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Master thesis | Original study

Anesthetic implications in patients with previous bleomycin exposure: a narrative review

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Abstract

Bleomycin lung toxicity is still a big fear for many anesthetists and their patients after bleomycin therapy. Clinicians avoided using high oxygen concentrations and hypoxic mixtures perioperatively since early publications of fatal respiratory failure were thought to be caused by a high inspiratory oxygen fraction. Up until today, bleomycin is still a frequently used chemotherapeutic. Anesthetists will therefore encounter patients who were exposed to bleomycin. Several other risk factors like age, renal insufficiency, cumulative dose, and smoking have been linked to the development of bleomycin-induced pneumonitis (BIP), and recent insights have questioned the link between hyperoxia and lung toxicity. This review provides an overview of evidence- and opinion-based recommendations concerning

Keywords: **Bleomycin, bleomycin lung toxicity, bleomycin-induced pneumonitis, oxygen, anesthesia.**

Introduction

Bleomycin (Figure 1), an antitumor antibiotic, is a chemotherapeutic drug still widely used to treat germ cell tumors of the testes, Hodgkin lymphomas, and squamous cell carcinomas of the head and neck. The drug has been very effective in treating these malignancies, but its major limitation is its pulmonary toxicity, also known as bleomycin-induced pneumonitis (BIP)1. The incidence is estimated to be up to 10%[1–3]. We will first explain the concept of BIP, its risk factors, diagnostic tests, and treatment. We will then discuss the management of patients with previous bleomycin exposure and the approach to BIP perioperatively.

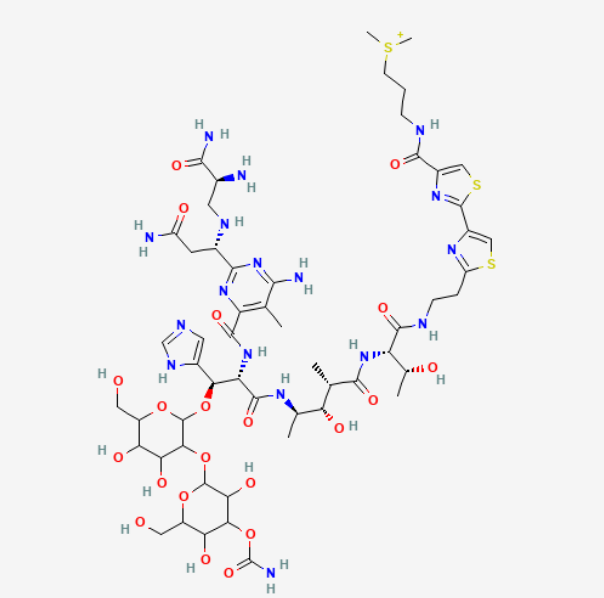

Fig. 1 — Chemical structure of bleomycin.

Methods

An extensive literature review was performed using PubMed and The Cochrane Library. The Medical Subject Heading (MeSH) terms were used to search for articles. The initial literature search included reports from 2000 up to November 2022. Because of the limited number of relevant articles, I extended this search to 1990. The search string included keywords “bleomycin” and “bleomycin-induced pneumonitis”, “bleomycin lung toxicity”, “oxygen” and “anesthesia”. Our search included articles of patients treated with bleomycin who had

subsequently anesthesia or were treated with oxygen. And secondly, articles about the diagnosis and treatment of BIP. Animal and in vitro studies were excluded. Data were supplemented by exploring the reference list of previously found relevant articles. This manuscript was approved after ethical review (MP025359, SCONE) and adheres to the applicable EQUATOR guidelines. A PRISMA flow chart is presented in Figure 2.

Results

Pharmacology of bleomycin

Bleomycin was isolated from the fungus Streptomyces verticillus for the first time in 1966[2]. It is inactivated by bleomycin hydrolase, an enzyme with lower skin and lung activity. Hence, the lungs and skin are most prone to toxicity[4]. Bleomycin hydrolase activity is high in the bone marrow, which explains its minimal myelosuppressive effect and is, therefore, particularly well suited as a multiagent chemotherapy drug. The kidneys primarily eliminate bleomycin; half of the dose is cleared within 4 hours and 70% by 24 hours. Renal impairment can significantly decrease the clearance of bleomycin[5]. Table I summarizes the physicochemical properties of bleomycin.

Bleomycin and lung toxicity

Bleomycin is still a popular chemotherapeutic because of its effectiveness and few myelosuppressive side effects. Still, its major drawback is the fear of lung toxicity, also known as bleomycin-induced pneumonitis (BIP). Eventually, it can progress to fibrosis. The exact mechanism of BIP is not entirely resolved. Still, it is thought to involve a relative deficiency of bleomycin hydrolase in the lungs, oxidative damage, genetic susceptibility, and the elaboration of inflammatory cytokines[1]. Several other distinct pulmonary syndromes have been associated with bleomycin exposure, such as bronchiolitis obliterans organizing pneumonia (BOOP) and eosinophilic hypersensitivity[1,6]. In patients receiving bleomycin therapy for treating germ cell tumors, BIP incidence is as high as 10% and can be critical up to 20%[7]. In the case of lymphomas, pulmonary toxicity can be as high as 18%, with a mortality rate of 24%[8]. This may, however, be an underestimate. The TE3 study showed that 70.5% of the patients had subtle parenchymal changes consistent with fine sub-pleural linear opacities on a computed tomography (CT) scan[9]. Lung toxicity can start during treatment and up to months or even years after discontinuing the therapy[10–13]. Other rare but

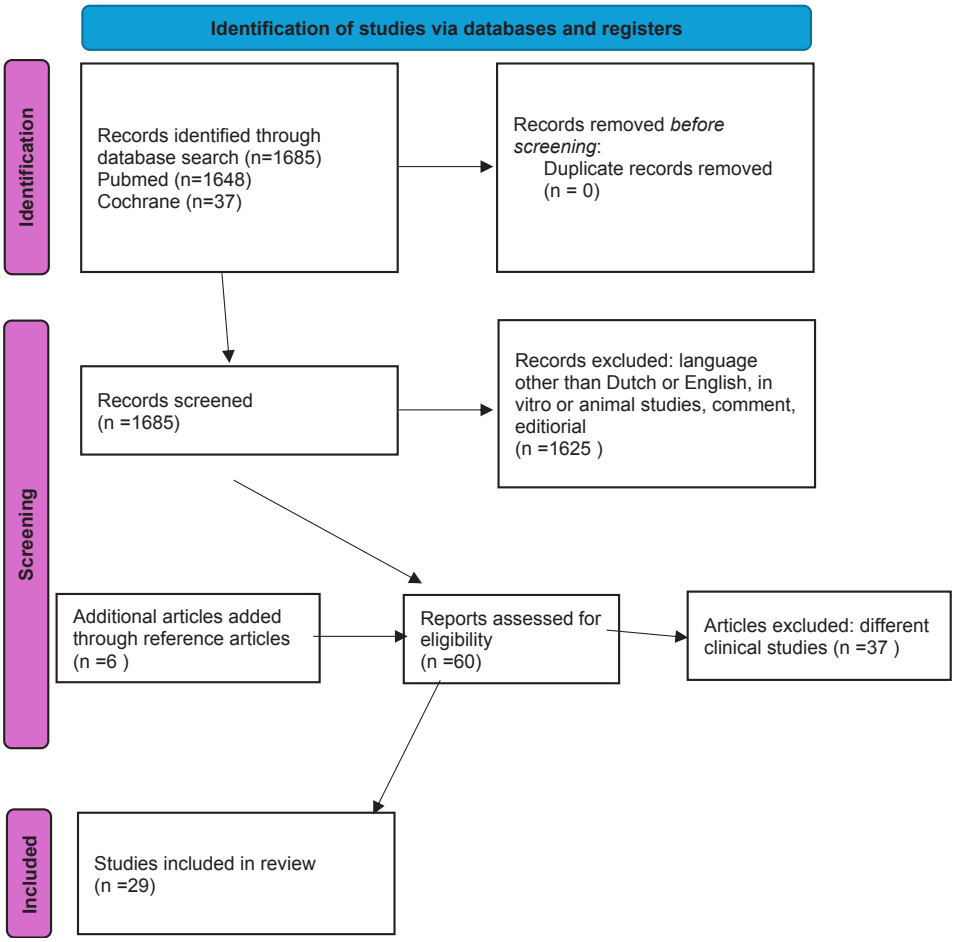

Fig. 2 — PRISMA flow diagram.

Table I. — Physicochemical properties of bleomycin.

Chemical nomenclature	Bleomycinamide, N^1-[3- (dimethylsulfonio)-propyl]-
Empirical formula	$C_{55}H_{84}N_{17}O_{21}S_3^+$
Molecular weight	1415.55 g/mol
Appearance	White to yellowish powder
Melting point	71 ºC
Water solubility	20 g/L

severe and sometimes fatal pulmonary complications include pneumothorax and pneumomediastinum, as published in case reports[11,14]. Hence, the anesthesiologist should be aware of it.

Clinical diagnosis of BIP can be difficult since symptoms mimic other conditions in cancer patients, like pneumonia and pulmonary metastasis. Patients present with aspecific symptoms like fever, non-productive cough, dyspnea, tachypnea, and bibasal crepitations on auscultation[1]. The most sensitive symptom for predicting BIP is cough, followed by dyspnea[15]. Chest radiography can reveal bibasal infiltrates but can also present with lobar infiltrates. Abnormalities may be seen earlier on CT scan and present as small linear and subpleural nodular lesions or ground glass opacifications (Figure 3)[16]. Chest radiography has extremely low sensitivity, and high-resolution computed tomography (HRCT) is the preferred investigation when BIP is suspected[15]. Pulmonary function tests can aid in the diagnosis of BIP. Spirometry and lung volumes can show a restrictive pattern with decreases in forced vital capacity (FVC) and total lung capacity (TLC)[1]. In the past, the diffusion capacity of carbon monoxide (DLCO) was the primary test to predict lung toxicity, but it appeared not to be specific to bleomycin alone. Many physicians obtain a baseline set of pulmonary function tests at the start and during treatment. However, their correlation with increased toxicity is weak, and it should not be the first-line investigation for suspected lung toxicity[15]. Because of the very aspecific presentation, the diagnosis of BIP is often obtained after exclusion. Infectious diseases should be ruled out by blood tests and cultures, and malignancies by radiography. Different diagnostic criteria have been applied to diagnose BIP. Some studies defined BIP as dyspnoea requiring steroids, while others used radiography criteria for fibrotic changes. One study used acute respiratory distress syndrome (ARDS) as a clinical parameter for bleomycin toxicity[17]. According to a best-practice clinical guideline for using bleomycin, the final diagnosis of BIP is based on a combination of systemic symptoms such as non-productive cough and dyspnea with characteristic radiological findings on HRCT[15].

Risk factors for bleomycin-induced pneumonitis

Several risk factors have been described to contribute to the development of BIP: age, renal impairment, bleomycin dose, and smoking. As mentioned in a retrospective study from NHS, age is a risk factor: patients above 40 had an increased risk of developing bleomycin-induced pulmonary toxicity[3]. Another study from the Mayo Clinic in 2005 with 141 patients confirms this statement[8]. A reasonable explanation might be a decreased ability to heal from pulmonary tissue damage or a reduced kidney function with increasing age. Because treatment-related toxicity remains a substantial

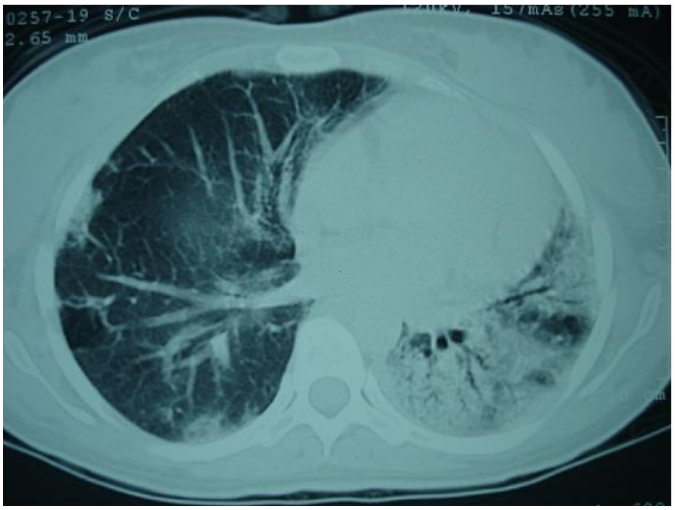

Fig. 3 — CT scan of a patient with bleomycin-induced pneumonitis.

concern, it is common practice for some Hodgkin lymphoma regimens to exclude bleomycin in older patients[18–20]. Renal insufficiency is another risk factor for developing bleomycin toxicity[3,21]. The drug is excreted unchanged for 70% by the kidneys, and its half-life is 2 to 5 hours in patients with normal kidney function but could be prolonged to even 30 hours when glomerular filtration rates are substantially reduced[4]. Hence, a fall in glomerular filtration rate puts the patient at a higher and prolonged risk for developing BIP because of low levels of the enzyme bleomycin hydrolase. The rate of developing pulmonary complications was three times higher in patients with a glomerular filtration rate of less than 80 ml/min in an NSH report of 835 patients treated with bleomycin[3]. Renal function can also be compromised by renal damage from cisplatin, frequently used concomitantly with bleomycin, or by a mechanical obstruction secondary to an abdominal tumor. Close monitoring of the renal function of patients receiving bleomycin is necessary, especially in patients with prior or progressing renal dysfunction during therapy. Doses above 300 and 450 units are associated with a substantial rise in pulmonary toxicity. The risk of developing BIP was 8.5%, with a bleomycin dose above 300 units[3]. There is consensus and even a black box warning that the cumulative dose of the drug should not exceed 400 units. It is still unclear if BIP is mainly dose-dependent since toxicity has also occurred at doses as low as 20 to 60 units[21]. Current or former cigarette smoking is associated with an increased risk for BIP1. Smoking was a risk factor for postoperative ARDS In a review of 316 patients from the Mayo Clinic who had received bleomycin chemotherapy and subsequently had surgery[17].

The most controversial risk factor is hyperoxia and bleomycin exposure. The concept of oxygen restriction arose following the landmark paper by Goldiner et al. in 1978[22]. Five patients treated with bleomycin in their institution developed severe respiratory distress three to five days after retroperitoneal lymph node excision. Eventually, all five died after mechanical ventilatory support and, in one case, after extracorporeal membrane oxygenation. The authors assumed that oxygen concentration and fluid management might have contributed to the high postoperative mortality. The implementation of a new protocol was applied. Oxygen exposure was reduced, and fluid management was carefully monitored with a Swan Ganz catheter. After implementing these new standards, none of the 12 patients who had post-bleomycin surgery developed acute respiratory distress syndrome or deceased from postoperative pulmonary complications. Goldiner presumed that the inspired oxygen fraction (FiO2) should be kept as low as possible perioperatively and that there should not be excessive fluid overload. Furthermore, the contradiction of supplemental oxygen after bleomycin was widely recognized during the 1980s based on the studies of Goldiner. However, the studies consisted of a limited number of patients and the first group was studied retrospectively, whereas the second group was studied prospectively with intensive monitoring. A strong causal link between bleomycin, oxygen, and pulmonary complications was not found, and researchers started to question this proposed causal relationship. Donat et al. examined 77 bleomycin-treated patients undergoing 97 major surgeries over eight years. The mean bleomycin dose of 437 exceeded the recommended dose to be below 400 units, and the mean latency to bleomycin and oxygen was 6.4 months. Intraoperative oxygen was not the cause of postoperative pulmonary complications. The mean oxygen concentration in the pulmonary complication group was 0.39 and 0.41 in the non-pulmonary complication group. They concluded that excessive crystalloid administration was the main cause of postoperative respiratory failure, not oxygen[23]. In most surgeries, keeping the oxygen as low as possible is feasible, and the FiO2 can be lowered as soon as the patient is intubated and ventilated. Wuethrich et al. showed that a three-minute preoxygenation with 100% FiO2 is safe, while perioperative FiO2 was kept at 30%[24]. This finding is interesting since we would otherwise put patients unnecessarily in danger while preoxygenating with hypoxic mixtures. By extension and in line with the belief that oxygen in combination with bleomycin might be harmful, hyperbaric oxygen (HB02) was avoided in patients post-bleomycin exposure. However, HBO2 has been used closely with bleomycin without persistent pulmonary complications. A case series of fifteen patients showed the safe administration of HBO2. The main indication for therapy was radionecrosis. Total bleomycin dose ranged from 40 to 225 IU. The median age at the time of HB02 was 52 years (range 22-77). Median bleomycin-to-HBO2 latency was 34 months. Three patients received HBO2 within six months and seven within two years of their last bleomycin exposure[25]. It is interesting and reassuring that oxygen supply under hyperbaric conditions can be administered safely after bleomycin exposure. This is the only study investigating the effect of oxygen alone as a risk factor on the development of BIP. Only 15 patients were studied, though the results further question the need for strict perioperative oxygen restriction for

patients exposed to bleomycin years ago. The risk of lung toxicity after bleomycin treatment seems to decrease over time, as we notice the incidence is highest during and up to 6 months after exposure. In a study investigating the risk factors of BIP in patients with germ-cell tumors, the median latency of exposure to toxicity was 4.2 months, and the 5-year free BIP rate was 93%[3]. Although, we still must be cautious since some reports of late lung injury after years of bleomycin treatment have been described[13,26].

Treatment of acute bleomycin-induced pneumonitis

Treatment for BIP includes the withdrawal of chemotherapy, supportive measures with ventilatory support with prolonged protective ventilation, and corticosteroid administration. If necessary, lung-protective ventilation with PEEP titration should be applied. No randomized controlled trials are available regarding the effectiveness of corticosteroids, but some case reports describe good recovery in symptomatic patients. Infection should be ruled out before starting corticosteroids. As mentioned above, bleomycin can give different patterns of pulmonary injury: organizing pneumonia, hypersensitivity pneumonitis, interstitial pneumonitis, and eventually fibrosis. The latter does not always respond to glucocorticoids. The optimal dose and duration of glucocorticoid therapy are unknown. Based on clinical experience and case reports, authors advise starting with 0.75 to 1 mg/kg prednisone for at least four weeks, followed by a dose reduction based on clinical findings[12]. There are no data on whether there is a protective effect of glucocorticoids perioperatively. In extreme cases, patients need extracorporeal membrane oxygenation (ECMO). VV-ECMO has been used to minimize ventilator-induced lung injury and even as a bridge to transplantation in selected cases[27]. The mortality rate is high. Six case reports of BIP required ECMO support, and the cumulative survival was 33% (2/6)[28].

Discussion

As anesthesiologists, we must be especially aware of lung complications in patients who received bleomycin. Not everyone has the same risk of developing lung toxicity. There are several contributing risk factors, and patients with multiple risk factors are more at risk. In a study by O' Sullivan, the median time to develop BIP is 4.2 months. The probability of developing BIP is 32% for a patient above 40 years old with a cumulative bleomycin dose > 300 units and a glomerular filtration rate of less than 80 ml/min. If the patient only had one risk factor, his probability would be 5.4%, 8.5%, and 11.4% in the group for age above 40 years, glomerular filtration rate <80ml/min, and bleomycin dose >300 units, respectively3. We will further discuss a patient's pre-, per- and postoperative management after bleomycin exposure, followed by the management of someone who develops BIP perioperatively. Figure 4 presents a flow chart that can be used as a guideline for patients treated with bleomycin.

Preoperatively

The preoperative management is mainly based here on the risk of developing BIP. A patient still under bleomycin therapy which needs urgent surgery, poses more risk than someone exposed more than five years ago. We can state that patients who are still undergoing their chemotherapy course and had exposure until six months ago are at high risk for BIP. They should have a preoperative consultation with an anesthetist. Patients should be assessed for risk factors like age, renal impairment, cumulative dose, and smoking[1,3,8,17,19,20]. Also, check for other concomitant chemotherapy use, like cisplatin which is nephrotoxic and increases bleomycin toxicity by reducing its elimination3. A blood test with particular attention to kidney function is mandatory. A new dry, unproductive cough or exertional dyspnea are symptoms of BIP and require further investigation[15]. Most patients get pulmonary function tests during their chemotherapy, but they are unreliable predictors of bleomycin toxicity[15]. Also, a normal chest X-ray is unreliable in excluding BIP. In doubt or when BIP is suspected, HRCT is preferred when possible[15]. We recommend contacting the pneumologist or oncologist for high-risk patients to check for signs of BIP during treatment. Corticosteroids can be started perioperatively in agreement with the attending physician. The risk of developing BIP after five years of exposure is much less, but not zero. There are case reports of late BIP; theoretically, there is a lifelong risk. The need for a preoperative consultation will be based on the surgery and the ASA score of the patient. However, a preoperative visit can also be reassuring and informative concerning personal risk factors and individual anesthetic plans. Some patients know the possible link between lung toxicity and oxygen after bleomycin and might have questions concerning using oxygen during anesthesia.

Perioperatively

The main concern perioperatively is the use of supplemental oxygen. Although the evidence that

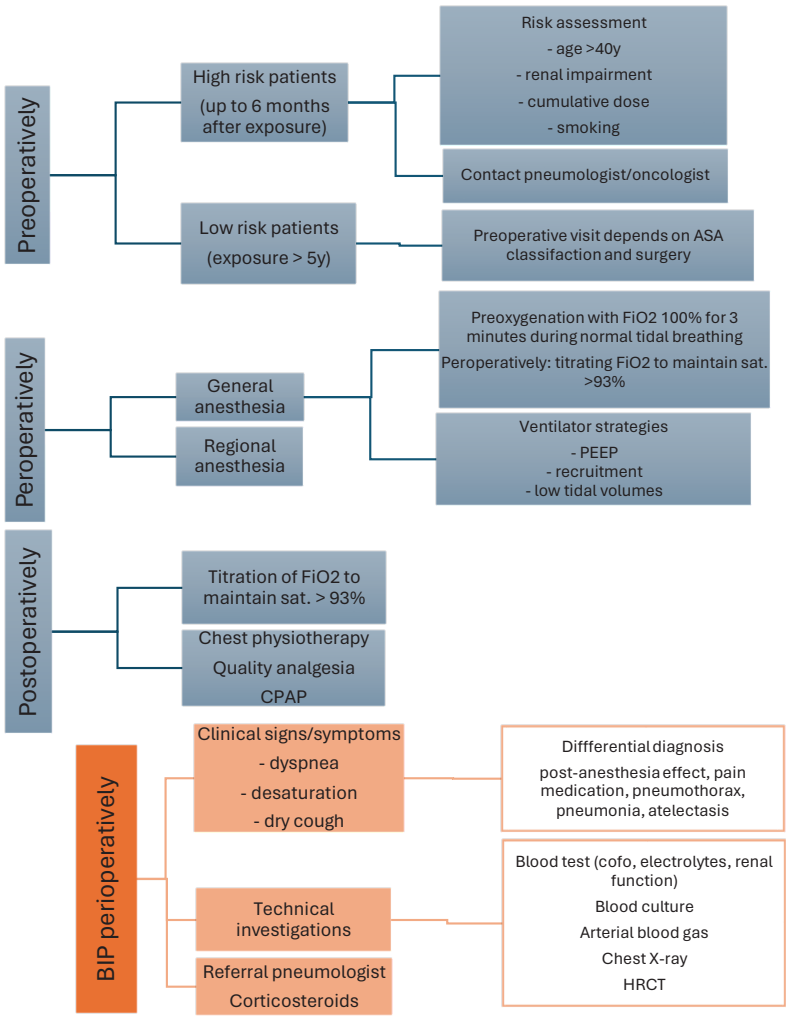

Fig. 4 — Flowchart anesthetic management after bleomycin exposure.

high fractions of inspired oxygen may increase the risk of BIP in humans is largely anecdotal, many authors still advise being cautious with oxygen. Titrating the FiO2 as low as possible to target saturations above 93% is suitable for most patients and if they have normal hemoglobin levels. There is no superior anesthetic technique for patients post-bleomycin exposure. Every case should be extensively reviewed and will be based on the location and magnitude of the surgery and the patient's characteristics. A locoregional technique can be a good alternative if it allows satisfactory surgical anesthesia. It avoids the use of oxygen and ventilatory-associated pulmonary complications. A recent study has shown that pre-oxygenation with 100% oxygen can be safely administered for three minutes[24]. Ventilatory strategies to prevent atelectasis and volutrauma should be applied as well. Positive end-expiratory pressure (PEEP) and recruitment maneuvers will limit the amount of oxygen required. Fluids should be given somewhat more restrictive than liberal[29]. Anesthetic monitoring should at least include continuous oxygen saturation. The use of an arterial line for subsequent PaO2 monitoring should be based individually on the patient's characteristics and the extent of the surgery.

Postoperatively

Careful titration of oxygen should also be maintained postoperatively. Only use high fractions of oxygen when needed or in urgent cases. Chest physiotherapy, good analgesia, proper upright position in bed and continuous positive airway pressure (CPAP) are easy tools to minimize the need for oxygen.

Bleomycin-induced pneumonitis perioperatively

When BIP is suspected perioperatively, referral to or discussion with a pneumologist specialized in interstitial lung disease is recommended. The most sensitive symptom of BIP is a cough[15]. Unfortunately, this symptom is not very specific in the postoperative care setting, and patients will instead present with dyspnea or arterial oxygen desaturation. The differential diagnosis of a patient in respiratory distress would be post-anesthesia effect and pain medication, pneumothorax, pneumonia,

atelectasis, and acute lung oedema. Pulmonary function tests can be considered, but patients are often too weak to perform this test immediately postoperative. HRCT is the investigation of choice in suspected BIP, but in the acute setting only sometimes available. Although chest radiography has very low sensitivity, it is the easiest and fastest tool for imaging the lungs, excluding pneumothorax[15]. In adjunction, lung ultrasound can also be used to look for pneumothorax or oedema. Blood tests focusing on infectious parameters to rule out infection and arterial blood gas to monitor the extent of respiratory failure are recommended.

Conclusions

Bleomycin is still a frequently used chemotherapeutic. Anesthetists will therefore encounter patients who were exposed to bleomycin. The use of supplemental oxygen is still controversial. Although most studies regarding oxygen and bleomycin are retrospective or prospective, we conclude that the risk of developing BIP is not negligible. The highest incidence of BIP is up to 6 months after bleomycin therapy and seems to diminish over time[3]. Although, case reports of late BIP prove that there is a rare but possible lifelong risk of developing lung toxicity. Additionally, several risk factors increase the risk of BIP. These include age, renal insufficiency, cumulative dose, and smoking. Treatment of BIP consists of pausing ongoing bleomycin therapy, ventilatory support, and corticosteroids. The perioperative management of patients after bleomycin exposure is based on their risk for developing BIP. The use of PEEP or offering regional anesthesia can be used to avoid high oxygen fractions. We advise titrating FiO2 to target saturation at least above 93%[29]. Preoxygenation with 100% oxygen is safe for a short period and does not put the patient at risk for disastrous desaturations[24]. Anesthetists should also be aware of the possible lung toxicity after bleomycin exposure, including pneumothorax and pneumomediastinum[1,14]. In case of suspicion of BIP perioperatively, discussion with a pneumologist is recommended. Based on the available literature, we suggest the following recommendations regarding bleomycin exposure and anesthesia.

1. Caution regarding oxygen therapy, patients should not be denied oxygen therapy in case of hypoxia.
2. The lowest FiO2 that provides adequate tissue oxygenation should be provided if supplemental oxygen is needed.
3. Preoperative anesthesia consultation with risk factor analysis is highly recommended for high-risk patients with a history of bleomycin therapy.
4. Patients should carry wallet cards or wrist bracelets, alerting caregivers to possible toxicity with high inspiratory concentrations of oxygen.

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References

1. Sleijfer S. Bleomycin-Induced Pneumonitis. Chest 2001; 120: 617–24.
2. Meadors M, Floyd J, Perry MC. Pulmonary Toxicity of Chemotherapy. Semin Oncol 2006; 33: 98–105.
3. O'Sullivan JM, Huddart RA, Norman AR, Nicholls J, Dearnaley DP, Horwich A. Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. Annals of Oncology 2003; 14: 91–6.
4. Evans WE, Yee GC, Crom WR, Pratt CB, Green AA. Clinical Pharmacology of Bleomycin and Cisplatin. Drug Intell Clin Pharm 1982; 16: 448–58.
5. Alberts DS, Chen H-SG, Liu R, Himmelstein KJ, Mayersohn M, Perrier D et al. Bleomycin pharmacokinetics in man. Cancer Chemother Pharmacol 1978; 1. doi: 10.1007/BF00253118
6. Reinert T, Baldotto CS da R, Nunes FAP, Scheliga AA de S. Bleomycin-Induced Lung Injury. Journal of Cancer Research 2013; 2013: 1–9.
7. Simpson A, Paul J, Graham J, Kaye S. Fatal bleomycin pulmonary toxicity in the west of Scotland 1991-95: a review of patients with germ cell tumours. Br J Cancer 1998; 78: 1061–6.
8. Martin WG, Ristow KM, Habermann TM, Colgan JP, Witzig TE, Ansell SM. Bleomycin Pulmonary Toxicity Has a Negative Impact on the Outcome of Patients With Hodgkin's Lymphoma. Journal of Clinical Oncology 2005; 23: 7614–20.
9. Shamash J, Sarker S-J, Huddart R, Harland S, Joffe JK, Mazhar D et al. A randomized phase III study of 72 h infusional versus bolus bleomycin in BEP (bleomycin, etoposide and cisplatin) chemotherapy to treat IGCCCG good prognosis metastatic germ cell tumours (TE-3). Annals of Oncology 2017; 28: 1333–8.
10. Batra S, Vaid AK, Bhargava R, Gupta S. Lungs on fire. Case Reports 2013; 2013: bcr2013010388–bcr2013010388.
11. Keijzer A, Kuenen B. Fatal Pulmonary Toxicity in Testis Cancer With Bleomycin-Containing Chemotherapy. Journal of Clinical Oncology 2007; 25: 3543–4.
12. White DA, Stover DE. Severe Bleomycin-Induced Pneumonitis. Chest 1984; 86: 723–8.
13. Uzel I, Ozguroglu M, Uzel B, Kaynak K, Demirhan O, Akman C et al. Delayed onset bleomycin-induced pneumonitis. Urology 2005; 66: 195.
14. Barras M, Uhlmann M. Spontaneous Pneumomediastinum and Bilateral Pneumothoraces in a Patient with Bleomycin-Induced Pneumonitis. Eur J Case Rep Intern Med 2017 Oct 9; 2. doi: 10.12890/2017_000727
15. Watson RA, De La Peña H, Tsakok MT, Joseph J, Stoneham S, Shamash J et al. Development of a best-practice clinical guideline for the use of bleomycin in the treatment of germ cell tumours in the UK. Br J Cancer 2018; 119: 1044–51.
16. Rimmer MJ, Dixon AK, Flower CDR, Sikora K. Bleomycin lung: computed tomographic observations. Br J Radiol 1985; 58: 1041–5.
17. Aakre BM, Efem RI, Wilson GA, Kor DJ, Eisenach JH. Postoperative Acute Respiratory Distress Syndrome in Patients With Previous Exposure to Bleomycin. Mayo Clin Proc 2014; 89: 181–9.
18. Follows GA, Barrington SF, Bhuller KS, Culligan DJ, Cutter DJ, Gallop□Evans E et al. Guideline for the first□

line management of Classical Hodgkin Lymphoma — A British Society for Haematology guideline. Br J Haematol 2022; 197: 558–72.
19. Cheng PTM, Villa D, Gerrie AS, Freeman CL, Slack GW, Gascoyne RD et al. The outcome of older adults with classic Hodgkin lymphoma in British Columbia. Blood Adv 2022; 6: 5924–32.
20. Thomas TS, Luo S, Reagan PM, Keller JW, Sanfilippo KM, Carson KR. Advancing age and the risk of bleomycin pulmonary toxicity in a largely older cohort of patients with newly diagnosed Hodgkin Lymphoma. J Geriatr Oncol 2020; 11: 69–74.
21. McLeod BF, Lawrence HJ, Smith DW, Vogt PJ, Gandara DR. Fatal bleomycin toxicity from a low cumulative dose in a patient with renal insufficiency. Cancer 1987; 60: 2617–20.
22. Goldiner PL, Carlon GC, Cvitkovic E, Schweizer O, Howland WS. Factors influencing postoperative morbidity and mortality in patients treated with bleomycin. BMJ 1978; 1: 1664–7.
23. Donat SM, Levy DA. Bleomycin associated pulmonary toxicity: is perioperative oxygen restriction necessary? Journal of Urology 1998; 160: 1347–52.
24. Wuethrich PY, Burkhard FC. No Perioperative Pulmonary Complications after Restricted Oxygen Exposition in Bleomycin-Treated Patients: A Short Report. ISRN Anesthesiol 2011; 2011: 1–3.
25. Torp KD, Carraway MS, Ott MC, Stolp BW, Moon RE, Piantadosi CA et al. Safe administration of hyperbaric oxygen after bleomycin A case series of 15 patients. Undersea Hyperb Med 2012; 39(5):873-9
26. Jóna Á, Miltényi Z, Ujj Z, Garai I, Szilasi M, Illés Á. Late pulmonary complications of treating Hodgkin lymphoma: bleomycin-induced toxicity. Expert Opin Drug Saf 2014; 13: 1291–7.
27. Narayan V, Deshpande C, Bermudez CA, Golato JM, Lee JC, Diamond J et al. Bilateral Lung Transplantation for Bleomycin-Associated Lung Injury. Oncologist 2017; 22: 620–2.
28. Odish MF, McGuire WC, Thistlethwaite P, Crotty Alexander LE. Bleomycin-induced lung injury treated with venovenous extracorporeal membrane oxygenation (ECMO) and ultra-protective ventilator settings. BMJ Case Rep 2020; 13: e236474.
29. Battadelhaizeglini D, Robba C, Rocco PRM, De Abreu MG, Pelosi P, Ball L. Perioperative anaesthetic management of patients with or at risk of acute distress respiratory syndrome undergoing emergency surgery. BMC Anesthesiol 2019; 19: 153.

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