD</td>
<td>CD-30</td>
<td>Hodgkin lymphoma</td>
</tr>
</tbody>
</table>
## Appendix III
tyrosine kinase inhibitors

<table>
<thead>
<tr>
<th>Common name</th>
<th>Trade name</th>
<th>Target</th>
<th>Usual indications (examples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>Gleevec MD</td>
<td>BCR-ABL, c-kit</td>
<td>MCL, GIST</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Sprycel MD</td>
<td>BCR-ABL, c-kit</td>
<td>LMC</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Tasigna MD</td>
<td>BCR-ABL, c-kit</td>
<td>LMC</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>Bosulif MD</td>
<td>BCR-ABL, SCR</td>
<td>LMC</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>Iclusig MD</td>
<td>BCR-ABL</td>
<td>LMC</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Iressa MD</td>
<td>EGFR</td>
<td>Lung cancer (EGFR+)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Tarceva MD</td>
<td>EGFR</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Afatinib</td>
<td>Giotrif MD</td>
<td>EGFR</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>Xalkori MD</td>
<td>ALK</td>
<td>Lung cancer (ALK+)</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Zykadia MD</td>
<td>ALK</td>
<td>Lung cancer (ALK+)</td>
</tr>
<tr>
<td>Alectinib</td>
<td>Alecensa MD</td>
<td>ALK</td>
<td>Lung cancer (ALK+)</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Tykerb MD</td>
<td>Her2, EGFR</td>
<td>Breast cancer (HER2+)</td>
</tr>
</tbody>
</table>

Non-exhaustive list, certain targeted therapies have more than one therapeutic target and more than one indication.
## Appendix III

Tyrosine kinase inhibitors

<table>
<thead>
<tr>
<th>Common name</th>
<th>Trade name</th>
<th>Target</th>
<th>Usual indications (examples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>Inlyta MD</td>
<td>VEGF</td>
<td>Kidney cancer</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Sutent MD</td>
<td>VEGF, PDGF, c-kit</td>
<td>Kidney cancer, GIST</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Votrient MD</td>
<td>VEGF, PDGF, c-kit</td>
<td>Kidney cancer</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>Stivarga MD</td>
<td>VEGF, PDGF, c-kit</td>
<td>Meta-colorectal cancer</td>
</tr>
<tr>
<td>Vémurafénib</td>
<td>Zelboraf MD</td>
<td>BRAF</td>
<td>Melanoma (BRAF+)</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>Tafinlar MD</td>
<td>BRAF</td>
<td>Melanoma (BRAF+)</td>
</tr>
<tr>
<td>Trametinib</td>
<td>Mekinist MD</td>
<td>MEK-1/MEK-2</td>
<td>Melanoma (BRAF+)</td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>Cotellic MD</td>
<td>MEK-1/MEK-2</td>
<td>Melanoma (BRAF+)</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>Zydelig MD</td>
<td>PI3Kdelta</td>
<td>LLC</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>Venclexta MD</td>
<td>BCL-2</td>
<td>LLC</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>Imbruvica MD</td>
<td>Bruton</td>
<td>Lymphoma, CLL</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>Ibrance MD</td>
<td>CDK4 et CDK6</td>
<td>Cancer sein</td>
</tr>
</tbody>
</table>

Non-exhaustive list, certain targeted therapies have more than one therapeutic target and more than one indication.
## Appendix III
Tyrosine kinase inhibitors

<table>
<thead>
<tr>
<th>Common name</th>
<th>Trade name</th>
<th>Target</th>
<th>Usual indications (examples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus</td>
<td>Afinitor&lt;sup&gt;MD&lt;/sup&gt;</td>
<td>mTOR</td>
<td>Kidney cancer, GIST</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>Caprelsa&lt;sup&gt;MD&lt;/sup&gt;</td>
<td>VEGF, EGFR, RET</td>
<td>Thyroid cancer</td>
</tr>
<tr>
<td>Sorafénib</td>
<td>Nexavar&lt;sup&gt;MD&lt;/sup&gt;</td>
<td>VEGFR, PDGF, c-kit</td>
<td>Liver, kidney cancer</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>Erivedge&lt;sup&gt;MD&lt;/sup&gt;</td>
<td>Hedgehog pathway</td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>Cabometyx&lt;sup&gt;MD&lt;/sup&gt;</td>
<td>C-MET, RET, VEGR-2</td>
<td>Kidney cancer</td>
</tr>
</tbody>
</table>

Non-exhaustive list, certain targeted therapies have more than one therapeutic target and more than one indication.
## Appendix IV

### Oral therapy precautions

<table>
<thead>
<tr>
<th>TO DO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check the label (dose, name, dosage, etc.)</td>
</tr>
<tr>
<td>Understand when and how to take the drug (with or without food, etc.)</td>
</tr>
<tr>
<td>Store the drug according to instructions</td>
</tr>
<tr>
<td>Wash hands after handling</td>
</tr>
<tr>
<td>Reduce the number of people coming into contact with cytotoxic drugs</td>
</tr>
<tr>
<td>Caregivers must wear disposable gloves if handling or using a dispos</td>
</tr>
<tr>
<td>Ask for a separate pill organizer for the cytotoxic agents</td>
</tr>
<tr>
<td>Keep the information about the measures to take in case of accidental exposure</td>
</tr>
<tr>
<td>Return to the pharmacy any damaged, outdated or unused tablet for destruction</td>
</tr>
<tr>
<td>Inform the other health care professionals that you are taking oral chemotherapy (e.g. surgeons, dentists, etc.)</td>
</tr>
<tr>
<td>Flush twice when taking the drug and for 4 to 7 days afterwards.</td>
</tr>
<tr>
<td>Ask the pharmacist questions in case of uncertainty</td>
</tr>
</tbody>
</table>
Appendix V
Forms of handling to avoid

<table>
<thead>
<tr>
<th><strong>DO NOT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Crush, cut, pound or chew the tablets</td>
</tr>
<tr>
<td>Throw anti-neoplastic agents in toilets or garbage cans</td>
</tr>
<tr>
<td>Store where children might access them</td>
</tr>
<tr>
<td>Share drugs</td>
</tr>
<tr>
<td>Double or omit a dose</td>
</tr>
<tr>
<td>Store in a damp place or in direct sunlight or near food and beverages</td>
</tr>
<tr>
<td>Assume that there are no handling risks associated with oral chemotherapy</td>
</tr>
</tbody>
</table>

Appendix VI
PO CHUM chemo document

3-page advice leaflet
To attach to any document given to the patient


Kouroukis CT et al., Canadian supportive care recommendations for the management of neutropenia in patients with cancer, Curr Oncol 2008;15:9-23

Smith TJ et al., 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline J Clin Oncol 2006;24:3187-205

References (cont’d)

- Guide de prévention ASSTSAS 2008
- NIOSH list 2016 [https://www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf](https://www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf)
- Lalla RV et al., MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy, Cancer 2014 May 15;120(10):1453-61
- GEOQ ([www.geoq.com](http://www.geoq.com))