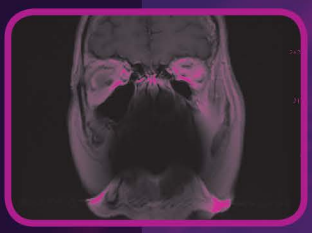
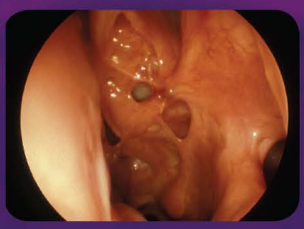


MANUAL OF HEAD AND NECK SURGICAL ONCOLOGY

Nicholas Stafford

Contents

4 Systemic therapy in head and neck cancer

Angela Waweru and Martin H. Robinson

The basic principle of systemic therapy is DNA damage, either directly or indirectly leading to cell death.

Although the mainstay of non-surgical management in head and neck malignancies is radiotherapy, concurrent systemic therapy has a definite role, and has been shown to improve overall survival as well as progression free survival. In patients with incurable and/or metastatic disease, response to chemotherapy – even partial – can have a dramatic improvement in patients' symptoms and quality of life.

As will be discussed later, there are four main areas where systemic therapy is employed in the treatment of head and neck malignancies. Here, we discuss the main chemotherapeutic agents currently in use, common and serious side effects as well as the management of these.

Platinum agents: cisplatin and carboplatin

Platinum agents are among the most widely used chemotherapeutic agents. For many years, cisplatin was the only platinum agent available; however, analogs have been developed in a bid to reduce toxicity while maintaining efficacy.

Cisplatin's main mechanism of action is by binding to DNA causing adducts, the most lethal being intrastrand adducts that impair DNA replication and repair as well as inducing apoptosis. It is administered intravenously, over 1–2 hours; side effects include renal toxicity, nausea and vomiting, peripheral neuropathy, ototoxicity (tinnitus and deafness), infertility, and myelosuppression.

Prevention of cisplatin renal toxicity is achieved by ensuring an adequate baseline glomerular filtration rate (GFR) (>50 mL/min), hyperhydration prechemotherapy and being mindful of concomitant use of other nephrotoxic agents. Urine output is monitored during

administration. Cisplatin is highly emetogenic. Management of nausea and vomiting has, however, improved with the advent of 5-HT_3 antagonists, e.g. ondansetron, used in combination with dexamethasone. Persistent or worsening ototoxicity requires reduction in the dose of cisplatin and if this does not improve symptoms, consideration should be made to stopping the drug otherwise patients are at risk of developing permanent tinnitus and hearing loss.

Carboplatin is an analog to cisplatin, it is a much more stable compound with a similar mode of action as cisplatin; it has less toxicities as there is a slower rate of DNA adduct formation and has comparable or less efficacy compared to cisplatin. It is eliminated as an intact molecule and its dose is therefore based on renal function [Calvert formula: Dose = AUC + (GFR + 25)].

It has more hematological toxicities compared to cisplatin with higher rates of myelosuppression recorded – thrombocytopenia is usually dose limiting. Emesis, nephrotoxicity, and neurotoxicity are uncommon. Other rare side effects include rash and anaphylaxis. Carboplatin can be substituted for cisplatin in patients with poor renal function in the palliative setting.

5-Fluorouracil (5FU)

5FU is an antimetabolite; these are drugs that interfere with DNA synthesis and therefore cell replication. It is an inactive compound that goes through complex metabolic activation. It is usually administered intravenously, although oral prodrugs now exist, e.g. capecitabine, that are preferentially activated in tumor cells.

In head and neck carcinoma treatment, 5FU is used in combination with cisplatin as their different modes of intracellular action lead to higher rates of cell kill; it is given as an infusion over 4 days as opposed to bolus administration; the main toxicities with this mode of administration are related to mucus membranes – e.g. mucositis; rare side effects include cardio toxicity (arrhythmias, coronary spasms), ataxia, and skin rash. Myelosuppression with infusional 5FU is uncommon.

Taxanes

These are agents that inhibit micro tubular disassembly. This prevents normal growth and differentiation of microtubules that are required for cell replication.

Docetaxel is the main agent used in head and neck cancer treatment typically as part of induction chemotherapy; it is excreted by hepatic metabolism via the cytochrome p450 system and therefore patients on drugs that affect this system (e.g. antiepileptic drugs) have altered docetaxel metabolism.

The main toxicities are myelosuppression (mainly neutropenia), hypersensitivity reactions, sensory peripheral neuropathy, fluid retention, and skin and nail changes.

Targeted biological agents

Targeted therapies are set to overtake the use of conventional chemotherapy in many disease sites. Certainly, in the context of head and neck malignancies, epidermal growth factor receptor (EGFR) inhibition has been shown to act synergistically with radiotherapy and improves overall survival when compared to radiotherapy alone.

The role of these agents is evolving and is discussed briefly toward the end of this chapter.

Acute oncology - management of toxicities

Bleeding and bruising

Thrombocytopenia due to chemotherapy-related myelosuppression e.g. carboplatin, (or occasionally disease-related marrow infiltration) should be managed according to approved guidelines. A platelet count of < 50 can result in bleeding and or bruising from minor trauma. Higher incidences of intracranial hemorrhage have been recorded when there is sepsis plus a platelet count of < 10. Typical management would include the following:

- Stop any drugs that could exacerbate bleeding such as antiplatelet therapy, warfarin or low molecular weight heparin
- In a stable patient with a platelet count of 10 or less, 1 unit of platelets should be administered
- Patients with sepsis and a count of < 20 should have 1 unit of platelets administered
- Patients with evidence of bleeding in association with thrombocytopenia (platelets < 50) should receive 1 unit of platelets

Diarrhea

Diarrhea can be a life-threatening complication of systemic therapies such as 5FU or cetuximab. If left untreated, prolonged or severe diarrhea can lead to acute kidney injury and hypovolemic shock. All patients with moderate or severe symptoms should be monitored closely, this includes, stool chart, fluid balance records, daily U&Es and abdominal examination to check for signs of peritonism. Stool micobiology and culture (MC&S) should be obtained to check for the possibility of an infective component:

- Mild to moderate diarrhea (increase by 2–3 or 4–6 bowel movements respectively) can be managed by stopping anticancer therapy after discussing with the appropriate team; stop any laxatives; loperamide on a PRN basis up to 16 mg/24 h plus codeine phosphate 30–60 mg PRN 4–6 hourly.
- Severe diarrhea (increase of > 7 bowel movements): manage as above, and admit the patient for IV rehydration; consider adding octreotide. Buscopan can be administered via a syringe driver for diarrhea-related abdominal cramps (80 mg/24 h)

Mucositis

Typically seen with anti-metabolite drugs such as 5FU. Oral mucositis is commonly mistaken for candidiasis. (Any evidence of candidiasis should be treated with fluconazole syrup 50 mg o.d. for 7 days.) Patients with mucositis complain of sore mouth with sticky saliva. As higher rates of mucositis are seen in neutropenic patients, management in the first instance should be to exclude neutropenia; typical management of mucositis:

- Mouth care with combination of alcohol free mouthwash such as Biotene and Difflam mouthwash used pre-meals. Avoid chlorhexidine mouthwash
- Oxcetacaine and antacid taken half an hour before main meals can help with pain management. If swallowing is difficult, Mucilage 10 mL can used as an adjunct just prior to meals
- Systemic analgesia is gradually titrated up until effective pain control is reached, starting from regular soluble paracetamol 1 g QDS up to regular opiates if indicated. Care should be taken to avoid Oramorph solution due to its high alcohol content; morphine hydrochloride is preferable
- In severe cases, inpatient management is required for rehydration and dietetic support that could include parenteral nutrition (NG or TPN). Ongoing systemic therapy should always be stopped in these instances

Nausea and vomiting

Nausea and vomiting related to chemotherapy can be acute (<24 h) or delayed (2–5 days). Certain agents such as cisplatin are highly emetogenic. Almost all chemotherapy regimens include prophylactic antiemetics and patients are given oral antiemetics to take home and this usually includes 72 hours of oral dexamethasone 4 mg BD. Early management is of importance as protracted nausea and vomiting could lead to renal failure. This includes the following:

- Domperidone 10 mg TDS PO or metoclopramide 10 mg TDS IV if the patient is unable to swallow
- Ondansetron 4–8 mg BD or granisetron 3 mg IV for acute or delayed emesis
- If symptoms persist, consider third-line agents such as haloperidol 1.5 mg PO/SC every night as well as metoclopramide 30–60 mg/24 hour given via a syringe driver
- IV fluids will be required if significant reduction in oral intake is reported. After discussing with the oncologist, stop anticancer therapy in moderate to severe cases of emesis
- Be mindful of other causes of emesis – e.g. electrolyte disturbance, bowel obstruction, causes related to the underlying disease.

Neutropenic sepsis

Neutropenia is defined as follows:

- Mild neutropenia: absolute neutrophil count 1000–1500 μL

- Moderate neutropenia: absolute neutrophil count 500–1000 μL
- Severe neutropenia: absolute neutrophil count < 500 μL

The absolute neutrophil count is 6000 μL if the whole cell count is 10,000 /μL and 60% are neutrophils.

All patients who have received any chemotherapeutic agent within 6 weeks are at risk of neutropenic sepsis that could be fatal. Patients may be critically ill with minimal signs and in cases of profound neutropenia may not mount a pyrexia:

- Obtaining a focused history and perform an examination to try and identify a source. Often the source of infection is unidentifiable
- Appropriate investigations include urgent FBC, U&E, LFT, clotting screen, CRP, lactate, serum glucose, blood cultures – peripheral and from central venous access devices. Other cultures as dictated by history and examination findings
- Commence IV antibiotics according to local protocol – this should be administered within 1 hour of patient arrival. Do not wait for confirmatory FBC result. A typical regime would be tazocin 4.5 g QDS plus gentamicin
- IV fluids to maintain urine output of 30 mL/min, oxygen to maintain 94% saturation
- Early appropriate referral to critical care departments in patients should be made; especially in those who are receiving neoadjuvant chemotherapy with an aim to proceed to curative surgery or chemoradiotherapy or those undergoing curative or adjuvant treatment

Chemotherapy in practice

Induction chemotherapy

Chemotherapy administered prior to definitive treatment of locally advanced disease downstages the disease, thereby improving the chance of cure while eliminating micrometastases. As surgical and radiation techniques improve, rates of loco-regional control have also improved. There is now an increased focus on reduction of the rates of metastatic disease by way of induction chemotherapy.

Evidence exists to support the role of cisplatin and 5FU in this setting (Monnerat et al. 2002). More recently, the addition of docetaxel has shown further improvements in local control and increase in survival (Posner et al. 2007, Vermorken et al. 2007). A typical regime used in clinical practice is TPF: docetaxel 75 mg/m^2 day 1, cisplatin 75 mg/m^2 day 1 and 5FU 1000 mg/m^2 day 1–4, every 3 weeks. Response is assessed after two cycles with a maximum of three cycles administered. A note is required about nasopharyngeal carcinomas: this disease subsite was not studied in the latter two trials and therefore cisplatin and 5FU remain the regime of choice here.

Increased rates of organ preservation are observed when induction TPF is used in locally advanced laryngeal cancers.

The question of induction chemotherapy versus primary concurrent chemoradiotherapy is currently under investigation.

Concurrent chemotherapy with radiotherapy

In unresectable locally advanced malignancies, or in cases were organ preservation is sought, concurrent chemoradiotherapy is the treatment of choice. Soo et al. (2005) compared combination chemoradiotherapy with surgery and adjuvant radiotherapy in patients with stage III/IV non-metastatic head and neck cancer (non-nasopharyngeal, non-salivary). Results revealed no difference in disease free or overall survival at 6 years median follow-up. The overall organ preservation rate was 45% and higher rates were observed in laryngeal and hypopharyngeal lesions. The study has been criticized as it was not statistically powered to detect small differences in disease free or overall survival rates between the two arms.

There is robust evidence supporting the role of concurrent cisplatin with primary radiotherapy. Pignon's meta-analysis (2000) reported an additional 8% survival benefit. Cisplatin is a potent radiosensitizer – in this context, it acts by inhibiting three of the five Rs of radiobiology: repair of sublethal DNA radiation damage, repopulation of malignant cells, reoxygenation by preferentially killing hypoxic cells as well as killing micrometastases.

Patient selection is important as there is a significant increase in treatment-related toxicities. A good performance status (0–1) is required as well as ensuring a thorough past medical history has been obtained.

The dosing schedule commonly used is cisplatin 100 mg/m^2 on week 1, 4, and 7. Increasingly, weekly cisplatin (40 mg/m^2) for 6 weeks is being used as it is better tolerated.

Adjuvant chemoradiotherapy

Patients with positive surgical resection margins and evidence of extra-capsular spread in pathologically involved nodes are at particular risk of loco-regional disease recurrence.

Two recent trials have demonstrated the benefit of chemotherapy in the postoperative setting. The RTOG study (Copper et al. 2004) and EORTC study (Bernier et al. 2004) both demonstrated a reduction in rates of loco-regional disease recurrence. The latter study also suggested an improvement in overall survival.

The chemotherapeutic agent of choice is cisplatin, typically at 100 mg/m^2, 3 weekly. Its mode of action is as described for primary concurrent chemoradiotherapy.

Palliative chemotherapy

The main role of chemotherapy in this setting is to reduce the bulk of disease and consequently improve symptoms. Objective response rates have been recorded at approximately 30% of cases. A combination of cisplatin and 5FU is considered to be first-line treatment. Carboplatin

can be substituted for cisplatin if GFR < 40 mL/min. Increasingly, the addition of cetuximab to the chemotherapy is being used as a minor improvement in overall survival has been reported. This is discussed below.

Sadly, the response rate of second-line therapies is disappointing (< 10%). Agents under evaluation include taxanes, gemcitabine, capecitabine, and targeted therapies.

Although response to palliative chemotherapy is moderate and short lived, any response may produce a significant improvement in the patient's quality of life.

EGFR inhibition

EGFR is a tyrosine kinase transmembrane protein involved in cell signaling and growth. The epidermal growth factor (EGF) binds to EGFR, initiating signaling cascade. Abnormally activated EGFR has been shown to be associated with carcinogenesis. A significant number of head and neck malignancies overexpress EGFR and this confers a poorer prognosis. Inhibition of apparently activated EGFR signaling cascade has been exploited in the treatment of malignancies.

Cetuximab is a recombinant chimeric (mouse-human) monoclonal antibody that binds with high affinity to human EGFR and inhibits growth, promotes apoptosis and decreases vascular endothelial growth receptor production.

Bonner et al. (2006) showed a statistically significant improvement in overall survival when cetuximab was combined with radiotherapy versus radiotherapy alone (54 months vs. 28 months $p = 0.02$). Criticisms have been made, however, as the study was not compared to concurrent chemoradiotherapy. NICE recommends the use of concurrent cetuximab-radiotherapy in patients who have contra-indications to cisplatin (e.g. poor renal function and ototoxicity). It is given intravenously as a loading dose 1-week preradiotherapy with weekly infusions during the radiotherapy course.

It also has a role in the palliative setting – the extreme study showed that its addition to cisplatin and 5FU improved overall survival compared to chemotherapy alone. Further agents are also under evaluation looking at EGFR1 and EGFR2 inhibition.

Common and important toxicities include infusion-related reactions, acneiform rash, diarrhea, stomatitis, nausea and vomiting, headaches, interstitial pneumonitis, and electrolyte disturbance including hypomagnesemia and hypokalemia:

- Research is currently underway into the role of bevacizumab in nasopharyngeal carcinomas. The RTOG 0615 study is exploring whether the addition of this targeted agent to concurrent chemoradiotherapy can reduce the risk of distant metastasis. Bevacizumab is a humanized monoclonal antibody that selectively binds to human VEGF, reducing tumor vascularization, thereby inhibiting tumor growth. There are serious comorbidities associated with bevacizumab that include

arterial thromboembolic events, gastrointestinal perforation, fistula and intra-abdominal abscesses, hemorrhages, hypertension proteinuria, and necrotizing fasciitis.

Summary

Non-surgical management of head and neck cancers is increasingly adopted. Where chemotherapy and radiotherapy were once the preserve of unresectable and palliative cases only, non-surgical oncological management has become an important component for the treatment of this group of patients.

Systemic therapy is an important part of a multimodality approach in the treatment of locally advanced malignancies. Palliative chemotherapy has an important role in improving symptoms and subsequently quality of life in what can be debilitating recurrent or metastatic disease.

In the neoadjuvant setting, chemotherapy may reduce the likelihood of distant metastases while improving the locoregional control provided by definitive surgery or radiotherapy. Primary concurrent chemotherapy improves overall survival when compared to radiotherapy alone in locally advanced disease. In patients for whom cisplatin is contraindicated, cetuximab is licensed by NICE for use in combination with radiotherapy. For patients with positive resection margins or evidence of extracapsular spread in malignant lymphadenopathy, addition of chemotherapy to adjuvant radiotherapy reduces the rate of loco-regional disease recurrence.

Research into using cetuximab with both primary concurrent chemoradiotherapy and post op chemoradiotherapy is underway. The RTOG 0522 trial looked at the addition of cetuximab to concurrent chemotherapy plus accelerated radiotherapy in stages III–IV head and neck squamous carcinomas – there was no improvement of either progression-free or overall survival. Future studies will continue to evaluate the role of biological agents with more advanced radiation techniques.

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MANUAL OF
HEAD AND NECK SURGICAL ONCOLOGY

Tumors in the head and neck region often present major challenges given the complexity of the regional anatomy. *Manual of Head and Neck Surgical Oncology* has been designed to provide trainee ENT, plastic and maxillofacial surgeons with rapid access to the basic knowledge and principles required for management of the common tumors of the head and neck.

Introductory chapters on the principles of chemotherapy, radiotherapy and imaging are followed by chapters devoted to specific procedures such as neck dissection, maxillectomy and skull base surgery. The book also includes information on nutritional and speech and language considerations.

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