Hematological Toxicity in Lung Cancer

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Abstract

The toxicity of tumor cells after chemotherapy (Ch) and radiotherapy (RT), administered alone or in combination, is dose dependent. Aggression to the bone marrow, which is expressed by a reduction in circulating blood cells, is often the main dose-limiting toxicity in the treatment of lung cancer due to the risks of anemia, bleeding, and infection.

Prophylactic treatment with granulocyte colony-stimulating factors (G-CSF) or biosimilars is available to reduce the risk of Ch-induced neutropenia/febrile neutropenia.

The American Society of Clinical Oncology (ASCO) made recommendations (level of evidence II) on the treatment of anemia with erythropoiesis-stimulating agents (ESA). For patients with Ch-induced anemia, the committee recommended starting ESA when hemoglobin (Hb) approaches 10 g/dL, to increase the Hb level and decrease transfusions. A recent phase III study demonstrated the definitive positive impact of darbepoetin r-HuEPO (DARB). DARB was not inferior to placebo for OS and PFS and was superior to placebo for transfusion for Hb ≤8.0 g/dL.

In the last decade, systemic therapy for stage IV NSCLC has been selected for the presence of specific biomarkers. All of these patients should undergo molecular testing for programmed death ligand 1 (PD-L1) protein expression and mutations. The hematologic

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toxicity of these molecules is considered a rare toxicity (frequency <1%) but can be very significant.

1 Introduction

In this chapter, normal bone marrow (BM) physiology is presented followed by a synthesis of current knowledge about the toxicity of these two treatments (Ch and RT), either alone or in combination. Later, supportive treatments and management of these side effects are discussed. Finally, we will finish with the hematological toxicity (HT) of biomarker-directed therapies and new empirical treatment regimens in metastatic lung cancer (LC).

The toxicity of tumor cells after ChRT, administered alone or in combination, is dose dependent. Aggression to the BM is expressed by a reduction in circulating blood cells and is often the main dose-limiting toxicity due to the risks of anemia, bleeding, and infection. The strategies aimed at protecting the hematopoietic cells or the stroma of BM from death induced by treatment, as well as the acceleration of hematopoiesis after treatment, would theoretically allow more intensive treatments in LC, reducing the associated risks mentioned before. To know the true impact of the treatment, either individually or combined in a sequential or concomitant way, and act accordingly, it is necessary to know the structure and function of the BM as an organ. Thus, pluripotent stem cells replicate and differentiate into lymphoid or myeloid lines through a complex process regulated by a network of hematopoietic growth factors and by cellular interactions. The cascade through myeloid differentiation leads to erythrocytes, platelets, granulocytes, and macrophages, while lymphoid differentiation leads to T and B cells. Families of growth factors (or cytokines) that control these processes of replication and differentiation have been identified. Hematopoietic progenitor cells and their daughter cells are enveloped in a stroma of endothelial cells, adventitious cells, fibroblasts, macrophages, and fat cells in the sinus of the BM. This microscopic medium provides physical support and direction of the development of the replication process. Furthermore, the topographic distribution of the BM is especially relevant to know possible local effects of RT in the treatment of LC. The most functional and important locations are the pelvis, the vertebrae (these two represent 60% of the total BM), as well as the ribs, sternum, skull, scapulae, and proximal portions of the femur and humerus. It is important to remember that hematopoietic stem cells are also found in the spleen and peripheral bleeding (Plowman et al. 1991).

BM dysfunction in neoplastic processes can be due to different etiologies:

1. Depletion or direct damage to hematopoietic stem cells
2. Functional or structural damage to the stroma or microcirculation
3. Lesion of other helper cells that have a regulatory or hemostasis function

The consequences of the aggression of cytotoxic and radiotherapeutic treatment to BM must be understood in the context of the mechanisms previously described. However, it may be difficult to elucidate the most important variables due to limitations in the evaluation, both of the structure and of the function of the BM. Peripheral determination of blood cells fails to demonstrate the true extent of BM suppression or tolerance to additional cytotoxic therapy, mainly due to the BM ability to temporarily compensate for insult. To evaluate quantitative and functional aspects of BM cultures of progenitor cells, histopathological studies (aspirate and BM biopsy) and determination by radioisotopes or stromal cell cultures can be performed, although to a limited extent.

2 Hematological Toxicity in Chemotherapy

Myelosuppression caused directly by Ch depends not only on the agent used, but also on individual patient factors, such as age, previous pathologies, and general condition. Important

factors in relation to the type of Ch administered are the dose, the interval between the doses, the route of administration, and the use of one or more antitumor agents. On the other hand, the site of action of the antineoplastic drug within the cell cycle also seems to influence myelosuppression.

The damage is the result of a depletion of the total number of stem cells (the stem cell pool) with a pattern of delayed myelosuppression that occurs when peripheral blood cells die and cannot be replaced. Ch myelotoxicity results in a decrease in blood cell production rather than an immediate elimination of peripheral cells (Ratain et al. 1990).

Due to differences in the half-life of peripheral blood cells, myelosuppressive drugs first result in leukopenia followed by thrombocytopenia, the former being generally more severe than the latter. Therefore, the neutrophil and platelet nadir is normally found between 7 and 15 days after drug administration. For most compounds, neutropenia and thrombocytopenia are reversible and not cumulative. In addition to direct cytotoxicity at the progenitor cell level, erythrocytes have a longer half-life, so the mechanism involved may be direct hemolysis after administration or a decrease in endogenous erythropoietin production secondary to renal failure due to cisplatin (CDDP) (Pivot et al. 2000). Pluripotent stem cells are protected from the toxic effects of Ch due to their slow proliferation.

Ch-induced febrile neutropenia (FN) is a life-threatening complication of cancer treatments, when it presents with infection and sepsis. It is seen most frequently during the initial cycles of myelosuppressive therapy (Timmer-Bonte et al. 2005). FN is defined as an absolute neutrophil count (ANC) of $<0.5 \times 109/L$, or $<1.0 \times 109/L$ that is predicted to fall below $0.5 \times 109/L$ in 48 h, associated with fever or clinical signs of sepsis (Crawford et al. 2010). As a consequence of FN, delays in antitumor treatment and dose reduction can occur, which can negatively affect tumor control (Khan et al. 2008). For instance, poor outcomes in cancer patients have been attributed to the failure in the delivery of planned Ch regimens for LC (Lyman 2009).

Early recognition of patients at risk of complications from FN can be achieved using risk indices such as the one developed by the Multinational Association for Supportive Care in Cancer (MASCC) (De Souza Viana et al. 2008). Using the MASCC score, patients with 21 or more points are considered high-risk FN. Identifying patients at risk for bacteremia facilitates the appropriate initiation of antibiotics (Klastersky et al. 2010).

Patient-related risk factors should be evaluated in the overall risk assessment for FN before each cycle of Ch is administered. Special attention should be paid to high-risk elderly patients (65 years and older). Other risk factors that can influence the risk of FN include advanced stages of the disease, previous episodes of FN, lack of use of G-CSF, and absence of antibiotic prophylaxis. The risk of FN associated with Ch regimens should be taken into account when assessing the need for prophylactic intervention. In recent years, the Clinical Index of Stable Febrile Neutropenia (CISNE) (Table 1) has been emerging as a very useful prognostic score for predicting serious complications in outpatients with solid tumors and episodes of stable FN. The CISNE score identifies six variables associated with serious complications and classifies patients into three prognostic classes: low risk (0 points), intermediate risk (1–2 points), and high risk (3 points or more). The results of a multicenter validation study suggest that the CISNE score may be more accurate than the MASCC score (Carmona-Bayonas et al. 2015).

On the other hand, new Ch regimens associated with targeted agents have been shown to improve OS. This is the case with the addition of cetuximab or bevacizumab to Ch in patients with

Table 1 Clinical Index of Stable Febrile Neutropenia (CISNE) score

Characteristics	Points
ECOG-PS ≥2	2
Stress-induced hyperglycemia	2
Chronic obstructive pulmonary disease	1
Chronic cardiovascular disease	1
Mucositis National Cancer Institute ≥2	1
Monocytes <200 per μ/L	1

NSCLC (Pirker et al. 2009; Reck et al. 2009). A higher incidence of FN has been reported in patients receiving bevacizumab and Ch compared to Ch alone (Sandler et al. 2006).

The elevated risk of FN should be considered when using certain Ch regimens, such as the combination of docetaxel with carboplatin (CB) (Milward et al. 2003). One of the main toxicity factors for a certain Ch agent is the pharmacodynamic interaction when combined with other anticancer drugs. One of the general principles for combining different drugs is that they must have different limiting toxicity, although a sum of these myelotoxic effects generally occurs. However, there is an exception to this rule; it is the case of the combination of paclitaxel with CB: paclitaxel decreases platelet toxicity of CB in relation to a nonpharmacokinetic mechanism (Calvert et al. 1999).

The most common Ch regimens currently used in NSCLC include combinations of CDDP or CB with other drugs (gemcitabine, vinorelbine, paclitaxel, docetaxel). All have been shown to have similar efficacy in stage IV, although the observed toxicities, including HT, differ between them (Schiller et al. 2002). These combinations of Ch cause grade 3 and 4 neutropenia in a range of 40–70%, with FN in less than 10%. Grade 3 and 4 platelet toxicity has been observed in 1–55% of patients, with the combination of CDDP and gemcitabine increasing the percentage of thrombocytopenia (Cardenal et al. 1999). Patients with CB-based Ch were more likely to experience thrombocytopenia (Luo et al. 2011). Regarding anemia, the percentages vary between 10% and 30%, being the regimens based on CDDP and gemcitabine or vinorelbine, which produced a higher percentage of patients with anemia (Kelly et al. 2001).

The sequence of administration is also a relevant factor. An increase in myelotoxicity has been reported when CDDP is administered before paclitaxel. Platelet toxicity is not prominent in regimens that include paclitaxel associated with CB, suggesting that paclitaxel could protect. The combination of CDDP and etoposide (ET) produces less neutropenia than cyclophosphamide, doxorubicin, and vincristine (CAV), although with more anemia (Fukuoka et al. 1991). The HT profile with the combination of ET and CB is similar to that found with CDDP, except that it presents a higher percentage of thrombocytopenia.

It is important to note the possible HT of pemetrexed. This is a multidirectional antimetabolite that inhibits several key folate-dependent enzymes in the thymidine and purine biosynthetic pathways, including thymidylate synthase. It is currently approved for use in patients with NSCLC and malignant mesothelioma. The appearance of HT from this new drug, which can produce life-threatening complications during the early phase of development, prompted the urgent need to identify possible predictive factors for these HT. An association was found between elevated plasma homocysteine (HC) concentration, which is indicative of impaired folate functional status, and an increased risk of HT from pemetrexed (Kao et al. 2010).

The decrease in the incidence of toxicity after vitamin supplementation confirms the importance of the above. But this correlation between folate functional status and vitamin supplementation is not observed in other CDDP-based Ch regimens, as it is in Ch regimens with pemetrexed (Minchom et al. 2014). However, further studies might be necessary to increase the rate of successful supplementation and to test the biomarker potential of HC levels after supplementation to predict Ch-induced neutropenia in CDDP-based regimens. This is because post hoc analysis of this randomized clinical trial (RCT) showed that patients in the successfully supplemented arm (9/36 = 25%) had less neutropenic toxicity (0% vs. 69%; $p = 0.02$) compared to patients who received no supplements.

3 Hematological Toxicity in Radiotherapy

In the case of irradiation in the LC, the acute toxicity of BM depends on the irradiated volume and the radiation dose and its rate. Although compensatory mechanisms are primarily relevant to understanding long-term effects, some of the

effects are acute. Thus, when limited volumes are irradiated to BM, such as 10–15%, the remaining bone marrow responds by increasing the progenitor cell population. That is why BM, as an organ as a whole, is capable of regenerating the previously irradiated area through a compensatory effect to satisfy the needs of hematopoiesis, avoiding acute toxicity. This compensatory phenomenon can be observed by factors (CSF) of the cell stroma that suggest the involvement of a humoral mechanism.

It has been shown that there is an extensive communication and compensation network in the BM after the assault with RT, and this can be summarized as follows:

1. Regeneration in the field of irradiation
2. Hyperactivity in nonirradiated regions
3. Extension of the BM production function in previously inactive areas (Tubiana et al. 1979)

This repairing or compensatory capacity of the BM makes the RT-induced BM toxicity in LC difficult to observe clinically. However, exclusive irradiation using standard fractionation produces a subclinical but quantifiable HT, which we will describe in more depth later when we move to combination therapy (ChRT) and compare the resulting myelotoxicity using RCT studies related to RT alone as a reference.

4 Hematologic Toxicity After Combined Chemo- and Radiotherapy

The selective action of Ch agents for different hematopoietic cell populations determines the temporal consequences of BM tolerance to RT after Ch. Furthermore, when using wide irradiation fields before Ch, the expected tolerance is lower. This may be due not only to the suppression or ablation of certain segments or portions of the BM, but also to the increased sensitivity of the unexposed areas of the BM that, at that time, are in a period of hyperactivity. This situation occurs in the case of sequential treatments of RT and Ch, further complicating the issue of combined treatments. In the case of small cell lung cancer (SCLC), one study is worth highlighting (Abrams et al. 1985). These authors randomized 42 patients to receive Ch alone or in combination with thoracic RT. In the group that received the combination treatment, an increase in HT was observed as well as in the circulating number of progenitor cells, suggesting that the toxicity of the concomitant treatment is additive. It was found that:

(a) The combination of Ch with thoracic RT produces more HT during the irradiation period than when Ch is administered alone.
(b) This increase in HT may be explained by a toxicity that is generally subclinical, although measurable, of thoracic RT when administered alone.
(c) The potential HT induced by irradiation itself may vary in relation to the time, the volume of treatment, the irradiated region, and the treatment fields used. In other words, the greater the volume treated and the greater the amount of cardiac circuit and BM involved in the irradiated fields, the greater the toxicity.

In recent decades, it has been observed that both the timing of the administration of RT (early or late) in the concurrent combined treatment and the fractionation (accelerated hyperfractionation versus standard fractionation) have a relevant role in the development of HT in patients with SCLC. In one RCT (Murray et al. 1993), a group of patients were randomized to early concurrent RT (in the 3rd week) versus late concurrent RT (in the 15th week). It was observed that although the differences between neutropenia and thrombocytopenia greater than or equal to grade 3 were not statistically significant, grade 3 anemia was higher in the late RT arm ($p < 0.03$).

In an RCT (Jeremic et al. 1997), 107 patients received daily low doses of Ch plus early hyperfractionated RT (weeks 1–4) simultaneously with Ch versus late RT (weeks 6–9), without finding statistically significant differences in HT. In the same year, the EORTC group (Gregor et al. 1997) published an RCT of patients with limited-stage

SCLC comparing sequential ChRT with alternating treatment, reporting that the latter regimen was as effective as sequential administration, but caused higher rates of HT grade 3 and 4. Another RCT (Turrisi et al. 1999) compared concurrent Ch with hyperfractionated RT versus the same concomitant Ch with standard fractionated RT, observing greater toxicity in the hyperfractionated treatment. Finally, the RCT of concurrent versus sequential ChRT (Takada et al. 2002) also observed a higher HT in the concurrent arm.

Finally, in the clinical trials on SCLC that address issues related to RT, it is important to highlight the CONVERT study (Concurrent Once-Daily Versus Twice-Daily Radiotherapy) (Faivre-Finn et al. 2017) that provides us with new information on HT secondary to the RT of more limited fields, on the technology currently used, and on different fractionation schemes. Between April 7, 2008, and November 29, 2013, 547 patients were enrolled in an RCT and assigned to receive concurrent ChRT twice daily or concurrent ChRT once daily. With a median follow-up of 45 months (IQR 35–58), the median overall survival (OS) was 30 months (95% CI 24–34) in the twice-daily group versus 25 months (95% CI 21–31) in the other group. The most common grade 3–4 adverse event for toxicity secondary to Ch was neutropenia (197 [74%] of 266 patients in the twice-daily group versus 170 [65%] of 263 in the once-daily group). Most toxicities were similar between the two groups, except for the grade 4 neutropenia rate, which was significantly higher in the RT twice-daily arm (129 [49%] vs. 101 [38%]; $p = 0.05$). This RCT seems to demonstrate that limited RT fields (involved fields) and 3D and/or IMRT techniques can have a significant impact on the development of HT.

In the early 1990s, a series of RCTs in NSCLC were conducted that evaluated both the effectiveness and toxicity of concurrent or sequential ChRT versus RT alone. Three hundred and fifty-three patients were randomized (Le Chevalier et al. 1991) to receive 65 Gy of exclusive RT versus RT at the same dose, preceded by three cycles of vindesine, lomustine, CDDP, and cyclophosphamide. In the exclusive RT group, three times less of HT was observed than in the combined therapy group. Another study randomized (Dillman et al. 1990) 155 patients to receive two cycles of CDDP and vinblastine followed by 60 Gy of RT versus RT alone at the same dose. Although HT was not fully explained in this study, neutropenic infection was found to be more prevalent in patients receiving Ch, with twice the number of hospital admissions due to serious infections compared to patients receiving RT alone.

In a later study (Trovo et al. 1992), 173 patients with stage III NSCLC received 45 Gy versus CDDP 6 mg/m^2 daily concurrently with RT at the same dose as the other group. The HT of combined treatment was only slightly higher than that of RT alone. In 1993, 331 patients received 56 Gy administered by split-course versus the same RT schedule plus CDDP 30 mg/m^2 administered each week of RT, versus the same total dose of RT administered continuously with a daily dose of CDDP 6 mg/m^2 during RT (Schaake-Koning et al. 1992). Grade 3–4 HT was observed to be four times higher in the RT plus weekly CDDP group compared to RT alone and twice as high in the concurrent treatment with daily CDDP versus weekly CDDP.

In another RCT (Sause et al. 1995) of patients with stage III NSCLC, the patients who underwent sequential ChRT had a longer survival than the group who underwent exclusive hyperfractionated RT or normofractionated RT. However, grade 3 or higher neutropenia was observed in 50% of the combined treatment patients and was absent in the other two arms of the study. In another RCT (Jeremic et al. 1996), 169 patients were randomized to receive hyperfractionated RT at 1.2 Gy/2 times daily up to a total dose of 64.8 Gy versus the same dose of RT plus 100 mg of CB on days 1 and 2, and 100 mg of ET on days 1 and 3 of each week of RT, compared to a third group in which the same RT was administered plus 200 mg of CB administered on days 1 and 2, and 100 mg of ET on days 1 and 5 of the first, third, and fifth weeks of RT. Greater toxicity was observed in the combined treatment group, especially in the second treatment arm.

After observing a greater efficacy with sequential treatment of ChRT, but with a higher incidence

of HT than with exclusive RT, the next step was to demonstrate that HT with concurrent treatment would be higher than with sequential treatment. In an RCT (Furuse et al. 1999), 320 patients with stage III NSCLC were assigned to receive concurrent ChRT with CDDP, vindesine, and mitomycin plus 56 Gy given in a split-course (28 Gy followed by a rest period of 10 days, and then repeated) versus the same Ch schedule plus sequential RT of 56 Gy. A greater immunosuppression was observed in the concurrent treatment arm.

Along the same lines, a second RCT compared concurrent (group A) versus sequential (group B) ChRT with CDDP and vinorelbine in locally advanced NSCLC (Zatloukal et al. 2004). Grade 3 or 4 toxicity was more frequent in arm A, with a significantly higher incidence of leukopenia (53% versus 19%, $p = 0.009$). However, in the concurrent ChRT arm, an increase in OS was observed.

The combination of concurrent treatment of ChRT with weekly paclitaxel at a dose of 60 mg/m^2 versus RT alone after induction Ch in inoperable stage IIIA or IIIB NSCLC has also been investigated (Huber et al. 2006). Ch induction was well tolerated, presenting 3.8% grade 3 or 4 leukopenia (2.1% grade 4). HT was equivalent in the RT-alone group and in ChRT, with no grade 3 or 4 toxicity.

Cancer and Leukemia Group B (CALGB), in a randomized phase II study (Vokes et al. 2002) of CDDP with gemcitabine or paclitaxel or vinorelbine as induction Ch followed by concomitant ChRT for stage IIIB NSCLC, studied efficacy and tolerance of these treatments. HT was presented separately for induction Ch and for concomitant ChRT treatment. In the first, grade 3–4 granulocytopenia was observed in 50% of patients in all three treatment arms. However, in the gemcitabine group, 25% of the patients also had grade 3 and 4 thrombocytopenia. In concurrent treatment, important differences were found in the three study treatment groups. Patients treated with gemcitabine and paclitaxel developed grade 3 and 4 granulocytopenia in 51% and 53%, respectively. However in the vinorelbine group, this HT was observed in 27% of the patients. In addition, platelet toxicity was found to be higher (50%) in the group concurrent with gemcitabine. Subsequently, the CALGB developed another RCT (Vokes et al. 2007) where 366 patients were randomly assigned to arm A, which involved immediate concurrent ChRT with CB area under the concentration-time curve (AUC) of 2 and administered paclitaxel 50 mg/m^2 weekly for 66 Gy of chest RT, or arm B, involving two cycles of CB AUC 6 and paclitaxel 200 mg/m^2 given every 21 days followed by identical ChRT. They found no differences in survival between both arms. Treatment adverse events during induction Ch in arm B included grade 3 and 4 granulocytopenia in 18% and 20% of patients, respectively. Neutropenia increased significantly in arm B, reflecting the cumulative effect of induction Ch.

Another RCT (Hanna et al. 2008) demonstrated that consolidation with docetaxel after CDDP/ET and concurrent RT results in greater toxicity, without increasing survival compared to CDDP/ET and concurrent RT in patients with unresectable stage III NSCLC. 10.9% of the patients receiving docetaxel experienced NF, and 28.8% of the patients were hospitalized during the docetaxel versus 8.1% in the observation arm. 5.5% died from complications secondary to docetaxel.

In recent years, three major RCTs have been conducted on radical ChRT in unresectable stage III NSCLC with secondary HT results to treatment.

The first was the RTOG 0617 study (Bradley et al. 2015), which aimed to compare OS after 60 Gy (standard dose), 74 Gy (high dose), 60 Gy plus cetuximab, or 74 Gy plus cetuximab. All patients also received Ch with paclitaxel and CB simultaneously. Two weeks after ChRT, consolidation Ch was administered. The median OS was 28.7 months for group A and 20.3 months for group B (HR 1.38, 95% CI 1.09–1.76, $p = 0.004$). The median OS in patients who received cetuximab was 25.0 months (95% CI 20.2–30.5) compared with 24.0 months (19.8–28.6) in those who did not receive cetuximab (HR 1.07, 95% CI 0.84–1.35, $p = 0.29$). Anemia grade 3 and 4 was similar between cetuximab plus 74 Gy and cetuximab plus 60 Gy groups (9% and 0% vs. 5% and

1%, respectively). Similar results were observed in grade 3 and 4 lymphopenia: arm A presented 8% and 0%, while arm B had 12% and 2%, respectively. Grade 3 and 4 thrombocytopenia was found in 6% and 2% in arm A versus 10% and 6% in arm B, respectively.

The second was the PROCLAIM study (Senan et al. 2016) that evaluated OS with concurrent ChRT with pemetrexed/CDDP followed by consolidation pemetrexed (arm A) versus concurrent ChRT with CDDP/ET followed by consolidation Ch with doublet without pemetrexed (arm B). Group A was not superior to group B in terms of OS with a median of 26.8 versus 25.0 months (HR 0.98, 95% CI 0.79–1.20, $p = 0.831$). Group A had a significantly lower incidence of any grade 3–4 drug-related adverse event (64.0% vs. 76.8%; $p = 0.001$), including neutropenia (24.4% vs. 44.5%; $p = 0.001$).

The third study, the PACIFIC trial (Antonia et al. 2017), has produced a paradigm shift in the treatment of unresectable locally advanced stage III NSCLC. This phase III study compared the anti-programmed death ligand 1 antibody durvalumab as consolidation therapy with placebo in patients with stage III NSCLC who did not have disease progression after two or more cycles of platinum-based ChRT. The total HT was not specified in detail, but grade 3–4 anemia in each arm was close to 3%. In the first published OS analysis (Antonia et al. 2017), with a median follow-up of 25.2 months, the OS at 24 months was 66.3% (95% CI, 61.7–70.4) with durvalumab compared to 55.6% (95% CI, 48.9–61.8) in the placebo group ($p = 0.005$). Updated analyses confirm these results with a median follow-up of 4 years (Antonia et al. 2018).

5 Preventive or Support Treatment of Hematologic Toxicity After Concurrent ChRT in Lung Cancer

5.1 Neutropenia

Prophylactic treatment with granulocyte colony-stimulating factors (G-CSF) is available to reduce the risk of Ch-induced neutropenia. FN is a life-threatening complication of myelosuppressive therapy that often may require hospitalization and may result in interruptions of the Ch regimen planned. Known risk factors for FN allow clinicians to stratify patient risk and initiate G-CSF prophylaxis. The strongest evidence supporting the use of G-CSF to prevent FN comes from three level I meta-analyses (Lyman et al. 2002; Bohlius et al. 2008; Kuderer et al. 2007). The latter presented information from 13 RCTs and 3122 patients with lymphoma or solid tumors, where G-CSF was used in conjunction with standard Ch, resulting in a significant reduction in early mortality.

However, G-CSF prophylaxis varies greatly in clinical practice, both at the time of administration and in the patients to whom it is offered. In 2005, the European Organization for Research and Treatment of Cancer (EORTC) created a European Guidelines Working Group to review the available evidence and its recommendations for the appropriate use of G-CSF in adult patients receiving Ch (Aapro et al. 2006), updating in 2010 (Aapro et al. 2011). They recommend assessing advanced age (greater than or equal to 65 years) and total neutrophil count as adverse risk factors related to the patient and assessing the risk of FN before administering each cycle of Ch (Table 2). It is important that after an episode of FN, patients receive G-CSF prophylaxis in subsequent cycles. There are Ch schemes that are considered high risk (>20%) or intermediate risk (10–20%) of FN. In high-risk regimens, prophylaxis with G-CSF is still recommended. In intermediate-risk regimens, patient-related risk factors that may increase the overall risk of FN should be carefully considered. Previously, a small level II study suggested a tendency for improved long-term survival in patients with favorable-prognosis SCLC receiving VICE Ch (vincristine-ifosfamide-CB-ET) plus G-CSF compared with Ch alone (Woll et al. 1995). Furthermore, a harmful effect with the use of this cytokine has been observed in patients with intrathoracic stage SCLC who were treated with concomitant ChRT, as well as in extrathoracic stages treated with high doses of Ch (Adams et al. 2002). In 1996, the American Society of Clinical

Table 2 Common Ch regimens associated with intermediate or high risk of FN

Malignancy	FN risk factory (%)	Chemotherapy regimen
Small cell lung cancer	>20	Doxorubicin/cyclophosphamide/etoposide Topotecan Ifosfamide/carboplatin/etoposide Vincristine/ifosfamide/carboplatin/etoposide
	10–20	Cyclophosphamide/doxorubicin/vincristine Etoposide/carboplatin Topotecan/cisplatin Tirapazamine/cisplatin/etoposide/irradiation Cisplatin/vincristine/doxorubicin/etoposide
	<10	Cyclophosphamide/doxorubicin/vincristine Paclitaxel/carboplatin
Non-small cell lung cancer	>20	Docetaxel/carboplatin Etoposide/cisplatin Cisplatin/vinorelbine/cetuximab
	10–20	Vinorelbine/ifosfamide/gemcitabine Paclitaxel/cisplatin Docetaxel/cisplatin Vinorelbine/cisplatin
	<10	Paclitaxel/carboplatin Gemcitabine/cisplatin Bevacizumab/paclitaxel/carboplatin

Oncology (ASCO) recommended to avoid the use of G-CSF in patients who had received concomitant ChRT. Four years later, ASCO specified that the use of G-CSF should be avoided in patients with ChRT if the mediastinum had been irradiated (Ozer et al. 2000) as in the case of LC, due to a significant increase in grade 3–4 thrombocytopenia and excess deaths due to pulmonary toxicity. However, the CONVERT trial provided more information on concomitant mediastinal RT and G-CSF administration (Sheikh et al. 2011). Thirty-eight patients with limited-stage SCLC were randomized to receive RT once daily (66 Gy in 33 fractions) or twice daily (45 Gy in 30 fractions) concurrently with CDDP and ET, plus G-CSF as primary or secondary prophylaxis or as a therapeutic measure during an episode of FN. Thirteen (34%) patients received G-CSF at the same time as RT. With a median follow-up of 16.9 months, no treatment-related deaths were observed. Seven (54%) patients experienced grade 3–4 thrombocytopenia and 5 (38%) experienced grade 3–4 anemia. Thirty-one percent required platelet transfusions. No bleeding episodes were observed. There were no cases of grade 3–4 acute pneumonitis. These data suggest that with modern three-dimensional (3D) conformal RT, G-CSF administration at the same time as ChRT does not increase the risk of pulmonary toxicity, but it does increase the risk of thrombocytopenia.

Antibiotic prophylaxis to prevent infection and its related complications in cancer patients at risk of developing neutropenia is controversial (Cullen et al. 2005). Two meta-analyses (Gafter-Gvili et al. 2005; Herbst et al. 2009) and one systematic review (van de Wetering et al. 2005) indicated that the evidence is too limited to allow conclusions to be drawn about the relative advantage of antibiotics over primary prophylaxis with G-CSF. Antibacterial prophylaxis has resulted in substantial reductions in infection-related mortality in neutropenic patients and is recommended for high-risk patients. The results of a meta-analysis of 52 trials of neutropenic patients with primarily hematologic malignancies demonstrated the efficacy of fluoroquinolones (FQ) in preventing bacterial infections without an increase in resistant organisms (Gafter-Gvili et al. 2007). Levofloxacin is the recommended FQ according to national guidelines. High-dose levofloxacin (500–750 mg) has a broader scope of coverage compared to ciprofloxacin or moxifloxacin, by covering pseudomonas, other

gram-negative rods, and some gram-positive pathogens. Nevertheless, in certain high-risk patients with clear predictors of a worse prognosis (e.g., sepsis, pneumonia, fungal infections), the use of G-CSF in conjunction with antibiotics may be justified (Bennett et al. 1999). In 2002, a systematic review of RCTs conducted on the role of G-CSF in the treatment of SCLC was published (Berghmans et al. 2002).

Twelve studies were eligible; they were divided into three groups: (1) maintenance of dose intensity when Ch was administered in conventional doses and time intervals (seven trials); (2) accelerated Ch with an increase in dose intensity by reducing the delay between Ch cycles (five trials); and (3) Ch concentration in a shorter overall duration time with a smaller number of cycles (one trial). The results of the review were negative for all strategies: in the maintenance group, the administration of G-CSF was associated with a detrimental effect on OS; in the accelerated group, no significant impact on response rate or OS was found; and concentrated Ch was associated with no difference in response rate and reduced OS.

In patients receiving first-line Ch for advanced NSCLC, Ch-induced neutropenia is associated with significantly longer OS (Di Maio et al. 2005). Adjuvant Ch after radical surgery has become a standard treatment for early-stage NSCLC. CDDP-based Ch has been used in all recent clinical trials, showing a significant advantage for treatment compared to observation (Douillard et al. 2006). But despite the significant HT of these Ch regimens, the incidence of FN is notably less than 20%, and thus primary G-CSF prophylaxis is not recommended according to guidelines (Winton et al. 2005). Regarding the use of daily G-CSF versus pegylated G-CSF once per cycle, additional evidence has emerged since the publication of the latest EORTC guidelines. In addition, more filgrastim biosimilar molecules have been approved. These developments highlight the need to reevaluate the current evidence and update existing guidelines regarding the prophylactic use of G-CSF. The efficacy of standard and pegylated agents in the prophylaxis of FN is well established in terms of decreased risk of FN, severity and duration of FN episodes, and changes in Ch administration, without sustained evidence of superiority of either of these formulations (Wingard and Elmongy 2009). Following the expiration of the filgrastim patent in Europe in 2006, the European Medicines Agency has approved several biosimilar agents. A biosimilar biological medicine or Biosimilar is a version of an already authorized biochemical medicine with demonstrated similarity in physicochemical characteristics, efficacy, and safety, based on a comprehensive comparability exercise. MONITOR-GCSF was an international, multicenter, prospective, observational, open-label, pharmacoepidemiological study of 1447 cancer patients treated with myelosuppressive Ch in a total of 6213 cycles and who received prophylaxis with Zarzio®, one of the biosimilar agents of filgrastim (Gascon et al. 2016). LC was the second most frequent solid neoplasm in the study, with 466 patients (32.2%) of the total cohort. According to the EORTC guidelines, 56.6% of patients received prophylaxis correctly, 17.4% received over-prophylaxis, and 26.0% under-prophylaxis. The following incidence rates were recorded: Ch-induced grade 4 neutropenia 13.2% and 3.9% of cycles; 5.9% of the patients developed FN and in 1.4% of the cycles; hospitalizations secondary to FN in 6.1% of patients and in 1.5% of cycles; Ch alterations due to FN in 9.5% of patients and in 2.8% of cycles; and composite outcomes index 22.3% of patients and in 6.7% of cycles. In conclusion, the clinical and safety results of this biosimilar are within the range of historically reported data for the original filgrastim, underlining the clinical efficacy and safety of the biosimilar in daily clinical practice.

5.2 Anemia

Anemia, another known consequence of BM toxicity, has a multifactorial etiology that includes inadequate production of erythropoietin in response to the alteration of normal Hb levels. This anomaly is accentuated by Ch. On the other hand, the recombinant human erythropoietin (r-HuEPO) has been used to improve the anemia

seen in cancer patients by increasing the number of erythroid progenitors in both the bone marrow and the peripheral blood.

Several large community studies have shown that epoetin alfa effectively corrects anemia and improves quality of life in anemic cancer patients receiving Ch (Kosmidis et al. 2005). However, the contribution of r-HuEPO to the outcome of curative cancer treatment has been controversial (Macktay et al. 2007; Bohlius et al. 2009). A safety analysis in an RCT suggested a decrease in OS in patients with advanced NSCLC treated with r-HuEPO (Wright et al. 2007). ASCO has made recommendations with a level of evidence of II on the treatment of anemia with r-HuEPO (Rizzo et al. 2008). For patients with Ch-induced anemia, the Committee continues to recommend initiating an erythropoiesis-stimulating agent (ESA) in cases where Hb values approach or fall below 10 g/dL, thereby increasing Hb and decreasing indications for transfusion.

In a prospective phase II trial (Casas et al. 2003), the impact of the use of r-HuEPO on the maintenance of Karnofsky and Hb levels was studied in patients with LC who received concomitant treatment with ChRT after one cycle of induction Ch (11 SCLC and 40 NSCLC). In addition to finding a beneficial impact of the administration of r-HuEPO on the general status and Hb levels, it was also found to be a prognostic factor for OS in the multivariate analysis, together with classical factors such as weight loss, final improvement in Hb, SCLC histology, and, finally, Hb levels greater than 10 g/dL before ChRT.

A recent phase III noninferiority study (Gascón et al. 2020) has concluded on the positive impact of r-HuEPO, in this case with darbepoetin (DARB), on OS and PFS in anemic patients with NSCLC treated to a 12.0 g/dL Hb ceiling. Patients with stage IV NSCLC who were expected to receive two or more cycles of myelosuppressive Ch and Hb ≤11.0 g/dL were randomized 2:1 to 500 μg of blinded DARB or placebo every 3 weeks. The primary endpoint was OS, and the secondary endpoints were PFS and incidence of transfusions or Hb ≤8.0 g/dL from week 5 to the end of the efficacy treatment period. A total of 1680 patients received DARB and 836 placebo. DARB was not inferior to placebo for OS and PFS, and DARB significantly reduced odds of transfusion or Hb ≤8.0 g/dL. The objective tumor response was similar between the arms, and the incidence of serious adverse events (AE) was 31.1% in both arms.

5.3 Thrombocytopenia

Thrombopoietin (TPO), a factor synthesized for the stimulation of platelets with the intention of preventing bleeding problems after myelosuppressive Ch, is still under evaluation. TPO, a key physiological regulator of platelet production, has been found to be the most potent thrombopoietic cytokine studied to date. Unfortunately, the clinical development of recombinant human thrombopoietin has faced challenges related to the biology of TPO, observing a delayed platelet response peak and the presence of neutralizing antibodies against the pegylated molecule (Vadhan-Raj et al. 2005). A Cochrane review (Zhang et al. 2017) concludes that the available evidence is not sufficient to support the use of TPO-RAs to prevent Ch-induced thrombocytopenia (CIT) or to prevent recurrence of CIT in patients with solid tumors.

In addition to the development of specific cytokines for the production and secretion of different hematological cells, trials are currently being carried out with molecules such as glutathione on different methods of prevention of BM toxicity. Glutathione has been shown to be an effective chemoprotectant against CDDP-induced toxicity. Although the majority of experience is in ovarian cancer, RCTs in other types of tumors such as LC and head and neck tumors have shown a lower HT in patients who received glutathione (Schmidinger et al. 2000).

Other drugs, such as amifostine, have also shown a reduction in HT in RCTs that include LC patients treated with concomitant ChRT (Antonadou et al. 2003). However, in another RCT (Movsas et al. 2005) and in a phase II trial (Han et al. 2008), both in LC, amifostine was associated with a higher incidence of FN, so it does not seem useful to prevent the HT.

The use of intensity-modulated RT (IMRT) is another way to reduce BM toxicity using RT alone or in combination with Ch. This technique has been shown to significantly reduce radiation doses to critical tissues (Lujan et al. 2003). With the planning of IMRT, the volume of radiation in the BM at the thoracic level and in the cardiac circulation can be reduced, which allows reducing the irradiation on the blood cells both in RT alone and combined with Ch.

Finally, it is possible to monitor or even predict the occurrence of leukopenia or thrombocytopenia during the course of fractionated local RT using the variation in plasma concentration of the Flt-3 ligand as a biomarker for RT-induced BM damage (Huchet et al. 2003).

6 Hematological Toxicity After New Biomarker-Based Targeted Therapies in Stage IV NSCLC

In the last decade, year after year, systemic therapy for stage IV NSCLC was selected according to the presence of specific biomarkers. All patients with stage IV NSCLC should undergo molecular testing for the mutations and expression of the programmed death ligand 1 (PD-L1). Molecular alterations that predict response to treatment (e.g., EGFR mutations, ALK rearrangements, ROS1 rearrangements, and BRAF V600E mutations) are present in approximately 30% of these patients. Targeted therapy for these disorders improves PFS compared to Ch. Tyrosine kinase inhibitors such as gefitinib, erlotinib, and afatinib improve PFS in patients with EGFR mutations. In patients with overexpression of ALK protein, the response rate was significantly better with crizotinib, a tyrosine kinase inhibitor (TKI), compared to the combination of Ch-based pemetrexed and CDDP or CB (74% vs. 45%, respectively; $p < 0.001$) and PFS (median 10.9 months vs. 7.0 months; $p < 0.001$) (Rosell et al. 2012). With the new generations of TKI, these agents have been improved. In patients without biomarkers indicating susceptibility to specific targeted therapies, regimens containing immune checkpoint inhibitors (ICIs), either as monotherapy or in combination with Ch, are superior to Ch alone.

These advances in biomarker-based therapy have led to improvements in OS. For example, the 5-year OS currently exceeds 25% in patients with tumors that have high PD-L1 expression (tumor proportion score ≥50%) and 40% in patients with ALK-positive tumors (Arbour and Riely 2019). Any degree of lymphopenia and thrombocytopenia (63% and 54%, respectively) can be found after the administration of anti-EGFR, but severe toxicity is rare. The same occurs with anti-ALK targeted therapy, with some degree of anemia observed in 62% of patients, but without serious toxicities.

ICIs have radically changed the prognosis of several cancers with lasting responses. Cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death ligand 1 (PD-L1) represent ICIs that can be used as monotherapy or in combination with other agents .The toxicity profiles of ICIs differ from the side effects of cytotoxic agents, presenting new toxicities such as adverse events related to the immune system. Normally, these toxicities can occur in all organs. However, the main organs affected are the skin, digestive tract, liver, lungs, endocrine, and rheumatological systems. HT is considered as a rare toxicity with a frequency of 1%, but it can be very serious. Isolated cases of disseminated intravascular coagulation, acquired hemophilia, idiopathic thrombocytopenic purpura, and autoimmune hemolytic anemia (AHA) have been reported after ICI treatment. These occurred more frequently in patients treated for Hodgkin's lymphoma (Durrechou et al. 2020). In a recent article (Tanios et al. 2019) with 68 cases of AHA associated with ICI, they found 24 cases in patients with LC. Eighteen cases were due to nivolumab, five were due to pembrolizumab, and one was associated with atezolizumab. ICIs are believed to cause random activation of the immune system resulting in the formation of autoantibodies, activation of T-cell clones, and decreased function of regulatory T cells. AHA, although rare, is not the only hematologic

complication of ICIs. Several cases of autoimmune neutropenia, thrombocytopenia, and even pancytopenia have recently been published (Tokumo et al. 2018). Even in cases of combined treatments with Ch and ICIs for patients with metastatic NSCLC, the combination of CB, paclitaxel, atezolizumab (Socinski et al. 2018), and bevacizumab can produce an infrequent severe FN in 9% of cases. Treatment of immunotoxicity usually involves corticosteroid therapy or use of immunomodulators. In cases of HT due to ICIs, oral or intravenous (IV) corticosteroids are usually used, as well as G-CSF in cases of neutropenia. In refractory cases, IV immunoglobulins or cyclosporine treatment can be used. A complete blood count is essential to identify abnormalities before each infusion of treatment, although hematologic irregularities may not be identified with these tests. For those patients who develop toxicity with ICIs, and who are not candidates to receive other treatments for different reasons, early and adequate management of toxicity could allow resuming treatment with ICI.

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