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Neutropenia during frontline treatment of advanced Hodgkin lymphoma: Incidence, risk factors, and management

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ABSTRACT

Neutropenia, specifically febrile neutropenia (FN), can have profound sequelae (infection, hospitalization, mortality), and the risk of its development differs across chemotherapy regimens/according to patient characteristics. We conducted a comprehensive literature review regarding neutropenia in frontline treatment of adults with advanced Hodgkin lymphoma. Guidelines state primary prophylaxis (PP) with colony-stimulating factors (CSFs) should be implemented when the risk of FN is ≥20%; CSF PP is given with standard-of-care escalated BEACOPP, but the risk of FN with standard-of-care ABVD does not necessitate routine PP. Notably, the risk of neutropenia (including FN) is higher in clinical practice versus clinical studies, and physicians overestimate their adherence to CSF guidelines. ECHELON-1 demonstrated higher FN rates with brentuximab vedotin plus AVD (A + AVD) compared with ABVD (19% vs 8%) and led to the recommendation of PP with granulocyte-CSF (G-CSF) for all A + AVD patients, highlighting the importance of readjusting our risk-assessment thinking as standard backbone regimens are modified.

1. Introduction and methods

Advances in the multi-agent chemotherapy regimens used in advanced-stage Hodgkin lymphoma have dramatically changed disease prognosis. The most commonly used regimens now include ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone). Standard or 'baseline' BEACOPP is often 'escalated' utilizing increasing doses of etoposide, doxorubicin, and cyclophosphamide (Diehl et al., 2003; Engert, 2016). BEACOPP is generally considered to have a higher efficacy than ABVD, but is associated with a higher toxicity burden (Engert, 2016). Consequently, research is ongoing to incorporate new drugs into these standard ABVD and BEACOPP backbones to improve efficacy and/or reduce toxicity.

A common complication of myelosuppressive multi-agent chemotherapy regimens such as ABVD and BEACOPP is neutropenia. While neutropenia itself is not a troublesome adverse event (AE), severe neutropenia and, in particular, febrile neutropenia (FN) potentially have profound sequelae (Aapro et al., 2011; Klastersky et al., 2016; NCCN, 2019a, 2019c; Smith et al., 2015). There are two main strategies for reducing the occurrence and impact of neutropenia: (1) providing prophylactic myelopoietic support with growth factors (colony stimulating factors [CSFs]) and/or (2) lowering myelotoxicity through initial choice of chemotherapeutic agent or modifying the chemotherapeutic dose, using dose delays and reductions, and missing doses. Furthermore, the risk of neutropenia is an important consideration in the context of the evolving treatment of Hodgkin lymphoma. We therefore conducted a comprehensive review of the literature regarding neutropenia and its management in the frontline treatment of adults with advanced Hodgkin lymphoma.

We used the Medline database (via PubMed) to search for English-language articles published since database inception through to August 1, 2017 using the following two search strategies: 1. ("neutropaenia" OR "neutropenia" OR "white blood cell*") AND ("Hodgkin lymphoma" OR "Hodgkin's lymphoma" or "Hodgkin's disease" or "Hodgkin disease") – 1300 search results; 2. ("colony-stimulating factor"[All Fields] OR "colony-stimulating factors"[All Fields]) AND ("guideline"[Publication Type] OR "guidelines as topic"[MeSH Terms] OR "guidelines"[All Fields]) OR "systematic review"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) OR ("lymphoma"[MeSH Terms] OR "lymphoma"[All Fields]) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "malignancies"[All Fields]) – 371 search results. We manually reviewed all retrieved titles and abstracts for relevance, and further assessed full papers that we judged appropriate for inclusion in this review.

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Table 1
Overall risk of severe and febrile neutropenia (or associated consequences) in prospective studies of patients with Hodgkin lymphoma.

Study reference	Study population and characteristics	Reported incidence of neutropenia and associated complications	G-CSF permissible
Diehl et al. (2003)	Randomized controlled trial 1195 patients with advanced Hodgkin lymphoma (stage IIB, III, and IV)	Grade 4 leukopenia: COPP-ABVD (n = 260; 19%); BEACOPP (n = 469; 37%); $BEACOPP_{escalated}$ (n = 466; 90%) Grade 4 infection: COPP-ABVD (n = 260; 1%); BEACOPP (n = 469; 3%); $BEACOPP_{escalated}$ (n = 466; 8%)	Not specified
Federico et al. (2009)	Randomized controlled trial 317 patients with advanced Hodgkin lymphoma (stage IIB, III, and IV)	Grade 3/4 neutropenia: ABVD (n = 99; 34%); BEACOPP (n = 98; 54%); CEC (n = 98; 48%) Grade 3/4 infection: ABVD (n = 99; 2%); BEACOPP (n = 98; 14%); CEC (n = 98; 4%)	G-CSF given in addition to BEACOPP treatment (300 μg total, subcutaneously)
Cocorocchio et al. (2010)	Prospective single-arm study 82 patients with advanced Hodgkin lymphoma (stage IIA [bulky], IIB, III, and IV)	Grade 3/4 neutropenia: ChlVPP/ABVVP (n = 76; 32%) Grade 3/4 infection: ChlVPP/ABVVP (n = 76; 8%) FN: ChlVPP/ABVVP (n = 76; 8%)	Not specified
Younes et al. (2012a)	Prospective single-arm study 78 patients with advanced Hodgkin lymphoma (stage II [bulky], III, or IV)	Grade 3/4 granulocytopenia: Rituximab + ABVD (n = 78; 15% and 8%) Grade 3/4 infection: Rituximab + ABVD (n = 78; 3%)	Not specified
Younes et al. (2013)	Randomized controlled trial 51 patients with advanced Hodgkin lymphoma (stage IIA [bulky], IIB, III, and IV)	Grade 3/4 neutropenia: A + ABVD (n = 25; 80%); A + AVD (n = 26; 77%) Grade 3/4 FN: A + ABVD (n = 25; 20%); A + AVD (n = 26; 8%)	Not specified
Gordon et al. (2013)	Randomized controlled trial 854 patients with advanced Hodgkin lymphoma (stage III and IV)	Grade 3 lymphopenia: Stanford V (n = 426; 78%); ABVD (n = 428; 42%) Grade 3 and 4 leukocytopenia: Stanford V (n = 426; 36% and 19%); ABVD (n = 428; 28% and 5%)	Not specified
Russo et al. (2014)	Prospective single-arm study 82 patients with advanced Hodgkin lymphoma (stage IIB, III, and IV)	Grade 4 neutropenia: $ABVD_{DD\text{-}DI}$ (n = 82; 10%) Grade 3 febrile neutropenic infection: $ABVD_{DD\text{-}DI}$ (n = 82; 6%)	All patients received primary G-CSF as support for ABVD. Pegylated G-CSF was not allowed in the study.
Carde et al. (2016)	Randomized controlled trial 549 patients with advanced Hodgkin lymphoma (stage III and IV)	Grade 4 neutropenia: $ABVD_8$ (n = 275; 32%); $BEACOPP_{4+4}$ (n = 274; 65%) Grade 4 FN: $ABVD_8$ (n = 275; 6%); $BEACOPP_{4+4}$ (n = 274; 34%)	Prophylactic G-CSF was mandatory with $BEACOPP_{escalated}$
Connors et al. (2018)	Randomized controlled trial 1334 patients with previously untreated advanced Hodgkin lymphoma (stage III and stage IV)	Grade 3/4 neutropenia: ABVD (n = 659; 39%); A + AVD (n = 662; 54%) FN: ABVD (n = 659; 8%); A + AVD (n = 662; 19%)	Prophylactic G-CSF was recommended for patients received A + AVD

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ABVVP, etoposide, doxorubicin, bleomycin and vincristine; AVD, doxorubicin, vinblastine, dacarbazine; A + AVD, brentuximab vedotin + AVD; A + ABVD, brentuximab vedotin + ABVD; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CEC, cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxirubicin, vincristine, procarbazine, vinblastine, and bleomycin; ChlVPP, chlorambucil, vinblastine, procarbazine and prednisone; COPP, cyclophosphamide, vincristine, procarbazine, prednisone.

Here, we summarize the literature, focusing on the incidence of, risk factors for, and sequelae of neutropenia, in particular FN, and its management using CSF prophylaxis. We also evaluate how these aspects may potentially be affected within the context of the evolving treatment algorithm for Hodgkin lymphoma.

Incidences of neutropenic events in Hodgkin lymphoma (including FN if reported) are shown in Table 1. In general, based on the original studies, guidelines have classified BEACOPP as a chemotherapeutic regimen associated with a high risk of FN, and the risk of FN with ABVD is regarded as low-intermediate (depending on age) (Aapro et al., 2011; NCCN, 2019a).

1.1. Neutropenia, febrile neutropenia and its consequences

Neutropenia is a decrease in circulating neutrophils in the non-marginal pool and is defined in terms of the absolute neutrophil count (ANC), with a healthy person having an ANC of 1.5–8.0 × 10^9 cells/L. The severity of neutropenia is classified as mild (1.0–1.5 × 10^9 cells/L), moderate (0.5–1.0 × 10^9 cells/L), or severe (< 0.5 × 10^9 cells/L). Due to the infection-fighting role of neutrophils, physicians are also concerned about the duration of neutropenia and the presence of fever. FN is defined as an ANC of [or expected to fall to] < 0.5 × 10^9 cells/L in the presence of an oral temperature of > 38.3 °C or > 38.0 °C for 1 h (Klastersky et al., 2016; NCCN, 2019c).

The risk of developing neutropenia and/or FN is dependent on a variety of factors including the type of cancer, the chemotherapy regimen used, and patient characteristics, including a low neutrophil count at baseline (Lyman et al., 2014).

Certain chemotherapy agents and regimens are more myelosuppressive than others. For example, anthracyclines such as doxorubicin and alkylators such as cyclophosphamide, which are used in the ABVD and BEACOPP regimens in the frontline treatment of Hodgkin lymphoma, are considered particularly myelosuppressive. Consequently, the risk of neutropenia and FN is dependent on the components used and the intensity (drug dose delivered per time unit) of the chemotherapeutic regimen (Lyman et al., 2014; Lyman, 2009; Lyman and Kuderer, 2003). In Hodgkin lymphoma, data from clinical studies demonstrate the difficulties in obtaining a comprehensive view of risk of neutropenia with specific regimens due to inconsistencies in reporting (grade 3/4 neutropenia vs FN vs febrile [neutropenic/non-neutropenic] infection) (Carde et al., 2016; Viviani et al., 2011; Fossa et al., 2012).

It is also important to recognize that our true understanding of the risk of FN is complicated by the administration of myelopoietic support per clinical study protocols and/or medical society and institutional guidelines. Additionally, studies have found differences in the rate of CSF use not only with different regimens, but also across different regions (Schwenkglenks et al., 2010).

Myelosuppression increases with age (Repetto et al., 2003) and, consequently, the risk of neutropenia is increased in elderly patients (> 65 years) receiving chemotherapy (Aapro et al., 2011; Klastersky et al., 2016; NCCN, 2019a; Smith et al., 2015). The substantial contribution of age to therapeutic outcomes is such that several studies have investigated the effects of chemotherapy specifically in the elderly population with Hodgkin lymphoma (Ballova et al., 2005; Stamatoullas et al., 2015), and management guidelines have made specific recommendations regarding the elderly population and management of neutropenia (Repetto et al., 2003; NCCN, 2019b). For example, the rate of grade 4 or higher neutropenia in patients with Hodgkin lymphoma treated with ABVD or the Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone) was 64% in those aged ≥ 60 years versus 38% in patients aged < 60

years (Evens et al., 2013). Importantly, US and European guidelines for the management of disease recommend that escalated BEACOPP is either used with caution, or not at all, in individuals > 60 years of age (NCCN, 2019b; Eichenauer et al., 2014).

Other suggested risk factors for FN include advanced disease and comorbidities (both closely associated with age) (Smith et al., 2015; Lyman et al., 2014), bone marrow involvement (Moreau et al., 2009), poor performance status (NCCN, 2019a), and female gender (Scott et al., 2003).

In addition to risk of infection and fever, neutropenia also can increase the risk for hospitalizations (especially in patients with HL), and increases mortality (Dulisse et al., 2013). Patients with cancer receiving a reduced dose of chemotherapy due to neutropenic complications especially have a lower chance of remission and survival.

2. Management guidelines for primary prophylaxis with CSFs in Hodgkin lymphoma

2.1. CSFs

CSFs enhance the proliferation, maturation, and release of neutrophils into the bloodstream, resulting in a dose-dependent increase in circulating neutrophils. Granulocyte CSFs (G-CSFs) stimulate the growth of granulocyte colonies. G-CSFs available for the prevention of treatment-related FN are filgrastim, tbo-filgrastim (only available in the US), pegfilgrastim (a PEGylated form of G-CSF), lenograstim (a glycosylated form of G-CSF, only available in Europe), and filgrastim and pegfilgrastim biosimilars (Aapro et al., 2011; Klastersky et al., 2016; NCCN, 2019a; Smith et al., 2015). Short-acting G-CSFs filgrastim and lenograstim are administered daily (preferably subcutaneously) until post-nadir ANC recovery to normal or near-normal levels, and long-acting pegfilgrastim is administered as a single subcutaneous dose per chemotherapy cycle. It is generally understood that short-acting and long-acting G-CSFs are bioequivalent and clinical guidelines in both Europe and the US advocate the use of either (Aapro et al., 2011; Klastersky et al., 2016; NCCN, 2019a; Smith et al., 2015; Wang et al., 2015). A meta-analysis of 3493 patients in 17 randomized trials showed CSFs to be effective at reducing the incidence of FN, infection-related mortality, and all-cause mortality during chemotherapy treatment (Kuderer et al., 2007).

2.2. Key guidelines

The first guidelines on the use of CSFs were released in 2006 by ASCO (Smith et al., 2006); these were most recently updated in 2015 (Smith et al., 2015). Guidelines have also been released in the US by the National Comprehensive Cancer Network® (NCCN®), which releases regular updates (NCCN, 2019a, 2019b). In Europe, similar management guidelines have been released by both EORTC and ESMO (Aapro et al., 2011; Klastersky et al., 2016).

Guidelines are consistent in their recommendation for routine primary prophylaxis with G-CSF in patients receiving chemotherapy for whom there is a > 20% risk for FN based on patient-, disease-, and treatment-related factors (Aapro et al., 2011; Klastersky et al., 2016; NCCN, 2019a; Smith et al., 2015). As the risk of FN is greatest during the first course of chemotherapy, primary prophylaxis (use with first course of chemotherapy onwards) is recommended over secondary prophylaxis (use after an episode of severe or FN in the preceding course) (Klastersky et al., 2016). Additionally, since a previous episode of FN predisposes to further occurrence, it is important that the risk of FN and related complications is assessed at each cycle, and, if appropriate, secondary prophylaxis with CSF is initiated (Aapro et al., 2011; Klastersky et al., 2016; NCCN, 2019a, 2019c; Smith et al., 2015).

2.2.1. Use of CSFs with current standards of care in frontline advanced Hodgkin lymphoma

Based on the guidelines, standard current practice recommends routine primary prophylaxis with CSF is given when patients receive BEACOPP. For patients receiving chemotherapy regimens that are not considered to be high risk (e.g. ABVD), the decision regarding use of CSF prophylaxis can be confounded by the presence of additional risk factors that predispose patients to FN (Weycker et al., 2015). Prophylaxis with CSF is not recommended for routine use with ABVD, due to observed increased bleomycin-induced pulmonary toxicity (NCCN, 2019b; Martin et al., 2005). Two separate studies have confirmed that ABVD can be administered without safety concerns at the full-dose intensity without any CSF (Boleti and Mead, 2007; Evens et al., 2007).

In the early studies of BEACOPP versus ABVD (and cyclophosphamide, vincristine, procarbazine, and prednisone [COPP]), Diehl et al. reported G-CSF administration with 4% of COPP cycles, 14% of ABVD cycles, 10% of baseline BEACOPP courses, and 90% of escalated BEACOPP courses (Diehl et al., 1998). In 2007, Evens et al. published a retrospective review of all newly diagnosed patients with Hodgkin lymphoma treated at their institute in the US between 1996 and 2005. Among patients treated without empiric G-CSF, only 3/682 ABVD treatments were complicated by FN (Evens et al., 2007). The overall median normalized dose intensity for the 59 patients who received all ABVD cycles without G-CSF was 99.1%, leading the authors to conclude that ABVD may be fully and effectively administered without G-CSF support, regardless of a patient's ANC.

The influence of intensified treatment regimens on incidence of neutropenia and FN varies between regimens. With an intensified 6-cycle ChlVPP/ABVVP regimen (chlorambucil, vinblastine, procarbazine, doxorubicin, bleomycin, vincristine, and etoposide), Cocorocchio et al. reported grade 3/4 neutropenia in 32% of patients and FN in 8%, representing a considerable reduction in frequency compared with standard ChlVPP/ABVVP (Cocorocchio et al., 2010). In contrast, a retrospective study showed that the incidence of grade 3/4 neutropenia increased substantially with dose-dense ABVD compared with standard ABVD (58 vs 39%) (Tao et al., 2014). Despite routine CSF primary prophylaxis, Russo et al. reported grade 3 febrile neutropenic infection in 6% of patients treated with dose-dense and dose-intense ABVD (Russo et al., 2014).

2.2.2. Use of CSFs with new agents in frontline advanced Hodgkin lymphoma

Brentuximab vedotin is a new agent being investigated in the frontline treatment of advanced Hodgkin lymphoma. Brentuximab vedotin is a CD30-directed antibody-drug conjugate currently indicated for the treatment of patients with classical Hodgkin lymphoma after failure of autologous hematopoietic stem cell transplantation (auto-SCT), after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-SCT candidates, and for treatment of patients with classical Hodgkin lymphoma at high risk of relapse or progression as post-auto-SCT consolidation. Thus, our experience in Hodgkin lymphoma in the clinic has largely been based on the use of brentuximab vedotin as a monotherapy in patients with prior treatments. In the pivotal phase 2 study of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma, 20% of patients had grade 3/4 neutropenia, but there were no cases of FN reported in the 102 patients enrolled (Younes et al., 2012b). All 102 patients had undergone auto-SCT, 66% had received prior radiation therapy, and the median number of prior chemotherapy regimens excluding auto-SCT was 3.5 (range, 1–13).

In a phase I study to assess the safety of frontline A + AVD and A + ABVD combinations in patients with advanced classical Hodgkin lymphoma, Q2W 1.2 mg/kg brentuximab vedotin combined with ABVD was associated with pulmonary toxicity; whereas A + AVD was considered tolerable (Younes et al., 2013; Connors et al., 2017). In the study, the use of CSF was permitted in accordance with institutional standard of care and if grade 3/4 neutropenia was observed CSF

support was used as prophylaxis in subsequent cycles. The authors reported that CSF was given to 84% of patients. The rate of FN was 20% with brentuximab vedotin in combination with ABVD and 8% with brentuximab vedotin in combination with AVD; none of the patients with FN had received previous CSF prophylaxis (Younes et al., 2013).

ECHELON-1, a large, international, open-label, multicenter, randomized phase 3 trial, compared brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A + AVD) with ABVD as frontline therapy in 1334 patients with stage III or IV classical Hodgkin lymphoma (Connors et al., 2018). FN was reported in 19% of patients receiving A + AVD and in 8% of patients receiving ABVD. Discussion with the independent data and safety monitoring committee (after 75% of enrollment was complete) led to the recommendation of primary prophylaxis with G-CSF for patients who were yet to be enrolled and who would receive the A + AVD regimen, owing to the higher incidence of FN in that group. In the A + AVD group, the incidence of FN was lower among the 83 patients who received primary prophylaxis with G-CSF (defined as use of G-CSF by day 5 of treatment) than among those who did not (11% vs 21%).

Further exploratory analyses of the ECHELON-1 clinical trial (Connors et al., 2018) showed that in patients receiving G-CSF primary prophylaxis, brentuximab vedotin dose reductions (20% vs 26%) and dose delays (35% vs 49%) were decreased, and hospitalization rates reduced (29% vs 38% patients with at least one hospitalization) compared with patients who received no G-CSF primary prophylaxis, thereby maintaining the dose density of the A + AVD regimen given to patients (Straus et al., 2018). These data suggest that the concomitant administration of G-CSF within the first five days of treatment may improve the efficacy of A + AVD, as shown by reduced risk of modified progression-free survival events by 25% with A + AVD with G-CSF compared with A + AVD without G-CSF and by 42% compared with ABVD (Straus et al., 2018).

3. Conclusions

Chemotherapy-induced FN is a potentially fatal complication of cancer treatment, and the prevention of FN reduces hospital admissions, antibiotic usage, and the need for dose reductions or delays in chemotherapy administration. According to guidelines, in patients with Hodgkin lymphoma who are treated with BEACOPP, primary prophylaxis with CSFs should routinely be administered. ABVD, however, is considered a low to medium-risk regimen, and primary prophylaxis is only appropriate in a subgroup of patients with patient-related risk factors. As new regimens are established for the frontline treatment of Hodgkin lymphoma, clinicians must reassess the risk of neutropenia and provide patients with CSF support accordingly. Results from ECHELON-1 demonstrate that primary prophylaxis with G-CSF appeared to mitigate the increased risk of FN and its sequelae in the subgroup of A + AVD patients who received primary prophylaxis, allowing delivery of the full dose density of A + AVD, and potentially improving the efficacy of A + AVD compared with that seen in patients who do not receive G-CSF prophylaxis.

Conflicts of interest

Anna Sureda reports consultancy, advisory boards, and travel grants from Takeda.

Eva Domingo-Domenech has no conflicts of interest to disclose.

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Author contributions

AS and ED-D contributed to the conception and design of the article. AS and AG analyzed and interpreted data. All authors contributed to drafting and critical revision of the article, and approved the final version to be published.

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