# BHS guidelines on supportive care in lymphoma: Part 1

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## SUMMARY

Besides disease-directed therapy, patients with lymphoma are in need of a wide range of supportive measures. In the first part of this guideline the use of anti-emetic therapy, the use of granulocyte colony stimulating factor (G-CSF) and antibiotic prophylaxis for pneumocystis jirovecii are discussed. In part 2 of this guideline we will discuss cardiac support, prevention and treatment of tumour lysis syndrome and the role of physiotherapy.
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## INTRODUCTION

In Belgium, lymphomas are the eighth most common malignancy and the most common haematological malignancy. They accounted for 3,8% of all new cancer diagnoses in 2020 and they are respectively the fifth and seventh most common cancer diagnosis in males and females based on incidence numbers.[1]

Treatment for lymphoma patients has undergone an increased complexity with several new agents available as therapy. These novel therapies increase the need for supportive care in this patient group. In this article we reviewed the current available literature on supportive care for lymphoma patients.

## ANTI-EMETICS

Chemotherapy induced nausea and vomiting (CINV) is a side effect that has a significant negative impact on the quality of life of patients and a willingness to comply with therapy. It can result in anorexia, electrolyte abnormalities, decreased performance status and nutritional deficiency. In most patient surveys, CINV remains one of the most severe adverse effects of chemotherapy.[2] Several categories of CINV are recognised: acute (<24 hours after start of chemotherapy), delayed (24-160 hours of start chemotherapy), breakthrough (occurring despite appropriate prophylactic treatment), anticipatory (occurring before a treatment as a conditioned response to chemotherapy) or refractory CINV.[3]

The complete mechanism of CINV is currently not yet fully understood. It is postulated that the emetic response on chemotherapy goes by two different pathways, a peripheral and a central pathway. The peripheral pathway is involved in the acute phase emesis, while the central pathway is mainly responsible for the delayed phase. The main mediator of the peripheral pathway is serotonin (5-HT3). The central mechanism can be divided into a

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**TABLE 1.** Emetogenic potential of single antineoplastic agents.

| Degree of emetogenicity* | Chemotherapeutic agent | Degree of emetogenicity* | Chemotherapeutic agent |
|---|---|---|---|
| High (>90%) | Cisplatin | Low (10 -30%) | Paclitaxel |
| | Cyclophosphamide ≥ 1500 mg/m² | | Docetaxel |
| | Carmustine | | Mitoxantrone |
| | Dacarbazine | | Doxorubicin (liposomal injection) |
| | Anthracycline/ cyclophosphamide | | Etoposide |
| Moderate (30 – 90%) | Oxaliplatin | | Methotrexate |
| | Cytarabine >1000 mg/m² | | Mitomycin |
| | Carboplatin | | Gemcytabine |
| | Ifosfamide | | Cytarabine <1000 mg/m² |
| | Cyclophosphamide < 1500 mg/m² | | 5-Fluorouracil |
| | Doxorubicin | | Temsirolimus |
| | Epirubicin | | Bortezomib |
| | Daunorubicin | | Thalidomide |
| | Idarubicin | | Lenalidomide |
| | Bendamustin | | Ibrutinib |
| | Clofarabine | | Brentuximab |
| | Alemtuzumab | Minimal (<10%) | Bleomycin |
| | | | Busulfan |
| | | | Fludarabine |
| | | | Vinblastine |
| | | | Vincristine |
| | | | Sorafinib |
| | | | Pomalidomide |
| | | | Rituximab |
| | | | Pembrolizumab |
| | | | Nivolumab |

**Percentage of patients vomiting by single use of the product.*

cortical pathway, which is mediated by dopamine and histamine, and the chemoreceptor trigger zone, which is mediated by all of the above mentioned, and substance-P.[2-4] Risk factors for CINV include female sex, age <55 years and anxiety. Alcohol intake seems to be inversely correlated with the risk on CINV. Other risk factors on CINV which are not patient-related are the emetogenicity of the chemotherapy used, dose, frequency and, if radiotherapy is used, the site of radiation.[2] The latest revision of the classification of the emetogenicity of commonly used chemotherapeutic agents was proposed by Grunberg *et al.* and can be found in *Table 1*.[5,6]

The first drugs with anti-emetic potential used in patients undergoing chemotherapy were dopamine-receptor antagonists, such as metoclopramide, prochlorperazine and haloperidol. Later on, the association of these with corticosteroids proved to be a more effective prophylaxis for CINV.[3] The main breakthrough in CINV prophylaxis came with the discovery of the 5-hydroxytryptamine receptor antagonists or serotonin receptor antagonists (5-HT3 receptor antagonists). Since the beginning of the 90's there has been clear evidence that the 5-HT3 antagonists are superior in the reduction of CINV compared to dopamine antagonists like metoclopramide.[3,7,8] Since then, the 5-HT3 antagonists in combination with dexamethasone have become the agents of first choice against CINV.[2,3] The discovery of neurokinine-1 receptor antagonists (NK-1 receptor antagonists) in 2003 as a prophylactic drug for CINV and the subsequent combination of 5-HT3 receptor antagonists, NK-1 receptor antagonists and dexamethasone remains the most effective prophylactic drug regimen for CINV to this day.[2,3]

## 5-HT3 RECEPTOR ANTAGONISTS

The currently available 5-HT3 receptor antagonists in Belgium are granisetron, ondansetron, palonosetron and tropisetron.[9] Palonosetron is frequently called a second generation 5-HT3 receptor antagonist because of the marked longer half-life when compared to the other 5-HT3 receptor antagonists, respectively 40h and 6h. All 5-HT3 receptor antagonists except for palonosetron carry a cardiotoxicity warning because of a risk of QT-prolongation. This was noticed when high doses were used. For ondansetron an increase in Qtc is seen in single IV doses of 32 mg or more. For granisetron and tropisetron the caution for Qtc prolongation is based on animal models but was not seen in the currently recommended therapeutic doses.[4] Most common side effects of 5-HT3 receptor antagonists are headache, constipation and asthenia.[10] 5-HT3 receptor antagonists are all metabolised by the liver. Polymorphisms in cytochrome enzymes can lead to differences in half-life times between patients. This is particularly true in the case of tropisetron due to its complete metabolisation through CYP2D6 and its many existent polymorphisms.[4]

Palonosetron is superior in prevention of CINV in highly and moderately emetogenic chemotherapy when compared to the other 5-HT3 receptor antagonists.[3,11] The superiority of palonosetron was mainly seen in the delayed phase, an important side note in this matter is the fact that these studies compared 5-HT3 receptor antagonist against each other without the addition of NK-1 receptor antagonists.

Recently two types of extended-release granisetron were approved: GTDS (granisetron transdermal delivery system) a patch which provides slow release of granisetron and GERSC (Granisetron extended-release subcutaneous) a subcutaneous injection of a polymer linked with granisetron. Both products have the benefit of covering the acute and the delayed phase of CINV due to its increased half-life and thus giving a better overall control of CINV. In the phase III MAGIC trial, GERSC in combination with a NK-1 receptor antagonist and dexamethasone showed superior results in prevention of CINV in the delayed phase in patients treated with highly emetogenic chemotherapy compared to ondansetron with an NK-1 receptor antagonist and dexamethasone.[12]

The currently available NK-1 receptor antagonists in Belgium are aprepitant (Emend), fosaprepitant (Ivemend) and netupitant (the latter is only available as a combination with palonosetron under the brand name of Akynzeo).[9] NK-1 receptor antagonists significantly reduce emesis (both acute, but mainly delayed) when associated with 5-HT3-RA in highly emetogenic chemotherapy.

Aprepitant inhibits CYP3A4 and should therefore be used with caution in patients receiving pimozide, terfenadine, astemizole and cisapride or other medications, which are metabolised trough the CYP3A4 enzyme. Combination with etoposide, which is also metabolised through CYP3A4, has not shown any clinically relevant side-effects and can therefore be used with adequate monitoring. It is known that aprepitant can increase the plasma dose of oral dexamethasone with 50%.[4]

Most recently EMA has approved use of the combination of netupitant, a new NK-1 receptor antagonist and palonosetron with dexamethasone in the prevention of CINV as it showed superiority to palonosetron-dexamethasone in patients receiving highly emetogenic chemotherapy.[3]

## ALTERNATIVE AGENTS

Cannabinoids are thought to prevent CINV by antagonising cannabinoid receptors CB1 and CB2. They have shown to be equally effective as dopamine receptor antagonists. A trial comparing ondansetron/dexamethasone with ondansetron/dexamethasone and cannabiol (a cannabinoid) showed no additional benefit of cannabiol. Therefore, cannabinoids have no place in first line prevention of CINV, but can be considered in patients not responsive to 5-HT3 and NK-1 receptor antagonists.[2,3]

Olanzapine is an atypical antipsychotic agent with anti-emetic effects due to its ability to target dopaminergic, serotonergic, adrenergic and histaminergic receptors.[11]

Olanzapine in combination with palonosetron and dexa-

**TABLE 2.** Recommended Antiemetic Regimens for CINV Prophylaxis.

| Emetic Risk | Treatment for acute phase | Treatment for delayed phase |
|---|---|---|
| High | 3-drug combination (NK-1 receptor antagonist, a 5-HT3 receptor antagonist and dexamethasone) | NK-1 receptor antagonist and dexamethasone |
| Moderate | 2-drug combination (5-HT3 receptor antagonist and dexamethasone) | Dexamethasone |
| Low | Dexamethasone or 5-HT3 receptor antagonist | |
| Minimal | No prophylaxis recommended | No prophylaxis recommended |

methasone has proven equally effective in first-line prophylaxis of CINV in highly emetogenic chemotherapy as compared to aprepitant in combination with palonosetron and dexamethasone.[3,11]

There is evidence that olanzapine is a more effective agent in preventing breakthrough CINV then metoclopramide in patients who were treated with cisplatin or adryamicine-cyclofosfamide based regimes and who failed on fosaprepitant/palonosetron/dexamethasone prophylaxis.

At present time the use of olanzapine as anti-emetic is still off-label and is therefore reserved for patients resistant to the standard combination of an NK-1 receptor antagonist, a 5-HT3 receptor antagonist and dexamethasone.[11] Sedation is the most frequent side effect and dosage should be reduced from 10 to 5 mg/day in elderly and frail patients.

### ADVISED USE OF ANTI-EMETICS

For highly emetogenic chemotherapy and combination of anthracycline and cyclophosphamide a 3-drug combination regimen (5-HT3 receptor antagonist, NK-1 receptor antagonist and dexamethasone) is recommended.

For moderately emetogenic chemotherapy a 2-drug therapy regimen (5-HT3 receptor antagonist + dexamethasone) is recommended with palonosetron as first choice 5-HT3 receptor antagonist.[11]

For low or minimal emetogenic chemotherapy, dexamethasone or a 5-HT3 receptor antagonist alone (not reimbursed in Belgium) is recommended. Metoclopramide or prochlorperazine can be used as alternatives to dexamethasone.[2,3]

An overview is given in *Table 2*.

In patients with refractory CINV, changes in prophylaxis may be considered. These changes include association of an agent from a different drug class, increase of the dose of 5-HT3 receptor antagonist or a switch of agent within the same drug class. For patients receiving highly emetogenic chemotherapy who are refractory to the standard CINV prophylaxis, a switch to an olanzapine based regimen should be considered. In patients where anxiety is presumed as the main trigger of CINV, the use of a benzodiazepine such as alprazolam (0.5-2 mg daily) could be considered although caution with its use is advised in frail and older people due to the possible side-effects (sedation, amnesia, etc.).[3]

## G-CSF USE FOR CHEMOTHERAPY INDUCED FEBRILE NEUTROPENIA

Chemotherapy-induced febrile neutropenia (FN) in lymphoma patients is associated with lengthy hospital stays, increased in-hospital mortality and high hospital costs.[13]

Multiple studies and meta-analysis have shown that the use of G-CSF in primary prophylaxis reduces the duration and severity of neutropenia and reduces the incidence of febrile neutropenia.[13-16]

A Cochrane review looking at differences between primary prophylaxis with G-CSF and no primary prophylaxis in lymphoma patients confirmed a significant reduction in febrile neutropenia when using G-CSF but did not shown a significant difference in overall survival, tumour response nor in number of patients requiring intravenous antibiotics between primary prophylaxis and no prophylaxis.[15] International guidelines advise the use of G-CSF in primary prophylaxis in patients undergoing chemotherapy when the risk for febrile neutropenia (FN) associated with that particular chemotherapy regime is equal to or higher than 20%.[13,17,18]

In chemotherapy regimens with a FN rate of 10-20%, patient dependent characteristics should be taken into account when deciding whether or not to use G-CSF prophylaxis.

The most important of these patient-characteristic risk factors is older age (e.g. age ≥ 65 years). Other important factors have been found to be advanced stage disease,

previous episodes of FN, lack of antibiotic prophylaxis. Low performance state, low nutritional state, cardiovascular disease, renal and hepatic insufficiency have also been identified as possible risk factors.[18]

In regimens with less than 10% risk on FN the use of G-CSG prophylaxis is not recommended.[18,19]

A summary of the most used chemotherapy regimens sorted by the risk for FN can be found in *Table 3*.[20]

In G-CSF formulations, a distinction can be made between short-acting (lenograstim, tbo-filgrastim, filgrastim and filgrastim biosimilars) and the long-acting variants (pegfilgrastim, lipefilgrastim).

Short acting G-CSF are cleared through the kidneys and should be injected daily due to this rapid renal clearing. Long-acting G-CSF have an increased molecular size and thus avoid renal clearance. Clearing of these long-acting G-CSF occurs mainly by circulating neutrophils, which explains high circulating levels of G-CSF during neutropenia and an increased clearance when neutrophil counts recover.[14,18]

Multiple studies have demonstrated that prophylaxis with pegfilgrastim compared to short-acting G-CSF is associated with lower incidence of FN and FN-related hospitalisation. This effect may be caused by a reduced compliance by patients (daily injection for 10 days with short-acting G-CSF *versus* one- time injection per cycle for pegfilgrastim), while others suggest a better efficacy of the long acting G-CSF due to the clearing mechanism by neutrophils causing a well-balanced efficacy in neutropenic episodes. Thus, the use of pegfilgrastim is preferred over the use of short-acting G-CSF.[14,18]

## PNEUMOCYSTIS JIROVECII PROPHYLAXIS

Pneumocystis jirovecii (formerly known as pneumocystis carinii) is a ubiquitous microorganism first described in the early 1900's by Carlos Chagas who described it in the lungs of rats and guinea pigs. In the 1950's, Vanek and Jirovec identified it as a cause of interstitial pneumonia in immunocompromised and malnourished children.[21,22]

Later on, it became a major pulmonary pathogen in the 1980's due to the rise of HIV. When better antiviral agents became available for the treatment of HIV, its main incidence shifted to the broader group of patients receiving immunosuppressant drugs like glucocorticoids and chemotherapy.

The mortality rate of pneumocystis jirovecii pneumonia for non-HIV infected patients remains at high levels between 30% and 60% despite availability of adequate treatment. An important factor in the mortality is thought to be the delay in diagnosis due to its discrete symptoms.[21,23,24]

It is known that in HIV infected patients, a CD4+ lymphocyte count below 200 cells/mm$^3$ is a major risk factor for acquiring pneumocystis jirovecii pneumonia. In non-HIV infected patients with non-Hodgkin lymphoma, a similar risk on pneumocystis jirovecii pneumonia was seen when these patients had a CD4+ lymphocyte count below 200 cells/mm$^3$ before start of chemotherapy. It is important to note that a low CD4+ lymphocyte count is not an absolute requirement for acquiring pneumocystis jirovecii pneumonia as there are several cases published with a normal CD4+ lymphocyte count.[25-27]

The initiation of pneumocystis jirovecii prophylaxis in

**TABLE 3.** Chemotherapy by risk on FN.

| Chemotherapy by risk on febrile neutropenia (FN) | |
|---|---|
| >20% chance on FN | • Dose Adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)<br>• ICE (ifosfamide, carboplatin, etoposide)<br>• R-DHAP (rituximab, dexamethasone, cisplatin, cytarabine)<br>• MINE (mesna, ifosfamide, mitoxantrone, etoposide)<br>• BEACOPP (bleomycine, etoposide, adriamycine, cyclophosphamide, vincristine, procarbazine, predisone) |
| 10-20% chance on FN | • R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone)<br>• Bendamustine based regimes<br>• R-GemOx (rituximab, gemcitabine, oxaliplatin)<br>• Fludarabine based regimes<br>• ABVD (adriamycine, bleomycine, vinblastine, dacarbazine) |

**TABLE 4.** Recommended possible dosing schemes of prophylaxis.

| Prophylactic drug | Drug scheme |
|---|---|
| trimethoprim/sulfamethoxazole (TMP-SMX) | • 160/800 mg, once daily<br>• 160/800 mg, three times a week<br>• 320/1600 mg, three times a week in two separate gifts |
| Pentamidine (aerosolised) | 300 mg, every four weeks |
| Dapsone | 50 mg, twice daily |
| Atovaquone | 1500 mg, once daily |

patients with hematological malignancies is generally recommended for patients receiving chemotherapy regimens associated with a >3,5% risk for pneumocystis jirovecii pneumonia.[28]

The main group of patients with underlying lymphoma who accordingly are in need for pneumocystis jirovecii prophylaxis are patients who underwent severe lymphodepleting therapies such as alemtuzumab, treatment with prednisolone 20 mg/d or more (or an equivalent dose of glucocorticoids) for at least four weeks, treatment with purine-analogues and treatment with a PI3K inhibitor.[28-31] The suggested duration of the pneumocystis jirovecii prophylaxis for these patients is from the start of therapy until at least 6 months after the end of treatment and until normalisation of CD4+ counts in patients who received alemtuzumab or purine analogues.[29,31]

Pneumocystis jirovecii prophylaxis may also be considered in patients with underlying autoimmune disease, patients with central nervous system lymphoma who receive radiotherapy and/or high dose methotrexate with prolonged corticoid use and finally patients receiving gemcitabine-based therapies. In these groups prophylaxis is not seen as mandatory due to lack of evidence.[21,25,30] Here it is recommended to give prophylaxis for at least throughout active treatment.[29,31]

There has been a long-standing discussion whether or not patients with non-Hodgkin lymphoma who receive rituximab based therapies (such as R-CHOP) should be given pneumocystis jirovecii prophylaxis. In the original phase III trial of rituximab, there was no significant increase seen in the incidence of pneumocystis jirovecii pneumonia. Some post-market studies on the incidence of pneumocystis jirovecii pneumonia in patients with non-Hodgkin lymphomas who received rituximab based therapies showed an increased incidence. The most comprehensive meta-analysis of these studies did suggest an increased incidence of pneumocystis jirovecii pneumonia in these patients but the chance of acquiring pneumocystis jirovecii pneumonia was always lower than the 3.5% threshold to initiate the prophylaxis, therefore no prophylaxis is advised in this group.[32-34]

Trimethoprim/sulfamethoxazole (TMP/SMX) is the preferred first choice prophylaxis and has shown to reduce the incidence of pneumocystis jirovecii infection with 91% in immunocompromised patients with hematological malignancies.[21,35,36] The most reported side effects are drug-induced rash, headache, nausea, bone marrow suppression, hyperkalaemia, hepatitis and nephrotoxicity.[21,37] TMP/SMX has also the advantage of having activity against toxoplasma, nocardia and listeria.[25,29] Several dosing schemes exist and none of these has a significant superiority in prophylaxis, so they can be seen as equally effective (see *Table 4*).[17,21,29,35]

A special consideration must be taken into account when using TMP-SMX prophylaxis in patients who simultaneous receive high dose methotrexate. A combination of these two drugs might result in life threatening myelosuppression or renal failure. A safe alternative consists of stopping TMP-SMX as soon as high dose methotrexate is given and to restart TMP-SMX as soon as the methotrexate is excreted.[21]

Aerosolised pentamidine is a good alternative to TMP-SMX but remains a less effective prophylaxis then TMP-SMX.[21,36] Prophylactic dose of pentamidine aerosol is 300 mg every four weeks.[37]

Dapsone is also considered a safe alternative for prophylaxis in patients intolerant to TMP-SMX, the recommended prophylactic dose is 50 mg, twice daily. Before starting with dapsone, all patients should be checked for glucose-6-phosphate dehydrogenase deficiency due to its potential to induce severe haemolysis in these patients.[21] Other

**TABLE 5.** Indication and duration of prophylaxis according to the ECIL 2015 guidelines.

| Indication for prophylaxis | Malignancy/treatment | Duration of prophylaxis |
|---|---|---|
| Strongly advised | • Alemtuzumab<br>• Fludarabine/Cyclofosfamide/Rituximab<br>• Steroids (>20 mg/day prednisone for 4 weeks) | >6 months after completion of treatment |
| Optional | • Esc BEACCOP<br>• Fludarabine<br>• Cladribine<br>• Cerebral radiotherapy + high dose steroids | |

possible side effects are myelosuppression and methemoglobinemia. Atovaquone is a new and expensive anti-PCP agent. Is has shown to be effective against mild forms of pneumocystis jirovecii pneumonia and is used for PCP prophylaxis in patients intolerant for TMP-SMX. In Belgium there is currently no reimbursement for this indication.[21,28,29]

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