Revisiting bleomycin from pathophysiology to safe clinical use

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Abstract

Bleomycin is a key component of curative chemotherapy regimens employed in the treatment of curable cancers, such as Hodgkin lymphoma (HL) and testicular germ-cell tumours (GCT), yet its use may cause bleomycin-induced lung injury (BILI), which is associated with significant morbidity and a mortality rate of 1–3%. Diagnosis of BILI is one of exclusion and physicians involved in the care of HL and GCT patients should be alerted. Pharmacogenomic studies could contribute towards the identification of molecular predictors of bleomycin toxicity.

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on the aim to optimize individual use of bleomycin. We review all existing data on bleomycin’s most recent integrated chemical biology, molecular pharmacology and mature clinical data and provide guidelines for its safe clinical use.

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1. Introduction

Bleomycin is a key component of chemotherapy commonly employed in the treatment of Hodgkin lymphoma (HL) and testicular germ-cell tumours (GCT), the most highly curable cancers [1,2]. Nevertheless, bleomycin can cause severe life-threatening lung injury, which ranges from hypersensitivity pneumonitis and bronchiolitis obliterans organizing pneumonia (BOOP) to acute interstitial pneumonia and progressive pulmonary fibrosis [3]. Pulmonary toxicity is a known side effect of cancer chemotherapy [4], but a 1–4% death rate of bleomycin is judged unacceptable for patients with curable cancers [5,6]. Toxic effects of bleomycin are generally attributed to formation of free radicals [7] and organ specificity is driven by the bleomycin catalysing hydrolase, which is absent in lung and skin tissue, rendering these organs vulnerable to toxicity [8].

2. Pharmacology

2.1. Molecular pharmacology

Bleomycin sulphates are water-soluble glycopeptide products of the actinobacterium Streptomyces verticillus [9]. Drug formulations consist of a mixture of bleomycin analogues that differ in their cationic C-terminal amine. The chemical formulas used are primarily bleomycin A2 and B2 as illustrated in Fig. 1A. The crystal structures of bleomycin B2 and A2 reveal important interactions with DNA and cellular proteins (Fig. 1B).

Cytotoxic activity of bleomycin is through oxidation of deoxyribose of thymidylate and other nucleotides, which produce single-strand and double-strand breaks in DNA, chromosomal aberrations, gaps, fragments and translocations [10]. Bleomycin is deactivated by bleomycin hydrolase (BLMH), which is found predominantly in the liver, spleen, bone marrow, and intestine, but is poorly expressed in skin and lung, which relates to cutaneous effects and lung injury [11].

Resistance of tumours to bleomycin has been linked to high levels of hydrolase activity [12], but increased protein binding, decreased cellular uptake, drug inactivation by thiol and adaptation to oxidative stress and enhanced capacity to DNA repair may also participate [13].

2.2. Clinical pharmacology

Oral bioavailability of bleomycin is poor. On intravenous administration it has a terminal half-life of approximately 90 min, which increases exponentially as the creatinine clearance decreases [14]. In patients with a normal renal function approximately 65% of an administered dose is excreted in the urine as active bleomycin within the first 24 h [8], while renal dysfunction leads to significantly increased drug exposure [14]. Bleomycin poorly crosses the blood–brain barrier, however it does cross the placenta [15].

3. Pathophysiology of bleomycin-induced lung injury

Cytokines and free radicals are key effectors of BILI and are related to low levels of BLMH in lung, particularly in type II pneumocytes [3,16]. This feature renders lung cells vulnerable to toxic effects of bleomycin at mitosis [17]. On molecular level, bleomycin binds to DNA using iron ions as cofactor, and in the presence of oxygen generates hydroxyl radicals, which causes DNA breaks and leads to cell apoptosis of both epithelial and endothelial cells in lung [18].

Acute inflammation is central to development of BILI. Inflammatory exudate consists mainly of mononuclear macrophages, lymphocytes and neutrophils [19] (Fig. 2). Bleomycin stimulates alveolar macrophages to secrete inflammatory cytokines such as tumour necrosis factor (TNF), interleukin (IL)-1, IL-18 [20], IL-22 and IL-17a [21] and endothelial cells to secrete IL-6 [22,23]. Cytokines activate lymphocytes and upregulate the expression of adhesion molecules on endothelial cells facilitating inflammatory cells to adhere to the endothelium, influx into the interstitium and damage endothelial cells through the Fas–FasL pathway [24]. Fibroblasts are activated early in BILI through stimulation of fibronectin, which is produced by damaged endothelial cells or stimulation by cytokines, such as TNF, platelet derived growth factor (PDGF) and transforming growth factor β (TGFβ) [25]. Continued exposure of lung to bleomycin can lead to increasing collagen synthesis and deposition of various matrix proteins including collagens, elastin, and proteoglycans [26]. Moreover, bleomycin-activated alveolar macrophages stimulate the synthesis of hyaluronan, a connective tissue molecule that is seen in fibrotic lungs [17]. T lymphocytes are also involved in the inflammation driven lung damage. They release cytokines secreted during Th1 inflammation (e.g., IFN-γ) or Th2 inflammation (e.g., IL-13) that modulate the expression of growth factor activity through the STAT family of transcription factors [27].
Fig. 1. (A) Chemical structures of bleomycin A2 and bleomycin B2. (B) Structure of bleomycin A2 and bleomycin B2 in associated protein/DNA complexes. (A) Crystal structure of DNA-bound Co(III)-bleomycin B2 (pdbid: 2R2S [87]). The N-terminal fragment of Moloney murine leukaemia virus reverse transcriptase and a 7.5-bp oligonucleotide duplex are shown as ribbon, bleomycin B2 is shown as balls and sticks. (B) Bleomycin B2 from (A) is shown as sticks. (C) Structure of the copper (II)-bound bleomycin A2 complexed with the bleomycin-binding protein from bleomycin-producing Streptomyces verticillus (pdbid: 1JIF)[88]. The bleomycin-binding protein is shown as ribbons and bleomycin A2 as balls and sticks. (D) Bleomycin A2 from (C) is shown as sticks.
4. Incidence and risk factors

Pulmonary toxicity is reported to occur in up to 46% of patients treated with bleomycin-containing chemotherapy with a mortality rate approaching 1–3% [28–31].

A number of risk factors have been identified in several clinical studies. Those are cumulative dose, old age, reduced renal function, supplemental oxygen exposure, cigarette smoking and route of drug delivery (intravenous or intramuscular administration) [3]. Cumulative dose and reduced renal function are the best recognized. Additional risk factors include administration rate (bolus versus continuous infusion), combination with nephrotoxic drugs, e.g., cisplatin, and the use of growth factors [5]. More recently, pharmacogenetic studies have associated single nucleotide polymorphisms in the bleomycin hydrolase gene with drug activity and toxicity [32,33].

A linear association between total dose and severity of BILI has early been found in animals and in humans [31,34]. The incidence of BILI increases from 3% in patients receiving a cumulative dose of <300 IU of bleomycin, to 20% in patients treated with a cumulative dose of >500 IU [5,35]. However large inter-patient variability has been noted [3]. Fatal BILI has been described in patients treated with <100 IU of bleomycin, while others receiving >500 IU did not develop any pulmonary toxicity [36,37]. In another study no difference in the cumulative dose of bleomycin was found between patients who died of BILI and those who did not [38]. Generally, cumulative doses above 400 IU are associated with increased risk for BILI, although significant lung injury can occur with lower doses [3,37,39,40].

Patients’ age is also an established risk factor for the development of BILI. Patients older than 70 years have an increased susceptibility to develop BILI [41,42]. A Scottish study found that the occurrence of fatal BILI increased with each decade after the age of 30 years [38] and in a study of 141 patients with HL, BILI was present in 33% of patients older than 40 years and in 11% of patients below 40 years of age [6].

Declining of renal function leads to increased exposure to bleomycin [14,15]. A number of clinical studies have evidenced that increased bleomycin lung toxicity is clearly associated with decline in renal function to the point that renal dysfunction is a strong predictor of bleomycin lung damage [5,43,44].

Tobacco smoking, oxygen supplementation during anaesthesia and the use of granulocyte colony stimulating factor (G-CSF) are less defined risk factors. Smoking history has been suggested as a possible risk factor for developing BILI [45,46]. Administration of high oxygen concentrations in patients undergoing surgery after exposure to bleomycin has been inculpated for potentiating BILI [47], which is also
supported by animal studies [48], but this has been questioned by other investigators [38,49].

Regarding co-treatments, brentuximab vedotin (Adcetris™), a CD30 directed antibody–drug conjugate which recently gained FDA approval for treatment of patients with refractory HL, was found to increase pulmonary toxicity of bleomycin [50]. The contribution of G-CSF and chest irradiation in promoting bleomycin associated lung injury is debated [51–55].

In the field of pharmacogenomics, De Haas et al. found that the homozygous variant G/G of BLMH gene SNP rs1050565 (c.1327A>G) is associated with reduced survival and higher prevalence of early relapses in GCT patients treated with bleomycin-containing chemotherapy but failed to find differences in the development of bleomycin-induced pulmonary toxicity based on the BLMH genotype [33].

5. Diagnosis

Diagnosis of BILI is one of exclusion, due to lack of specific symptoms, findings and tests (Table 1). BILI is suspected on the presence of a constellation of signs and/or symptoms, imaging features and lung function tests in patients treated with intravenous bleomycin [3]. The earliest symptom is dyspnoea and the earliest sign is fine rales. Pleural effusion or pneumothorax findings may also exist [3,56–59]. The more of lung parenchyma is involved the higher the impact is on symptoms and respiratory function with acute respiratory failure and acute respiratory distress syndrome (ARDS) developing in severe cases [3,56].

Pulmonary function tests are altered at the early stages, with diffusion lung capacity of carbon monoxide ($D_{LCO}$) being the most sensitive indicator [60]. Although the decline of $D_{LCO}$ lacks specificity for bleomycin and/or association with symptoms, a decrease of $D_{LCO}$ of >40% of the pre-treatment value is commonly accepted as a warning sign urging interruption of bleomycin administration [60]. A decrease of lung volumes, such as total lung capacity and a decrease of vital capacity (VC) and forced expiratory volume at 1 s (FEV1), define a typical restrictive syndrome in patients with BILI and is associated with respiratory alkalosis and decrease of pO$_2$ and pCO$_2$ [52,61].

Chest radiography may show bilateral consolidation with combined alveolar and interstitial infiltrates. Patchy infiltrates may also be present unilaterally. A pleural reaction is sometimes present [3,56]. High-resolution chest tomography (HRCT; Fig. 3) is the gold standard test to evaluate both alveolar and interstitial findings [62]. Fiberoptic bronchoscopy with broncho-alveolar lavage (BAL) does not offer diagnostic advantages, but it can rule out other causes [63].

6. Treatment of bleomycin lung injury

Steroids (prednisone 1 mg/kg/day) are the treatment of choice after exclusion of infectious causes [3]. BOOP or hypersensitivity pneumonitis respond well to steroid therapy, which is not the case for interstitial pneumonia. However,
in some cases, even after initial efficacy of steroid therapy, patients may relapse after tapering [57].

Targeted drugs developed on other indications emerge now as novel therapies for the treatment of BILI. The chronic myeloid leukaemia drugs imatinib and nilotinib, with activity against BCR-ABL, seem to offer therapeutic potentials against BILIL because of their inhibitory activity against the PDGF receptor. These drugs tested in mouse models were found to attenuate the extent of lung injury and fibrosis and to diminish inflammatory cells and levels of IL-6, IL-1beta, TNF-alpha, TGF-beta1 and PDGFR-beta, with nilotinib being more potent [64–66]. A clinical case report showed also impressive resolution of life-threatening bleomycin-induced pneumonitis with imatinib [67].

7. Guidelines of safe clinical use

7.1. Hodgkin Lymphoma

Both gold standard chemotherapy regimens for HL, ABVD and BEACOPP incorporate bleomycin in combinations [68]. Therefore sensible use of bleomycin is of uppermost importance to provide most efficient and less toxic therapy per patient [69].

Taking into consideration known risk factors and accumulated clinical evidence it is suggested that:

Patients receiving bleomycin should be questioned for dyspnea, and have careful physical examination of thorax and chest radiography at each cycle. Reported dyspnea combined with fine rales is an alert for BILIL. Wherever available a monthly monitoring of DLCO is advised on the intent to discontinue bleomycin if DLCO drops below 35% of pretreatment value [70].

All patients should have renal function assessment before the initiation of bleomycin and before each consecutive cycle of chemotherapy. Bleomycin dose should be adjusted to 70–40% of normal dose in cases creatinine clearance drops below 50 mL/min [71].

Regarding co-treatments, bleomycin must not be given in combination with brentuximab vedotin [50]. G-CSF should be used with caution and only after an episode of febrile neutropenia, or in order to avoid treatment delays. Radiotherapy should be withheld for a minimum of four weeks post bleomycin administration to avoid pulmonotoxic synergy. Finally for HL patients on surgery who had recently been given bleomycin, careful fluid balance and avoidance of high O2 concentrations inhalation is recommended.

7.2. Testicular germ cell tumours

GCTs represent the most common solid cancers in young men with an increasing incidence [72]. Therapy optimization for metastatic GCTs by means of more efficient platinum regimens, patient risk categorization and reduced toxicity and duration of therapy, when appropriate, has lead to approximately 90% cure rate [73,74].

Although the use of bleomycin is not questioned in patients with intermediate or poor prognosis metastatic GCTs, it has been the field of controlled randomized studies in patients with good-risk GCTs, mainly due to concerns of pulmonary toxicity [38,75–79]. Several clinical research groups have worked on this issue but differences in the criteria for pulmonary toxicity, for discontinuation of bleomycin (and cisplatin) therapy and the reporting requirements make comparisons difficult. Rates of reported pulmonary toxicity vary from 5% to more than 50%, and mortality rates of 0–4% [38,78–80].

In the US, the Memorial Sloan-Kettering Cancer Center (MSKCC) Group suggests that four cycles of etoposide and cisplatin (4EP) are equivalent to three cycles of bleomycin, etoposide and cisplatin (3BEP) and should be considered as another standard regimen for the treatment of good-risk metastatic GCT [81]. Similarly the Indiana Group suggests 3BEP for good-risk patients and retains 4EP for patients older than 50, heavy smokers, or those with serum creatinine higher than 2 mg/dl [82].

In Europe, an EORTC group study compared EP to BEP for good-prognosis GCT patients showed that 3BEP is sufficient for good-prognosis GCTs. Moreover, acute BILIL was more frequent in patients treated with 4 versus 3 cycles of therapy (20% versus 14%) [83]. In another study the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG) suggests that 3BE500P is the treatment of choice for patients with good-risk metastatic nonseminomatous GCT and 4E500P should only be used if there is a contraindication for bleomycin [77]. Again, the Australian and New Zealand Germ Cell Trials Group found that three cycles of dose-intense BEP (30 kU bleomycin on days 1, 8, and 15; 100 mg/m2 etoposide on days 1–5; and 20 mg/m2 cisplatin on days 1–5, repeated every 21 days: 3B90E500P) outperforms four cycles of standard BEP (4B30E360P) by terms of survival and toxicity despite higher total bleomycin dose [84].

Finally, the M.D. Anderson Cancer Center (MDACC) group suggests that bleomycin should i. be suspended upon suspicious symptoms and/or signs or when there is a greater than 10% decline in FVC or more than 20% decline in DLCO and ii. be held at first cycle in patients with high volume lung metastases plus dyspnoea at presentation and/or pO2 <80 mmHg or both to decrease ARDS rate at treatment start [85,86].

8. Conclusions

Bleomycin-containing regimens remain the standard of care for HL and for patients with intermediate and poor-risk GCTs. Those patients need close medical monitoring
for early diagnosis of lung toxicity to prevent morbidity and mortality. Although no category 1 recommendations exist, the following are generally accepted guidelines in this setting:

- consider all risk factors for BILI when treating patients with HL or GCT;
- maintain dose-intensity/density in parallel with efforts to minimize potentially lethal BILI;
- carefully assess for symptoms or signs suggestive of pulmonary toxicity, perform DLco/FVC tests;
- discontinue bleomycin in case of clinical or radiographic signs of pulmonary toxicity and/or if significant declines in DLco;
- restrict the total bleomycin dose to less than 400 IU;
- consider omitting bleomycin at first cycle in the rare case of high volume choriocarcinoma, extensive lung metastases, hemoptysis or hypoxemia;
- limit as much as possible the inhaled oxygen concentration (<30%);
- cease smoking (lifelong);
- monitor the fluid balances to minimize the risk for clinically significant lung toxicity;
- consider substituting 4EP for 3BEP in good-risk metastatic GCTs for patients with higher risk for bleomycin toxicity (i.e., smokers, advanced age, renal insufficiency not amenable to correction before initiation of treatment, prior radiation therapy);
- efforts are currently undertaken to develop pharmacogenomic predictors of bleomycin toxicity by studying variants of the gene that encodes bleomycin hydrolase.

**Conflict of interest statement**

The authors have no conflict of interest.

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