

Early- and advanced-stage head and neck cancers – EML

The application sought the addition of cisplatin to the core list of the EML for the postoperative treatment, in combination with radiotherapy, of locally advanced head and neck squamous cell carcinoma (HNSCC). The application notes that, for this indication, carboplatin is not an acceptable alternative to cisplatin.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

About 90% of all head and neck cancers are squamous cell carcinomas, and HNSCC is the sixth leading cancer by incidence worldwide. Most HNSCCs arise in the epithelial lining of the oral cavity, oropharynx, larynx and hypopharynx (1, 2). Approximately one third of patients present with early stage-disease (T1–2, N0, using the TNM staging system of the American Joint Committee on Cancer (AJCC)), and the 5-year overall survival rate of HNSCC patients is about 40–50%. Treatment for early HNSCC usually involves single-modality therapy – either surgery or radiation; survival is comparable for the two approaches. Early-stage cancers have a very favourable prognosis: cure rates are high with surgery or radiation alone and chemotherapy or concurrent chemotherapy/radiation is not indicated.

In pathologically staged III–IVa/b head and neck cancer, combined postoperative radiotherapy/cisplatin has been shown to improve local–regional control and survival rates for patients with positive microscopic surgical margins and/or extracapsular nodal extension (3).

Public health relevance

Head and neck cancer encompasses many site-specific cancers, including oral cavity and oropharyngeal cancers. Studies have estimated the global incidence of all head and neck cancers to be between 400 000 and 600 000 new cases per year, with between 223 000 and 300 000 deaths per year (4). Alcohol and tobacco are known risk factors for most head and neck cancers, and incidence rates are found to be higher in regions with high rates of alcohol and tobacco consumption (5). During the past few decades, several countries have witnessed a decline in oral cavity cancer incidence that correlates with declining tobacco use. However, despite declining tobacco use since the 1980s, Canada, Denmark, the Netherlands, Norway, Sweden, the United Kingdom and USA have seen increasing rates of oropharyngeal and oral cavity cancers (4). Theories that human papillomavirus infection might be an additional risk factor for the development of certain head and neck cancers have emerged and are prompting research; epidemiological information regarding head and neck cancers is thus likely to change with further discoveries (4).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

A detailed history and physical examination, including complete head and neck examination with biopsy, are necessary to establish the diagnosis. Examination with a mirror or fibre optic scope is essential in diagnosing and staging lesions involving the larynx and pharynx.

Testing

A panoramic radiograph of the mandible and computerized tomography scan or magnetic resonance imaging of the neck may be done as indicated and are useful to assess the extent and stage of the cancer. A chest X-ray and pretreatment dental evaluation are recommended. For patients with advanced-stage disease who will receive concurrent chemotherapy and radiation, blood counts and blood chemistry may be done to assess critical organ function, including renal and hepatic function.

Administration and care of patients

Despite a lack of randomized comparative trials, both surgery and definitive radiation therapy appear to offer equivalent local tumour control and survival for early-stage head and neck cancers. Choice of treatment is based on various factors, including tumour accessibility, functional outcome, patient's health and preference, and the availability of treatment expertise. Surgery is the preferred treatment modality for early-stage oral cavity cancers and involves resection of the primary tumour, with or without lymph nodal dissection. Patients who are medically inoperable or who refuse surgery can be treated with definitive radiation therapy. Definitive radiation therapy is also the preferred approach for many patients with non-oral cavity tumours, in particular of the hypopharynx and supraglottic and glottic larynx, since it appears to provide a better functional outcome than larynx-sparing surgical approaches. For patients with residual disease after radiation therapy, salvage surgery is recommended; for those managed by surgery, postoperative radiation therapy is indicated in the presence of close or positive margins, lymphovascular or perineural invasion, or when a positive lymph node is identified, upstaging the tumour.

Administration of cisplatin requires intravenous infusion capacity. Adequate intravenous hydration and antiemetics should accompany the infusion of cisplatin, and blood counts and blood chemistry should be serially monitored during the course of treatment.

Concurrent chemotherapy increases the risk for radiation-related adverse effects including mucositis, dysphagia and dermatitis. Patients should be carefully monitored for these and supportive care provided as indicated. Care should be taken to maintain adequate hydration, nutrition and analgesia before, during and after completion of treatment. Optimal monitoring and supportive care require trained clinicians experienced in the management of these cancers and with access to inpatient care and laboratory services. Late treatment-related toxicities such as xerostomia, dysphagia, speech dysfunction, gastric tube

dependence, tracheostomy dependence, neuropathies, depression and cosmetic disfigurement can significantly impact quality of life and psychosocial well-being and therefore need to be identified and addressed.

Overview of regimens

Concurrent radiation and three doses of cisplatin are recommended.

Standard regimen

- **Concomitant chemotherapy–radiation**
 - cisplatin 100 mg/m² IV every 3 weeks (on days 1, 22, 43) x 3 cycles

The Committee noted that, despite a lack of large, randomized studies and therefore based on phase II trials and centre experience, there are many reports of cisplatin being administered weekly (at 40 mg/ m² IV) in an attempt to reduce the toxicity and increase the tolerability of concomitant chemotherapy and radiation.

Review of benefits and harms

Benefits

Early-stage head and neck cancers are highly curable with either surgery or radiation therapy, but certain high-risk features have been shown to significantly increase the likelihood of recurrence. Two randomized trials have demonstrated improved outcomes following the addition of concomitant cisplatin to postoperative radiation in patients with locally advanced disease or certain adverse risk features. Both studies compared concomitant cisplatin (100 mg/m² on days 1, 22 and 43) and radiotherapy with radiotherapy alone after surgery in patients with advanced-stage cancers of the oral cavity, oropharynx, larynx or hypopharynx.

The RTOG 9501/Intergroup trial randomized 459 patients and showed significant improvement in local–regional control rates and disease-free survival – but not overall survival – in the chemoradiation arm (6). The 2-year rate of local and regional control was 82% in the chemoradiation group versus 72% in the radiotherapy group; disease-free survival was significantly longer in the chemoradiation group (hazard ratio (HR) for disease or death, 0.78; 95% CI: 0.61–0.99; *P* = 0.04).

The EORTC 22931 trial randomized 334 patients and showed improved 5-year progression-free survival (47% vs 36%) and overall survival (53% vs 40%) for the concomitant cisplatin group compared with the radiation group (7). The estimated 5-year cumulative incidence of local or regional relapses was 31% with radiation compared with 18% after combined therapy.

A comparative analysis of data pooled from the two trials showed that extracapsular extension and/or microscopically involved surgical margins were the only risk factors for

which the impact of concomitant chemoradiation was significant in both trials (3). There was also a trend in favour of the combined modality arm in the group of patients who had stage III–IV disease, perineural infiltration, vascular embolisms, and/or clinically enlarged level IV–V lymph nodes secondary to tumours arising in the oral cavity or oropharynx. A 10-year follow up of the RTOG 9501/Intergroup trial confirmed the superiority of the combined arm for local–regional control and disease-free survival in the subgroup of patients with microscopically involved margins and/or extracapsular nodal spread (8).

Primary combined chemotherapy with cisplatin and radiation is also the standard for patients with locally advanced, unresectable tumours. In this setting, the addition of cisplatin to radiation improves disease control and overall survival. A meta-analysis of 50 studies showed an absolute benefit of 6.5% in overall survival (HR 0.81; $P < 0.0001$) for patients who received combined chemoradiation (9).

In the primary treatment setting, an international phase III study found that cetuximab improved outcomes compared with radiation alone in patients with locally advanced disease (10). Radiotherapy plus cetuximab was associated with a median overall survival of 49 months, compared with 29.3 months for patients treated with radiotherapy alone (HR for death 0.74; $P = 0.03$). Progression-free survival was also significantly extended (HR for disease progression or death 0.70; $P = 0.0006$). However, cetuximab has not been shown to be superior to cisplatin and is much more costly. It is therefore neither proposed nor recommended for inclusion on the EML for treatment of HNSCC at this time.

Harms and toxicity considerations

Common

Nausea and vomiting occur in almost all patients treated with cisplatin and is often severe, necessitating the use of antiemetic medications. Major dose-limiting toxicities of cisplatin include renal impairment (28–36%), ototoxicity (40–60% children; 10–31% adults) and myelosuppression (11). Ototoxicity usually manifests as tinnitus and high-frequency hearing loss. Myelosuppression can lead to anaemia, leukopenia and thrombocytopenia with associated complications.

In the RTOG 9501 trial, the incidence of acute toxicity of grade 3 or greater was 34% in the radiotherapy group versus 77% in the concomitant cisplatin arm. Similarly, in the EORTC trial, severe adverse effects were more frequent after combined therapy (41%) than after radiotherapy (21%) ($P = 0.001$) (6, 8).

Serious

Renal toxicity caused by cisplatin can be significant and may result in electrolyte abnormalities. Intravenous hydration is needed both before and after administration of cisplatin, particularly in elderly patients and patients with compromised renal function, to reduce the incidence of renal toxicity (12). Combining cisplatin chemotherapy with radiation significantly increases the rates of grade 3 and 4 radiation-related toxicity, including dysphagia, dermatitis and mucositis (6, 8).

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended the addition of cisplatin to the complementary list of the WHO Model List of Essential Medicines for the treatment, in combination with radiotherapy, of locally advanced head and neck squamous cell carcinoma. Compared with postoperative radiotherapy alone, the Committee considered that the benefits associated with the addition of cisplatin, in terms of local–regional control rates and disease-free survival, progression-free survival and overall survival, were of both clinical and public health relevance.

The Committee also considered that use of primary combined chemotherapy with cisplatin and radiation was associated with a clinical benefit, compared with radiation alone, in patients who have unresectable tumours.

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