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CLINICAL REVIEW

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Bleeding complications in patients with squamous cell carcinoma of the head and neck

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Abstract

Hemorrhage in recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) may be attributed to chemotherapy and local tumor irradiation. Evidence of the relationship between hemorrhage in R/M HNSCC and targeted therapies, including epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) inhibitors, or immune checkpoint inhibitors, is limited. We aimed to identify epidemiological and clinical data related to the occurrence of hemorrhage in R/M HNSCC and to explore its relationship with various therapies. We describe information obtained from literature searches as well as data extracted from a commercial database and a database from the author's institution (Istituto Nazionale dei Tumori of Milan). Evidence suggests that most bleeding events in R/M HNSCC are minor. Clinical trial safety data do not identify a causal association between hemorrhage and anti-EGFR agents or immune checkpoint inhibitors. In contrast, anti-VEGF agents are associated with increased, and often severe/fatal, hemorrhagic complications.

[Correction added on 16 Jun 2021, after first online publication: A new affiliation has been included for Prof. Licitra after the initial publication.]

KEYWORDS

antiangiogenic drugs, head and neck squamous cell carcinoma, hemorrhage, immune checkpoint inhibitors, molecular targeted therapies

1 | INTRODUCTION

Each year, approximately 700 000 new cases of head and neck squamous cell carcinoma (HNSCC) are diagnosed in adults globally, with 380 000 deaths, including more than 10 000 in the United States alone.[1] HNSCC is a heterogeneous disease and can arise in multiple anatomical locations within the head and neck area, including the lip and oral cavity, nasal cavity, paranasal sinuses, oropharynx, larynx, and nasopharynx.[1]

Hemorrhage is a frequent problem for patients with recurrent and/or metastatic (R/M) HNSCC and can occur as either acute catastrophic events, episodic major bleeds, or ongoing low-volume oozing.[2,3] In addition to spontaneous tumor bleeding, chemotherapy and local tumor irradiation have been reported as causes of hemorrhage in R/M HNSCC.[4] The chances of bleeding in recurrent disease can be high considering tissue sequalae following previous chemoradiotherapy (CRT), and prior chemotherapy, in particular, can contribute to hemorrhage secondary to chemotherapy-induced thrombocytopenia.[5] Free radicals can trigger thrombosis, obliterate the adventitial vasa vasorum, and cause adventitial fibrosis, premature atherosclerosis, and weakening of the carotid arterial wall.[6] This can result in carotid artery rupture (carotid blowout syndrome [CBS]), which requires prompt diagnosis and intervention to avert a fatal outcome. Furthermore, high fractional and total radiotherapy doses may influence the risk of vascular mucosal damage especially in the repeat irradiation setting.[4]

In addition to CRT, surgery has been implicated in causing hemorrhage in patients with R/M HNSCC. Pseudoaneurysms have been reported in patients up to 20 years after radical neck dissection and irradiation.[7] In addition, stripping of the carotid sheath in association with neck dissection can compromise nutrition of the local tissue, rendering the carotid artery more vulnerable to CBS.[6] The adoption of reconstructive techniques that use well-vascularized flaps has helped to reduce the risk of CBS following head and neck surgery.[6]

Bacterial infections at surgical sites in the head and neck have been identified as a potential cause of vasa vasorum thrombosis and arterial wall injury.[6,8] Surgical site infection also causes tissue necrosis and fistula formation. Patients with a pharyngocutaneous fistula are particularly at risk due to trypsin enzyme activity in saliva coming into contact with the arterial wall. Exposure to salivary enzymes may result in desiccation and digestion of the carotid artery wall, leaving it prone to rupture. In addition, direct tumor invasion and accompanying inflammation may play a role in weakening the arterial wall. In cases of acute hemorrhage associated with fistula and advanced necrosis, surgical ligation might be required, although, in most cases, endovascular techniques are now standard.[6]

With the advent of promising targeted therapies for patients with HNSCC, the question arises as to whether the risk of hemorrhage will be as severe as that associated with palliative chemotherapy. A range of targeted therapies approved by the US Food and Drug Administration (FDA) and the European Medicines Agency are available for the treatment of R/M HNSCC, including epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab, panitumumab) and EGFR tyrosine kinase inhibitors (gefitinib, erlotinib, lapatinib, afatinib, and dacomitinib). The vascular endothelial growth factor (VEGF) antibody, bevacizumab, and VEGF receptor inhibitors (sorafenib, sunitinib, and vandetanib) are also being investigated as treatments for HNSCC.[9] Currently, it is unclear whether a causal association exists between the use of these agents and the occurrence of hemorrhage in R/M HNSCC. More recently, immune checkpoint inhibitors (ICIs) have emerged as viable treatment options for R/M HNSCC, including the approved drugs pembrolizumab and nivolumab.[10–21] Based on clinical trial data for these agents, and other ICIs under evaluation (durvalumab and tremelimumab), there is insufficient evidence to suggest that these agents significantly contribute to an increase in the incidence of hemorrhage in R/M HNSCC.[10–24] Knowledge of the incidence of hemorrhage with ICIs will be particularly important for combination studies, such as the ongoing evaluation of pembrolizumab plus lenvatinib (a multikinase inhibitor) in patients with HNSCC.

In this review, we provide real-world evidence on the occurrence of hemorrhage in patients with R/M HNSCC and present clinical trial data regarding a possible causal relationship between various treatments and bleeding events in patients with R/M HNSCC.

2 | DATA SOURCES

We describe relevant epidemiological and clinical data related to the occurrence of hemorrhage in patients with R/M HNSCC for a range of anticancer treatments. Information and qualitative data from the following sources

were used: PubMed (1989–2019); the Truven MarketScan® Commercial Claims and Encounters database (2010–2015)[25]; and the Head & Neck Medical Oncology Department of the Istituto Nazionale dei Tumori of Milan database (1984–2016).[26]

2.1 | Definition of hemorrhage

Hemorrhage is defined in the *Introductory Guide for Standardised MedDRA Queries (SMQs) Version 22.0*[27] as the escape of blood from vessels ("bleeding"). Small hemorrhages are classified according to size as petechiae (very small), purpura (up to 1 cm), and ecchymoses (larger). A large accumulation of blood within a tissue is called a hematoma. The *Common Terminology Criteria for Adverse Events (CTCAE)*[28] grades hemorrhage as follows: grade 1 does not require any intervention, grade 2 requires medical intervention, and grade 3 requires surgical intervention. For the purpose of the studies described in this review, all hemorrhagic events were considered as CTCAE grade ≥2 unless specified otherwise.

2.2 | PubMed

For the purposes of this narrative review, PubMed search criteria were limited to R/M information and risk factors for hemorrhage in patients with advanced cancers, particularly those with R/M HNSCC. The focus on R/M was due to patients with R/M HNSCC being more prone to hemorrhage.[3] Only papers published in English were considered. The search strategy used key words and appropriate medical subject headings, which included combinations of "bleeding," "hemorrhage," "recurrent," "metastatic," "head and neck," "CRT," "radiation therapy," "surgery," "anti-angiogenic therapy," "anti-VEGF," "anti-EGFR," "checkpoint inhibitors," and "immunotherapies." The Google search engine was also employed, applying combinations of the same search terms.

2.3 | The Truven MarketScan database

For the purposes of understanding epidemiologic data for patients in the United States, the Truven MarketScan database (established 1995) is a medical and drug insurance claims database of approximately 174 million unique de-identified patients that includes active employees, early retirees, COBRA continuers, and their dependents insured by employer-sponsored health plans. It is composed of administrative claims data of patients with commercial insurance, and additional separate data files include patients covered by Medicare supplemental insurance. The Truven MarketScan Commercial Claims and Encounters database for the years 2010–2015 was used as a data source for the evaluation of hemorrhagic events in patients with head and neck cancers. The head and neck cancer study population included patients with an initial medical encounter for cancer of the pharynx, larynx, or oral cavity (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes 140–149 and 161) indicative of a diagnosis between 2010 and 2015. Patients with tumors of uncertain origin and benign neoplasms were excluded. The population was further stratified based on those who received cancer chemotherapy using Anatomical Therapeutic Chemical codes corresponding to antineoplastic agents and who had received radiation therapy on the basis of procedure (Current Procedural Terminology) codes.

Data analyses were performed to calculate the incidence and event rates for hemorrhage. A hemorrhage event was defined on the basis of the first listed ICD-9-CM diagnostic code provided from patients' medical encounters identified by the translation of 449 preferred terms (MedDRA Version 22.0) included in the SMQ for hemorrhage. In addition, a subset of 77 preferred terms from the hemorrhage SMQ localized in the area of head and neck was defined.

Assessment of the effect of risk factors for hemorrhage was limited to an assessment of history of prior hemorrhage in the 3-month period before first treatment. Subset analyses were performed to evaluate the subsequent rates of hemorrhagic events in patients stratified based on presence or absence of prior history of hemorrhage in the 3 months before initiating palliative radiation or chemotherapy for their respective cancers. Outcomes were reported as incidence rates per 100 patients (representing the proportion of patients experiencing a hemorrhagic event) and based upon incidence densities (reported as event rates per 100 patient-years).

The HNSCC study population in the Truven dataset included patients with an initial medical encounter for cancer of the pharynx, larynx, or oral cavity indicative of a diagnosis made between 2010 and 2015. Analysis of hemorrhagic events was conducted both in patients eligible for commercial insurance (aged <65 years) and in those eligible for Medicare with supplemental insurance (aged ≥65 years).

2.4 | Istituto Nazionale dei Tumori of Milan database

A total of 259 consecutive patients with R/M HNSCC, from whom we had complete data for the analysis of hemorrhagic events, were seen between 1984 and 2016 at the Head and Neck Medical Oncology Department of the

Istituto Nazionale dei Tumori of Milan. The incidence rates of bleeding in recurrent HNSCC, specific bleeding risk factors, and cause of death were assessed and resulting life expectancy and overall survival in patients with bleeding recurrence were evaluated.

The search included patients who were aged ≥18 years at diagnosis, with histologically confirmed advanced R/M HNSCC of the oral cavity, oropharynx, hypopharynx, larynx, or unknown primary site that was not amenable to curative surgery or radiotherapy, and with measurable disease (≥10 mm in the longest diameter). The search was further narrowed to patients with tumor progression or recurrence within 6 months of the last dose of platinum therapy in the adjuvant (i.e., with radiation after surgery) and primary (i.e., with radiation) setting (first population) or recurrent or metastatic setting (second population). Patients with primary anatomic location in the head and neck not specified in the inclusion criteria, nonsquamous histologies, and other sites (e.g., nasopharynx or salivary glands or paranasal sinuses) were excluded from the analysis.

Recurrence was defined according to date of relapse, time to relapse, type of recurrence (local, nodal, soft tissue, tracheal, parastomal, lung, or metastasis), size of recurrence, dose of radiotherapy on recurrence site, concomitant local infection, number of antibiotic therapies (≤3 or >4 lines), and data on hemorrhagic events. Systemic treatment at recurrence was defined by the number of chemotherapy lines at recurrence or metastatic disease. Hemorrhage characteristics during recurrence were assessed according to site, date of first hemorrhage, and type of hemorrhage (minor, major, or fatal). Minor hemorrhage was estimated as bright red blood of half a teaspoon or more per episode of coughing (~5 mL). Major hemorrhage was defined as fatal, life-threatening, symptomatic, causing a drop in hemoglobin of 20 g/L or more, leading to transfusion of two or more units of whole blood or red cells or about 200–240 mL, or about 1 cup, in 24 h. Finally, disease evolution was date of death (or last contact with the patient) and the cause of death (hemorrhage, progressive disease, toxicity, infection, or other). The conduction of the retrospective study was approved by the institutional Ethical Committee on 26th April 2017 (local study identifier INT 77-17). Approval for patient consent waiver was obtained through the Ethical Committee.

3 | HEMORRHAGIC EVENTS IN HNSCC: REAL-WORLD EVIDENCE

3.1 | The Truven MarketScan database

In the commercially insured population (aged <65 years) with R/M HNSCC who received both radiation therapy and systemic chemotherapy, the incidence rate for a hemorrhage event was 36.7%, and the event rate was 33.4 per 100 person-years. The incidence rate for the subset of 77 preferred terms specific to hemorrhage in HNSCC was 27.6%, and the event rate was 22.7 events per 100 patient-years. When these analyses were performed after adjusting for the experience of a hemorrhagic event in the 3-month period before the most recent treatment, the incidence rate for a hemorrhagic event was 50.7%, and the event rate was 63.4 per 100 person-years. The incidence rate for the set of preferred terms related to hemorrhage in HNSCC was 44.3%, and the event rate was 50.5 events per 100 patient-years.

In the supplemental Medicare coverage population (aged ≥65 years) with HNSCC who received both radiation therapy and systemic chemotherapy, the incidence rate for a hemorrhagic event, based upon hemorrhage SMQ was 53.4%, and the event rate for the hemorrhage SMQ was 52.1 per 100 patient-years. The incidence rate for the set of preferred terms was 38.4%, and the event rate for the preferred terms related to hemorrhage in HNSCC was calculated as 31.0 events per 100 patient-years.

The present analysis of the Truven MarketScan database suggests that patients with HNSCC who had received radiation or chemotherapy have a higher likelihood of hemorrhage given a history of hemorrhage prior to first treatment for recurrent disease than no prior history. Furthermore, these analyses suggest that this increased risk of bleeding given a prior history of bleeding may be worse in patients ≥65 years than in those <65 years of age.

3.2 | Istituto Nazionale dei Tumori of Milan database

In the Head & Neck Medical Oncology Department at the Istituto Nazionale dei Tumori of Milan,[26] hemorrhage events were analyzed from 259 consecutive patients with R/M HNSCC treated between 1984 and 2016, according to the presence or absence of hemorrhage from the cancer lesion itself in the context of R/M disease. The median follow-up time was 24 months (range, 1–303).

Patient demographics and disease characteristics of the 259 patients are listed in Table 1. In total, 110 of 259 patients (42%) with R/M HNSCC experienced at least one hemorrhagic event, of which 104 (95%) experienced hemorrhage in the head and neck (Table 2). Five patients (5%) had hemorrhage in the lung and one patient (1%) had hemorrhage in a site described as "other." Most hemorrhagic events occurred during first-line therapy, and most patients were receiving chemotherapy during the first hemorrhagic event (37, 34%) followed by anti-EGFR antibodies with or without chemotherapy (29, 26%) and immunotherapy (12, 11%)

TABLE 1 Demographics and disease characteristics of patients with HNSCC from Milan, Italy

	Number of patients, $n = 259$ (%)
Sex	
Male	198 (76)
Female	61 (24)
Age, years – median (range)	62 (24–93)
ECOG performance status	
0	51 (20)
1	195 (75)
2	12 (4)
3	1 (1)
Primary tumor location	
Oral cavity	97 (37)
Oropharynx	85 (33)
HPV-positive	28 (11)
Hypopharynx	22 (8)
Larynx	50 (20)
Carcinoma of unknown primary	5 (2)
AJCC clinical stage	
I	20 (8)
II	23 (9)
III	17 (6)
IV	198 (76)
Unknown	1 (1)
Intent to treatment	
Radical	222 (86)
Palliative	37 (14)
Surgery	129 (50)
Radiotherapy	173 (67)
Dose (Gy) – median (range)	62.1 (0–135)
Type of recurrence	
Local/nodal/soft tissue/tracheal	188 (72)
Lung	60 (23)
Bones	15 (6)
Hepatic	7 (3)
Intracranial	4 (1)
Other	9 (3)
Size of local recurrence	
<2 cm	5 (2)
2–2.9 cm	24 (9)
3–5 cm	74 (28)
>5 cm	140 (54)
Recurrence in field	143 (55)

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus.
Source: "Bleeding in recurrent and/or metastatic patients with head and neck squamous cell carcinoma: the experience at the Istituto Nazionale Tumori of Milan."

TABLE 2 Distribution of bleeding characteristics in patients with HNSCC from Milan, Italy

	Number of patients, $n = 110$ (%)
Bleeding event	
Minor[a]	76 (69)
Major[b]	34 (31)
Site of bleeding	
Head and neck	104 (95)
Lung	5 (4)
Other	1 (1)
Type of treatment during first bleeding episode	
Chemotherapy	37 (34)
Anti-EGFR ± chemotherapy	29 (26)
Immunotherapy	12 (11)
Timing of bleeding	
First line	39 (35)
Second line	25 (23)
Third line	9 (8)
Other line	5 (5)
No treatment	32 (29)

Abbreviations: EGFR, epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma.
[a]Minor hemorrhage: estimated as a bright red blood of half a teaspoon or more per episode of coughing (~5 mL).
[b]Major hemorrhage: defined as fatal, life-threatening, symptomatic, causing a fall in hemoglobin level of 20 g/L or more, leading to transfusion of two or more units of whole blood or red cells or about 200–240 mL, or about 1 cup, in 24 h.
Source: "Bleeding in recurrent and/or metastatic patients with head and neck squamous cell carcinoma: the experience at the Istituto Nazionale Tumori of Milan."

(Table 2). The proportion of patients who had at least one episode of bleeding versus the proportion without an episode of bleeding were similar in terms of the number of systemic therapies given for recurrence and the types of treatment (Table 3).

The findings from the present database analysis suggest that most bleeding events were minor and not linked to treatment, although cautious interpretation is warranted given the size of the patient population. The data analyses dealt mostly with patients previously treated with chemoradiation and suggest that its involvement in hemorrhagic events may be limited. In addition to chemoradiation, additional tentative etiologies of hemorrhage are under scrutiny, including the biology of the disease (e.g., infection with high-risk human papillomaviruses [HPVs]) and a range of emerging therapies such as antiangiogenic agents, anti-EGFR drugs, and immunotherapies.

TABLE 3 Association between bleeding and oncologic treatments in patients with HNSCC from Milan, Italy

	Patients not bleeding ($n = 149$)	Patients bleeding ($n = 110$)	Total patients ($N = 259$)
Systemic therapy at recurrence, *n* (%)			
Yes	133 (89)	104 (95)	237 (92)
No	16 (11)	6 (5)	22 (8)
Number of systemic therapies for recurrence, median (range)	2 (0–7)	2 (0–8)	2 (0–8)
Total number of lines of systemic therapy for recurrence, *n* (%)			
0	16 (11)	6 (5)	22 (8)
1	52 (35)	43 (39)	95 (37)
2	48 (32)	33 (30)	81 (31)
≥3	33 (22)	28 (25)	61 (24)
Line and type of treatment, *n* (%)			
First line	133 (89)	104 (95)	237 (92)
Anti-EGFR ± chemo	88 (59)	75 (68)	163 (63)
Chemotherapy	36 (24)	21 (18)	57 (22)
Immunotherapy	9 (6)	8 (7)	17 (7)
Second line	81 (54)	61 (55)	142 (55)
Anti-EGFR ± chemo	6 (4)	10 (9)	16 (6)
Chemotherapy	59 (39)	41 (37)	100 (39)
Immunotherapy	16 (11)	10 (9)	26 (10)
Third line	33 (22)	28 (25)	61 (24)
Anti-EGFR ± chemo	3 (2)	1 (1)	4 (1)
Chemotherapy	28 (18)	25 (23)	53 (20)
Immunotherapy	2 (1)	2 (1)	4 (1)

Note: Anti-EGFR therapy/chemotherapy: carboplatin + cetuximab; carboplatin + cetuximab + 5-FU; cisplatin + cetuximab; cisplatin + cetuximab + 5FU; cisplatin + cetuximab + taxane. Immunotherapy: nivolumab; nivolumab + lirilumab; pembrolizumab; tremelimumab + durvalumab.
Abbreviations: EGFR, epidermal growth factor receptor; 5-FU, 5-fluoruracil; HNSCC, head and neck squamous cell carcinoma.
Source: "Bleeding in recurrent and/or metastatic patients with head and neck squamous cell carcinoma: the experience at the Istituto Nazionale Tumori of Milan."

4 | THERAPIES FOR HNSCC AND RISK OF HEMORRHAGE

4.1 | Anti-EGFR therapies

EGFR is overexpressed in the majority of HNSCC cases and is a well-recognized therapeutic target. Clinical trials have therefore examined the efficacy and safety of targeted anti-EGFR agents such as cetuximab.[29–31] However, based on available data, it remains unclear whether a causal association exists between the use of cetuximab-based treatment regimens and occurrence of hemorrhage.

In a multinational randomized trial of high-dose radiotherapy plus cetuximab versus high-dose radiotherapy alone (424 patients with stage III or IV nonmetastatic, measurable HNSCC of the oropharynx, hypopharynx, or larynx), no hemorrhagic adverse events (AEs) were reported in either treatment arm.[32] In an open-label, uncontrolled multicenter phase II study of single-agent cetuximab in patients with R/M HNSCC who experienced disease progression on platinum-based therapy, the most common cetuximab-related AEs were skin reactions. There was one treatment-related death due to an uncommon infusion-related reaction, but there were no reports of hemorrhage.[31] Similarly, hemorrhage was not described among 117 evaluable patients in a randomized trial comparing cisplatin–cetuximab with cisplatin–placebo. However, the study reported grade 3 and 4 AEs only; it is unknown whether grade 1 or 2 hemorrhage events occurred.[33]

In a phase III randomized controlled trial comparing patients treated with cetuximab plus platinum–fluorouracil ($n = 222$) versus patients treated with platinum–fluorouracil alone ($n = 220$), 1.4% of patients in the cetuximab arm developed grade 3 or 4 tumor hemorrhagic events compared with 2.8% in the platinum–fluorouracil arm.[30] The AE profile in the chemotherapy alone group was

considered typical for a platinum–fluorouracil combination. The main grade 3 or 4 AEs, including tumor hemorrhage, were assessed by the investigators as being consistent with the safety profile of cetuximab.

Cripps et al. reviewed the evidence for inclusion of anti-EGFR therapies in guidelines for the treatment of HNSCC.[29] Of note, discussion of the development of the Cancer Care Ontario's Guideline included reference to tumor hemorrhage rates observed in the IMEX trial, a randomized phase III study that examined two different daily doses of the EGFR inhibitor, gefitinib, versus weekly intravenous methotrexate in patients with advanced R/M HNSCC.[34] Analysis of the safety data from the IMEX trial identified a new and unexpected safety finding of "tumor hemorrhage" in patients treated with gefitinib. The incidence of tumor hemorrhage seen in patients treated with gefitinib 250 and 500 mg was 8.9% ($n = 14/158$) and 11.4% ($n = 19/166$), respectively, compared with 1.9% ($n = 3/159$) in methotrexate-treated patients. In the gefitinib arm, tumor hemorrhage events included hemorrhagic tumor necrosis, and hemorrhage of the tumor, mouth, pharynx, tonsil, and tongue. The study did not assess whether the differences in tumor hemorrhage incidence were statistically significant; however, most of the tumor hemorrhages were classified as mild or moderate (CTCAE grades 1 or 2) and resolved while study treatment continued. Although three patients died as a result of tumor hemorrhage (two in the gefitinib 250 mg arm and one in the gefitinib 500 mg arm), these cases were not assessed as causally related to gefitinib therapy.

In summary, data on the use of anti-EGFR therapies in the treatment of patients with R/M HNSCC have not revealed a causal relationship between these therapies and hemorrhagic events.

4.2 | Angiogenesis inhibitors

Antiangiogenic drugs, specifically anti-VEGF agents, are associated with increased and often severe incidence of hemorrhage complications.[35,36] Management of bleeding in patients treated with anti-VEGF agents can be challenging as this complication is attributable, at least in part, to the efficacy of the drug.

Bevacizumab, a recombinant humanized anti-VEGF monoclonal antibody, is associated with an increased risk of severe or fatal hemorrhage compared with chemotherapy.[37] Several studies investigating angiogenesis inhibitor-based combination therapies in patients with R/M HNSCC have reported treatment-related bleeding complications (Table 4).[35,38–46] Seiwert et al. performed a phase I study evaluating the combination of bevacizumab, 5-fluorouracil, hydroxyurea, and concomitant radiotherapy for poor-prognosis patients with HNSCC.[44] Of 43 treated patients, two fatal hemorrhages were reported, one esophageal and one carotid blowout. The latter was thought to be secondary to tumor invasion of the carotid artery and was not evident at baseline. In another study, Cohen et al. investigated the combination of erlotinib and bevacizumab in 56 patients with R/M HNSCC.[38] Three patients (5%) experienced serious hemorrhagic events. Of four toxic effects that led to discontinuation, serious hemorrhagic events were responsible for two. One serious hemorrhagic event was fatal and determined to be of laryngeal origin; however, this did not occur at a site of active disease. The other hemorrhagic event occurred at a site of disease involvement in the floor of the mouth. Importantly, all three hemorrhagic events were associated with prior radiotherapy to the site.[38]

A recent phase III randomized trial evaluated the efficacy and safety of chemotherapy with or without bevacizumab in patients with R/M HNSCC.[35] The addition of bevacizumab to chemotherapy did not improve overall survival but improved the response rate and progression-free survival with increased toxicities. A higher rate of treatment-related grade 3–5 hemorrhage events (6.7% vs. 0.5%; $p < 0.001$) was observed with the bevacizumab/chemotherapy combination versus chemotherapy alone. In a single-arm, phase II trial of 27 patients treated with sorafenib, one patient experienced a fatal nasopharyngeal hemorrhage, although the death was considered to be unrelated to treatment.[42] In several other studies examining different anti-angiogenesis therapies, hemorrhagic events were not documented; this means that either hemorrhagic events did not occur or, if they occurred, they were beneath the threshold to be reported.[39,40,42,47] In general, anti-VEGF-based therapies are more commonly associated with hemorrhage.

4.3 | Immunotherapy: Nonimmune checkpoint inhibitors

Local and systemic immunotherapy modalities may lead to inflammation; therefore, local tumor vaccination and systemic immune stimulant clinical trial reports in HNSCC were reviewed. A phase I/II study evaluating JS1/34.5-/47-/GM-CSF, an oncolytic herpes simplex type 1 virus encoding human granulocyte-macrophage colony-stimulating factor (GM-CSF), in combination with CRT in patients with HNSCC reported injection site hemorrhage in two (12%) patients.[48] Hemorrhage did not result in any deaths or delay ongoing radiotherapy. A phase I study evaluated the safety, tolerability, and tumor response of VB4-845, a recombinant fusion protein that targets

epithelial cell adhesion molecule.[49] VB4-845 was administered as weekly intratumoral (IT) injections to 20 patients with HNSCC. Tumor bleeding was reported in four patients, with two events observed in nontarget tumors and two further events spatially separated from the injection site. However, none of these events were assessed as causally related to VB4-845. Thus, based on two studies, immunotherapy involving non-checkpoint inhibitors did not appear to be associated with bleeding.[48,49]

4.4 | Immunotherapy: ICIs

Recent advances in cancer immunotherapy are notable for the introduction of ICIs.[50] These agents inhibit negative regulatory components of the immune response, such as the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and the programmed cell death protein-1 (PD-1) and its ligand, programmed cell death ligand-1 (PD-L1), which lead to enhanced T cell action against cancer cells. The incidences of hemorrhage events in clinical studies of ICIs are summarized in Table 4.[10–24,51–55]

In 2016, two PD-1 inhibitors, nivolumab[11] and pembrolizumab,[10] were approved for the treatment of patients with R/M HNSCC who experience disease progression after platinum-based therapy. Furthermore, on June 10, 2019, the US FDA approved pembrolizumab for the first-line treatment of patients with R/M HNSCC when used in combination with platinum and

TABLE 4 Hemorrhage incidence in trials evaluating angiogenesis inhibitors in HNSCC

Reference	Study phase/design	*N*	Agent(s)	Rate of hemorrhage/bleeding
Elser et al.[39]	Phase II trial in patients with R/M HNSCC or nasopharyngeal carcinoma	27	Sorafenib	Hemorrhagic events not described
Seiwert et al.[44]	Phase I study in patients with poor-prognosis HNSCC	43	Bevacizumab + fluorouracil + hydroxyurea	Two hemorrhages; both fatal (one esophageal, one carotid blowout) investigator considered hemorrhages to be related to the investigational product
Cohen et al.[38]	Phase I/II study in patients with R/M HNSCC	48	Erlotinib + bevacizumab	Three serious hemorrhagic events of grade 3 or higher; one fatal
Williamson et al.[45]	Phase II study in patients with advanced and metastatic HNSCC	41	Sorafenib	Hemorrhagic events not described
Salama et al.[43]	Randomized phase II study in patients with intermediate-stage and T4N0-1 HNSCC	26	Bevacizumab + 5-fluorouracil + hydroxyurea + radiotherapy vs. 5-fluorouracil + hydroxyurea + radiotherapy	Hemorrhagic events not described
Hainsworth et al.[42]	Phase II trial in patients with LA HNSCC	60	Bevacizumab + erlotinib + CRT	Hemorrhagic events not described
Yoo et al.[46]	Prospective phase I trial of bevacizumab, erlotinib, and concurrent CRT in LA HNSCC	29	Erlotinib; bevacizumab	Hemorrhagic events not described
Gilbert et al.[41]	Randomized phase II trial in patients with R/M HNSCC	52	Sorafenib + cetuximab vs. cetuximab	Hemorrhagic events not described
Fury et al.[40]	Phase II trial in patients with stage III/IVB HNSCC	30	Bevacizumab + cetuximab + cisplatin + CRT + IMRT	Hemorrhagic events not described
Argiris et al.[35]	Phase III randomized trial of chemotherapy with or without bevacizumab in patients with R/M HNSCC	403	Bevacizumab + platinum-based chemotherapy vs. platinum-based chemotherapy	Higher rate of treatment-related grade 3 to 5 hemorrhage events (6.7% vs. 0.5%; $p < 0.001$) and treatment-related deaths (9.3% vs. 3.5%; $p = 0.022$) with BC vs. chemotherapy

Note: Trials determined from PubMed search ranging from 1989 to 2019 (search criteria described in section 2).

Abbreviations: BC, bevacizumab plus chemotherapy; CRT, chemoradiotherapy; HNSCC, head and neck squamous cell carcinoma; IMRT, intensity-modulated radiation therapy; R/M, recurrent and/or metastatic.

fluorouracil (all patients) or as a single agent (for patients whose tumors express PD-L1 based on a combined positive score of ≥1 as determined by an FDA-approved test).[1] Hemorrhage is not included as a warning or precaution in the prescribing information for either nivolumab or pembrolizumab.[10,11]

Recently, data have been published from clinical trials investigating safety and efficacy of the checkpoint inhibitor durvalumab, both alone, and in combination with the anti-CTLA-4 agent tremelimumab.[22–24] In the phase II CONDOR study,[22] patients with PD-L1-low/negative R/M HNSCC received durvalumab with or without tremelimumab. In the combination arm, bleeding events included hemorrhage in one (0.8%) patient, epistaxis in three (2.3%) patients, and hemoptysis in five (3.8%) patients. In the durvalumab arm, epistaxis and hemoptysis were each reported in one (1.5%) patient, whereas in the tremelimumab arm a single patient (1.5%) experienced hemoptysis. Among the 11 reported bleeding events, two in the combination arm were considered to be related to treatment, including one patient with epistaxis and one with hemoptysis (Tables 5 and 6). In the phase II HAWK study,[23] patients with R/M HNSCC and ≥25% tumor cell PD-L1 expression who had progressed on platinum-based chemotherapy received durvalumab monotherapy. Two patients (1.8%) experienced treatment-related hemorrhage (one patient with mouth hemorrhage and one patient with wound hemorrhage; Tables 5 and 6).

In the phase III EAGLE study,[24] patients with R/M HNSCC received durvalumab plus tremelimumab or durvalumab monotherapy (Tables 5 and 6). A review of all bleeding events within the hemorrhage SMQ revealed that the incidence was low and within the range reported in the published literature for patients with advanced cancer.[56] Most of the hemorrhage SMQ serious AEs (SAEs) were not considered to be related to study drug by the investigators and there were no clear trends across groups in the hemorrhage SMQ SAEs that led to death. During the study, 103 patients experienced 119 hemorrhage SMQ AEs; of these, 8 (3.4%) were thought to be related to study treatment in the durvalumab arm, 11 (4.5%) in the durvalumab plus tremelimumab arm, and 9 (3.8%) in the standard-of-care (SoC) arm (Table 6). There were no apparent differences across the treatment groups in proportions of patients experiencing hemorrhage SMQ AEs. However, in the durvalumab plus tremelimumab group, there were two patients who experienced treatment-related hemorrhage SMQ AEs of CTCAE grade 3 or 4 where there were none in the durvalumab or SoC arms. SAEs that were considered related to treatment were reported more frequently in the durvalumab ($n = 2$) and durvalumab plus tremelimumab ($n = 2$) groups than SoC ($n = 0$). Hemorrhage SMQ AEs considered to be related to treatment and leading to discontinuation of study treatment occurred in one patient in the durvalumab arm and no patients in the other arms. Overall, one patient in the durvalumab arm had a fatal treatment-related hemorrhage SMQ AE. Ultimately, an association between durvalumab or durvalumab plus tremelimumab and hemorrhage-related AEs was not identified.[24]

5 | SUMMARY

We analyzed and reviewed relevant epidemiologic and clinical data in patients with R/M HNSCC in order to further our understanding of the occurrence of hemorrhage in this tumor type. The availability of several sources of data, including the Truven MarketScan Commercial Claims and Encounters Database (2010–2015)[25] and the Istituto Nazionale dei Tumori of Milan database (1984–2016),[26] have allowed us to conduct a comprehensive review of bleeding events in R/M HNSCC. Several possible causes of hemorrhage in R/M HNSCC have been examined, including disease-related characteristics, traditional therapies (chemotherapy, radiotherapy), and emerging therapies (antiangiogenic and anti-EGFR agents, immunotherapies). The real-world findings from the Istituto Nazionale dei Tumori of Milan database suggest that most bleeding events were minor and initial analyses did not indicate an association with treatment. However, interpretation of these data should be approached with caution due to the small population of patients analyzed.[26]

Although systemic chemotherapy (especially when delivered intra-arterially) and local tumor irradiation are possible causes of intractable hemorrhage associated with head and neck neoplasms, real-world evidence from the Truven MarketScan Commercial Claims and Encounters database possibly cautions against an assumption that chemoradiation therapy is responsible for hemorrhagic events. These analyses suggest that individuals with HNSCC who had received radiation therapy and chemotherapy, with a history of hemorrhagic events in the 3 months prior to first treatment, experienced higher subsequent rates of hemorrhage than those with no previous history of hemorrhage. Although not providing a mechanistic explanation for the increased hemorrhagic risk, these data nevertheless indicate that patient and/or disease-related factors drive hemorrhagic events in at-risk individuals undergoing chemoradiation. While confirmation is required, the present analyses suggest that age may play a role, as patients ≥65 years of age had higher

TABLE 5 Hemorrhage incidence in trials evaluating immune checkpoint inhibitors

Reference	Study phase/design	*N*	Agent(s)	Tumor	Rate of hemorrhage/bleeding
Yervoy® US PI[55]	NA	NA	Ipilimumab	Melanoma	Hemorrhagic events not described
Hodi et al.[53]	Randomized phase III trial in patients with unresectable stage III or IV melanoma	676	Ipilimumab Ipilimumab + gp100 gp100	Melanoma	Hemorrhagic events not described
Larkin et al.[18]	Randomized phase III trial in previously untreated patients with unresectable stage III or IV melanoma	945	Nivolumab Nivolumab + ipilimumab Ipilimumab	Melanoma	Hemorrhagic events not described
Eggermont et al.[52]	Randomized phase III trial in patients with who had undergone complete resection of stage III melanoma	951	Ipilimumab Placebo	Melanoma	Hemorrhagic events not described
Opdivo® US PI[11]	NA	NA	Nivolumab	Melanoma NSCLC RCC HL HNSCC UC	Hemorrhagic events not described
Postow et al.[19]	Randomized phase I dose-escalation study in patients with treatment naïve metastatic melanoma	142	Nivolumab + ipilimumab Nivolumab + placebo	Melanoma	Hemorrhagic events not described
Ansell et al.[12]	Phase I study of patients with relapsed or refractory HL	23	Nivolumab	HL	Hemorrhagic events not described
Gettinger et al.[17]	Phase I study of patients with heavily pretreated NSCLC	129	Nivolumab	NSCLC	Hemorrhagic events not described
Ferris et al.[16]	Randomized phase III study of patients with R/M HNSCC	361	Nivolumab	HNSCC	Hemorrhagic events not described
Keytruda® US PI[10]	NA	NA	Pembrolizumab	Melanoma NSCLC HL UC Microsatellite instability-high cancer	Hemorrhagic events not described
Topalian et al.[21]	Phase I study of patients with advanced melanoma, NSCLC, castration-resistant prostate cancer, or renal-cell or colorectal cancer	296	Pembrolizumab	Advanced solid tumors	Hemorrhagic events not described
Armand et al.[13]	Phase I study of patients with relapsed or refractory HL after treatment with brentuximab	31	Pembrolizumab	HL	Hemorrhagic events not described
Chow et al.[15]	Phase Ib study in patients with R/M HNSCC	132	Pembrolizumab	HNSCC	Hemorrhagic events not described

TABLE 5 (Continued)

Reference	Study phase/design	*N*	Agent(s)	Tumor	Rate of hemorrhage/bleeding
Seiwert et al.[20]	Phase Ib study of patients with R/M HNSCC	104	Pembrolizumab	HNSCC	Hemorrhagic events not described
Bauml et al.[14]	Phase II study of patients with R/M HNSCC	171	Pembrolizumab	HNSCC	Hemorrhagic events not described
Tecentriq® US PI[54]	NA	NA	Atezolizumab	UC	Hemorrhagic events not described
Calabro et al.[51]	Phase II study of previously treated patients with unresectable malignant mesothelioma	29	Tremelimumab	Malignant mesothelioma	Hemorrhagic events not described
Siu et al.[22]	Safety and efficacy of durvalumab with or without tremelimumab in patients with PD-L1-low/negative recurrent or metastatic HNSCC: the phase 2 CONDOR randomized clinical trial	65 133	Durvalumab Durvalumab+ Tremelimumab	HNSCC	Minor bleeding events; two patients (1.5%) in combination arm with treatment-related bleeding
Zandberg et al.[23]	Durvalumab for recurrent or metastatic head and neck squamous cell carcinoma: Results from a single-arm, phase II study in patients with 25% tumor cell PD-L1 expression who have progressed on platinum-based chemotherapy	112	Durvalumab	HNSCC	Minor bleeding events; two patients (1.8%) with treatment-related bleeding
Ferris et al.[24]	Durvalumab with or without tremelimumab in patients with recurrent or metastatic head and neck squamous cell carcinoma (EAGLE): a randomized, open-label phase III study	237 246 240	Durvalumab Durvalumab+ Tremelimumab SoC	HNSCC	Minor treatment-related bleeding events 8 (3.4%) patients (durvalumab) 11 (4.5%) patients (durvalumab + tremelimumab) 9 (3.8%) patients (SoC)

Note: Trials determined from PubMed search ranging from 1989 to 2019 (search criteria described in section 2).

Abbreviations: HL, Hodgkin's lymphoma; NA, not applicable; NSCLC, non-small cell lung cancer; PI, prescribing information; RCC, renal cell carcinoma; SoC, standard of care; UC: urothelial carcinoma; US, United States.

TABLE 6 Bleeding incidence in the HAWK, CONDOR, and EAGLE trials

	HAWK[23]	CONDOR[22]		EAGLE[24]		
AE, *n* (%)	D (*N* = 112)	D + T (*N* = 133)	D (*N* = 65)	D + T (*N* = 246)	D (*N* = 237)	SoC (*N* = 240)
All bleeding AEs		9 (6.8)	2 (3.1)	36 (14.6)	37 (15.6)	30 (12.5)
Treatment-related bleeding AE	2 (1.8)	2 (1.5)	0	11 (4.5)	8 (3.4)	9 (3.8)
Tumor hemorrhage	0	0	0	1 (0.4)	1 (0.4)	1 (0.4)
Lymph node hemorrhage	0	0	0	0	1 (0.4)	0
Hematoma	0	0	0	0	0	1 (0.4)
Hemorrhage	0	0	0	0	1 (0.4)	0
Hemoptysis	0	1 (0.8)	0	3 (1.2)	4 (1.7)	0
Epistaxis	0	1 (0.8)	0	1 (0.4)	0	5 (2.1)
Pharyngeal hemorrhage	0	0	0	1 (0.4)	0	0
Mouth hemorrhage	1 (0.9)	0	0	2 (0.8)	1 (0.4)	1 (0.4)
Upper gastrointestinal hemorrhage	0	0	0	1 (0.4)	0	0
Palpable purpura	0	0	0	1 (0.4)	0	0
Petechiae	0	0	0	1 (0.4)	0	0
Purpura	0	0	0	1 (0.4)	0	0
Hematuria	0	0	0	0	1 (0.4)	0
Wound hemorrhage	1 (0.9)	0	0	0	0	0

Abbreviations: AE, adverse event; D, durvalumab; SoC, standard of care; T, tremelimumab.

rates of hemorrhage than those <65 years of age. The relationship between primary tumor location and occurrence of bleeding events is unclear from our analyses, although most patients in our study population had locally advanced disease. There were too few patients with HPV-positive oropharyngeal cancer to determine if HPV infection has an impact on risk of bleeding in R/M HNSCC. While half of the patients in our study population had received surgery, it is unclear if this impacted the carotid artery and thus the risk of bleeding with systemic therapy in at least some patients.

Clinical trials have examined the efficacy and safety of targeted anti-EGFR agents in patients with R/M HNSCC; however, based on available data, a causal association between these treatment regimens and occurrence of hemorrhage cannot be confirmed.[29–31] In addition, local and systemic immune stimulators do not appear to be associated with increased frequency of tumor hemorrhage in this patient population.[48,49] In contrast, antiangiogenic drugs, specifically anti-VEGF agents, are associated with increased and often severe incidence of hemorrhagic complications, based on a review of the current literature.[35,36] Stronger effort needs to be made to mitigate hemorrhagic risk in this population and more research needs to be conducted to identify pertinent risk factors.

No evidence to date was identified to suggest a class-effect of checkpoint inhibitors in risk of hemorrhage when treating R/M HNSCC with single-agent or combination checkpoint inhibitor therapy. With the FDA-approved PD-1 inhibitors nivolumab[11] and pembrolizumab[10] not listing hemorrhage-associated side effects in R/M HNSCC, and clinical trials for durvalumab and tremelimumab finding no evidence to support a causal relationship with bleeding-related AEs, checkpoint inhibitors so far present a viable option for treating R/M HNSCC without an increased hemorrhagic risk.

In conclusion, hemorrhagic episodes can be a frequent problem in patients with advanced cancer including those with R/M HNSCC, ranging from low-grade oozing to major episodic and catastrophic bleeding.[3] Hemorrhage can be caused by the cancer itself and may also be related to antitumor treatments such as prior radiation therapy or chemotherapy. Hemorrhage can be further exacerbated by addition of anti-VEGF agents, nonsteroidal anti-inflammatory drugs, and anticoagulants.[3] In patients at high risk of bleeding including those with a prior hemorrhage, treatment goals need to be aligned with this risk. Ultimately, the use of therapies that have maximal efficacy and minimal or no hemorrhage-related effects will be more desirable when selecting therapeutic options for patients with R/M HNSCC.

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CONFLICT OF INTEREST

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