THE ROLE OF CHEMOTHERAPY AND OTHER MODALITIES IN HEAD AND NECK CANCER*

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**ABSTRACT**

For patients with head and neck cancer (HNCA), therapy for earlier-stage disease has traditionally involved surgery and radiation, and chemotherapy has been relegated to palliation for metastatic disease. Recently, an increase in the use of antineoplastic agents for earlier stages of HNCA has been seen. The taxanes, 5-fluorouracil, and the platinum analogs cisplatin and carboplatin are the workhorses of HNCA chemotherapy. With increasing frequency, they are being combined with radiotherapy to improve locoregional control and organ preservation and to reduce the formation of distant metastases and the incidence of severe, acute, treatment-related adverse side effects, particularly mucositis. Although neoadjuvant therapy has yet to be conclusively proven to be beneficial, combined chemoradiation has shown some promise in randomized trials. Although the radiosensitizing effects of cisplatin are valuable, cisplatin is not tumor specific, and dose-related toxicities limit its use. Another clinical conundrum is posed by patients with metastatic disease, in whom combination chemotherapy trials consistently show increased response rates but no survival benefit. To boost survival rates, the current focus is on the development of targeted therapies, such as the epidermal growth factor receptor (EGFR) inhibitors erlotinib and gefitinib, which are small-molecule tyrosine kinase inhibitors, and cetuximab, a chimeric human-murine monoclonal IgG1 antibody. Emerging clinical data are demonstrating the value of EGFR inhibitors in HNCA, and additional studies are being planned to assess their value when combined with the traditional treatment modalities.

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Conventionally, the role of chemotherapy in patients with head and neck cancer (HNCA) has been limited to palliation. However, the role of chemotherapy in the definitive management of these malignancies has evolved tremendously in the past decade. Recent data from randomized trials support a role for chemotherapy as part of combined-modality, curative treatment strategies in the management of patients with unresectable disease or advanced HNCA. In addition, targeted biologic agents, such as epidermal growth factor receptor (EGFR) inhibitors, are being investigated in studies in which they are given with traditional chemotherapeutic agents.

**APPROACHES TO TREATING HEAD AND NECK CANCER**

The strategy for treating HNCA depends on the stage of the disease. For example, early-stage disease is treated with surgery alone. However, most patients are diagnosed with locally advanced disease and have historically been treated with curative intent with surgery followed by radiotherapy or radiotherapy alone. Most multi-institutional trials that included patients treated this way have resulted in locoregional recurrence rates...
of 30%, rates of distant metastasis formation of 25%, and 5-year survival rates of 40%, in addition to clinically significant sequelae from major surgery.\textsuperscript{1} The 5-year mortality rate for HNCA has not changed substantially in the past few decades despite advances in treatment modalities.\textsuperscript{2} Thus, the management of late-stage HNCA is relatively unsatisfactory, and optimal therapy remains a matter of debate, especially with regard to treatment intensity and sequencing. To increase cure rates while preserving organ function, chemotherapy is being used in 3 different approaches. One of these is as neoadjuvant chemotherapy, which refers to giving chemotherapy before locoregional therapy consisting of surgery or radiation. This approach attempts to downstage the tumor, which facilitates local therapy, and to eradicate micrometastatic disease. Another approach is concurrent chemoradiation, which is chemotherapy given at the same time as radiation. This approach not only treats local disease but also attempts to eradicate micrometastatic disease. The third approach is adjuvant therapy, which is chemotherapy given after local therapy. Because of the lack of a standard of care, the role of adjuvant therapy in HNCA will not be discussed here. Metastatic disease is treated with palliative chemotherapy.

**TRADITIONAL CHEMOTHERAPEUTIC AGENTS**

The primary agents used for treating HNCA are the platinum analogs, 5-fluorouracil (5-FU), and the taxanes, in addition to older agents, such as methotrexate and mitomycin C. Although useful, all of these agents have limited effectiveness and are associated with severe toxicities.

**Platinum Analogs**

The platinum-containing agents cisplatin and carboplatin are DNA cross-linking agents similar to, but not identical to, the alkylating agents. These platinum analogs act by cross-linking DNA in various ways, which prevents rapidly dividing cells from duplicating their DNA for mitosis. The damaged DNA then sets off DNA repair mechanisms, which activate apoptosis when repair proves impossible. Because of the molecular differences between the 2 agents, their dosing also differs. In HNCA, cisplatin is typically given in a single dose of 75 to 100 mg/m\textsuperscript{2} every 3 to 4 weeks.\textsuperscript{3} Prehydration is essential to prevent the renal damage that cisplatin can cause.\textsuperscript{4} Prehydration is usually accomplished by intravenously (IV) giving 1 L of normal saline, to which is added 20 mEq potassium chloride and 8 mEq magnesium sulfate over 1 to 2 hours to obtain a urinary flow rate of at least 100 mL per hour; posthydration consists of giving the same IV fluids. Because renal excretion is the main route of elimination for carboplatin, carboplatin dosing involves using the Calvert method, which is a calibration method based on kidney function. The Calvert method involves calculating the dose in milligrams by multiplying the target area under the concentration time curve (AUC) by the sum of the creatinine clearance (CrCl) plus 25 (ie, dose [mg] = target AUC x [CrCl + 25]).\textsuperscript{5} The target AUC can range from 1 to 8 mg/mL per minute, depending on whether radiation is being given concurrently or whether carboplatin treatment is given weekly or every 3 weeks. Whether cisplatin and carboplatin are interchangeable in treating HNCA depends on the role chemotherapy is expected to play. In general, cisplatin appears to be the superior agent, especially if radiotherapy is being used concurrently, because cisplatin is a better radiosensitizer than carboplatin. Two randomized trials have shown that superior disease-free survival and response rates resulted from cisplatin chemotherapy compared to carboplatin chemotherapy.\textsuperscript{3,6} No difference between the 2 drugs was observed in overall survival. However, because cisplatin is the better radiosensitizer, it is a better choice than carboplatin, even though its effect on survival has not yet been demonstrated. When palliation is the goal, platinum analogs can be used or therapy can be switched from 1 to the other to enhance tolerability. The use of cisplatin results in more nephrotoxicity, nausea and vomiting, and neurotoxicity than carboplatin. However, unlike cisplatin, carboplatin causes myelosuppression, specifically thrombocytopenia, and, in some cases, carboplatin can cause severe nausea and vomiting.

**5-Fluorouracil**

5-Fluorouracil is a prodrug that is broken down into 2 primary products: 5-fluourouridine-5'-triphosphate (FUTP) and 5-fluorodeoxyuridine-5'-monophosphate (FdUMP). The 5-FU product FUTP is incorporated into RNA, which causes impaired protein synthesis.\textsuperscript{7} However, the main mechanism of action occurs through inhibition of DNA; FdUMP forms a tight but reversible covalent bond with thymidylate synthetase, an enzyme needed for the synthesis of thymidine, 1 of the 4 building blocks of DNA. By inhibiting this key enzyme, 5-FU...
reduces the rate of DNA synthesis, replication, and repair. 5-FU is cell-cycle specific for the synthesis phase and tends to produce better response rates when given as an infusion.

As in colon cancer, in HNCA infusions of 5-FU appear to result in better response rates for several reasons. For example, compared to bolus delivery, a 24-hour infusion permits delivery of more drug to the site of action and exposes a larger number of tumor cells to 5-FU. In addition, the adverse effect profile of an infusion differs from that of a bolus and is considered more tolerable. The dose-limiting adverse effect of infusional 5-FU tends to be diarrhea, whereas, in bolus administration mucositis is more prevalent.

Furthermore, prolonged, continuous IV infusions have yielded higher response rates than IV bolus regimens. In a randomized trial in 44 patients with advanced and recurrent HNCA, cisplatin 100 mg/m² given on day 1 and a 24-hour infusion of 5-FU 1000 mg/m² given on days 1 through 4 was compared to cisplatin 100 mg/m² given on day 1 and bolus 5-FU 600 mg/m² given on days 1 and 8. The response rate for the infusion arm was 72% (4/18 who had a complete response [CR] + 9/18 who had a partial response [PR]), whereas the response rate for the bolus arm was 20% (2/20 CR + 2/20 PR). The difference in response between treatment arms was statistically significant (P < .01). However, continuous infusion often requires the patient to be admitted to the hospital when the patient does not have access to portable ambulatory care pumps. This requirement entails greater expense and places a larger burden on the healthcare system. In addition, continuous infusion may cause complications arising from the use of indwelling catheters.

The major adverse side effects associated with 5-FU are those that are dose limiting and include diarrhea, mucositis, and hand-foot syndrome. Other adverse effects include cardiac toxicity (which may result in angina and myocardial infarction), photosensitivity, skin reactions (eg, hyperpigmentation, nail bed changes, or rashes), gastrointestinal problems (eg, nausea or vomiting), and ocular side effects (eg, burning, tearing, or itching). Another complication involves dihydropropirimidine dehydrogenase (DPD), an enzyme needed in the initial and rate-limiting step in pyrimidine catabolism. The enzyme DPD regulates the amount of 5-FU available for anabolism, which thereby affects its pharmacokinetics, toxicity, and efficacy. Because the catabolic pathway does not function in patients with DPD deficiency, administration of standard doses of 5-FU results in altered 5-FU pharmacokinetics and severe toxicity that may cause mucositis, granulocytopenia, neuropathy, and death. This toxicity appears to result from decreased drug clearance, which markedly prolongs exposure to 5-FU. Recent evidence has shown that African Americans are more prone to DPD deficiency than whites (7.7% vs 2.3%) and therefore, are at greater risk from the toxicities associated with 5-FU administration.

**Taxanes**

The taxanes include paclitaxel and docetaxel. These agents work by disrupting the microtubular network in cells that are essential for mitotic and interphase cellular functions, specifically those that occur during the mitosis phase of the cell cycle. The taxanes bind to free tubulin and promote the assembly of tubulin into stable microtubules while inhibiting their disassembly. This effect leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Taxanes are specific for the mitosis phase of the cell cycle and also are excellent radiosensitizers. The taxanes’ mechanism of action through microtubule stabilization is unique among chemotherapeutic agents.

Taxanes have shown response rates similar to those of standard, first-line combination regimens. Phase II studies have evaluated the efficacy of docetaxel monotherapy in patients with HNCA. Cumulative response rates were approximately 30%, and higher response rates were observed in patients who had not received chemotherapy previously. Docetaxel also has been used with cisplatin and with cisplatin plus 5-FU. Although response rates that resulted from such combination regimens were shown to be superior to those that resulted from the use of docetaxel monotherapy, grade 3 and 4 adverse effects, especially mucositis, nausea, and neutropenia, also were more prevalent.

Paclitaxel is administered at a dose of 135 to 175 mg/m² as an IV infusion every 3 weeks and should be given before a platinum-containing agent when used in combination regimens. Docetaxel is given at a dose of 75 to 100 mg/m² as an IV infusion over 1 hour every 3 weeks. The main adverse effect associated with paclitaxel and docetaxel is dose-limiting leukopenia. Additional toxicities seen with paclitaxel include hypersensitivity reactions, alopecia, cardiac toxicity, peripheral neuropathies, and mucositis. Additional toxicities seen with docetaxel include peripheral edema and alopecia.
Before receiving docetaxel, all patients should be premedicated with oral corticosteroids, such as dexamethasone 8 mg twice a day for 3 days, starting 1 day before docetaxel is given to reduce the severity of fluid retention. Similarly, all patients receiving paclitaxel should be premedicated with dexamethasone 20 mg taken orally approximately 12 hours and 6 hours before the taxane is given, diphenhydramine 50 mg given IV 30 to 60 minutes before the taxane is given, and cimetidine 300 mg or ranitidine 50 mg given IV 30 to 60 minutes before the taxane is given to reduce hypersensitivity reactions.

**COMBINATION THERAPY**

As with most cancers, single-agent chemotherapy is rarely given in HNCA. Combination therapy has been attempted in patients with HNCA with varying degrees of success; the greatest success has been reported for the combination of cisplatin and 5-FU. Response rates for combination therapy are superior to those for monotherapy and are as high as 80%, although a survival benefit for combination therapy has been difficult to prove. Nevertheless, when used as neoadjuvant therapy or for metastatic disease, combination therapy has become the standard of care for most patients with HNCA. Table 1 is a summary of the major neoadjuvant trials that showed some benefit in terms of survival and/or distant failure, which is a marker for lack of eradication of micrometastatic disease. Most randomized neoadjuvant trials do not show a survival advantage. For example, The Head and Neck Contracts Program gave 1 cycle of induction cisplatin and bleomycin, then 6 cycles of cisplatin. No survival advantage was evident, but the study did show a reduction in distant metastases as the first site of failure. Two European trials—the Groupe d’Etude des Tumeurs de la Tete Et du Cou and the Gruppo di Studio sui Tumori della Testa e del Collo (GSTTC)—showed a survival benefit with 3 or 4 cycles of induction cisplatin and 5-FU; the GSTTC trial also showed a reduction in the distant failure rate. A large meta-analysis, the Meta-analysis of Chemotherapy on Head and Neck Cancer, which looked at the impact on survival of various chemotherapy regimens when added to locoregional treatment, showed an overall 2% survival advantage at 5 years for this approach, which increased to 5% when only cisplatin/5-FU studies were included. Neoadjuvant therapy has been somewhat more successful in preserving organ function in a variety of trials (Table 2). In the Veterans Affairs Laryngeal Cancer Study Group, a land-

### Table 1. Neoadjuvant Chemotherapy—Effects on Survival

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients, n</th>
<th>Chemotherapy</th>
<th>Survival Benefit</th>
<th>Distant Future Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNCP&lt;sup&gt;16&lt;/sup&gt;</td>
<td>462</td>
<td>Cisplatin and bleomycin x 1, Cisplatin x 6</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>GSTTC&lt;sup&gt;17&lt;/sup&gt;</td>
<td>237</td>
<td>Cisplatin and 5-FU x 4</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>GETTEC&lt;sup&gt;18&lt;/sup&gt;</td>
<td>318</td>
<td>Cisplatin and 5-FU x 3</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>MACH-NC&lt;sup&gt;19&lt;/sup&gt;</td>
<td>10 741</td>
<td>Various</td>
<td>2% at 5 yr; 5% in cisplatin and 5-FU trials</td>
<td>Yes</td>
</tr>
</tbody>
</table>

5-FU = 5-fluorouracil; GETTEC = Groupe d’Etude des Tumeurs de la Tete Et du Cou; GSTTC = Gruppo di Studio sui Tumori della Testa e del Collo; HNCP = Head and Neck Contracts Program; MACH-NC = Meta-analysis of Chemotherapy on Head and Neck Cancer.

Data from Head and Neck Contracts Program<sup>16</sup>; Paccagnella et al<sup>17</sup>; Domenge et al<sup>18</sup>; and Pignon et al<sup>19</sup>.

### Table 2. Neoadjuvant Chemotherapy—Effects on Organ Preservation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients, n</th>
<th>Chemotherapy</th>
<th>Survival Benefit</th>
<th>Organ Preservation</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Laryngeal Cancer Study Group&lt;sup&gt;20&lt;/sup&gt;</td>
<td>332</td>
<td>Cisplatin and 5-FU x 3 → RT vs none → S → RT</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>EORTC&lt;sup&gt;21&lt;/sup&gt;</td>
<td>202</td>
<td>Cisplatin and 5-FU x 3 → RT vs none → S → RT</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Richard et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>68</td>
<td>Cisplatin and 5-FU x 3 → RT vs none → S → RT</td>
<td>In favor of surgery arm</td>
<td>Yes</td>
</tr>
<tr>
<td>MACH-NC&lt;sup&gt;19&lt;/sup&gt;</td>
<td>10 741</td>
<td>Various</td>
<td>Trend in favor of surgery arm</td>
<td>n/a</td>
</tr>
</tbody>
</table>

5-FU = 5-fluorouracil; EORTC = European Organisation for the Research and Treatment of Cancer; MACH-NC = Meta-analysis of Chemotherapy on Head and Neck Cancer; n/a = data not available; RT = radiotherapy; S = surgery; VA = Department of Veterans Affairs.

Data from Pignon et al<sup>19</sup>; Department of Veterans Affairs Laryngeal Cancer Study Group<sup>20</sup>; Lefebvre et al<sup>21</sup>; and Richard et al<sup>22</sup>.
mark study in organ preservation, and the European Organisation for the Research and Treatment of Cancer (EORTC) trial, patients were randomized to receive induction cisplatin/5-FU (at least 2 cycles, and, if a response was seen, a third cycle), then radiation, or to receive surgery, then radiation.20,21 In these studies, no difference in survival was observed on the basis of treatment strategy, and an improvement in organ preservation was shown by a decrease in need for laryngectomy.20,21

However, a small trial in 68 patients done by Richard et al found the opposite.22 In that trial, results of surgery followed by radiation were found to be superior to those of chemotherapy followed by radiation (2-year overall survival: 69% vs 84%; \( P = .006 \)).22 Moreover, a large meta-analysis of 10741 patients found no difference in survival but a trend toward decreased survival (\( P = .1 \)) in the nonsurgery arm, which led the investigators to conclude that "we cannot exclude the negative impact of this strategy on survival."20

Neoadjuvant chemotherapy has shown some benefit in treating patients with resectable disease, albeit in terms of organ preservation rather than survival. However, the use of this approach followed by radiotherapy alone or by surgery if the primary tumor becomes resectable has not shown any survival benefit in treating initially unresectable disease; therefore, it is not recommended as a standard approach.23 Nevertheless, a 2004 randomized EORTC trial in patients with unresectable HNCA showed that the addition of docetaxel to 4 cycles of cisplatin/5-FU significantly improved overall survival (median survival: 14.5 months vs 18.6 months; \( P = .016 \)), which suggests that neoadjuvant chemotherapy should be reconsidered.24 However, for the most part, these generally disappointing results have fueled the trend towards replacing neoadjuvant chemotherapy with chemoradiation.

CHEMORADIATION

Unlike neoadjuvant chemotherapy, chemoradiation takes advantage of the radiosensitizing effects of chemotherapy. However, the radiosensitizing effects of chemotherapy are not tumor selective, and high rates of toxicity have been seen, especially with combination regimens. Because of its superior radiosensitizing ability, cisplatin is generally the drug of choice for the chemoradiation of HNCA.

In a meta-analysis that examined the various approaches to chemoradiation, the reduction in risk of death was 19% when both therapies were given concomitantly versus 5% for neoadjuvant chemotherapy and 2% for adjuvant chemotherapy.19 The concomitant approach produced an 8% absolute benefit at 5 years versus a 2% absolute benefit for neoadjuvant chemotherapy and a 1% absolute benefit for adjuvant chemotherapy. In an intergroup, phase III trial, radiation alone was compared to radiation plus cisplatin and radiation plus cisplatin/5-FU given in a split course.25 Patients received 3 cycles of treatment; radiation was given during the first and third cycles but omitted during the second cycle to decrease toxicity. The results showed that concomitant cisplatin/radiation was the superior regimen; the overall 3-year survival rate that resulted from this regimen was 37% versus 23% for radiation alone (\( P = .014 \)).

TREATMENT OF METASTATIC DISEASE

When treating metastatic HNCA, the same drugs are used as when treating the earlier stages of HNCA but are used for palliation rather than survival. The median duration of survival for patients with metastatic disease is a mere 6 months; the 1-year survival rate is 20% and is typically not increased by chemotherapy.

Several randomized trials have compared combination chemotherapy with single-agent chemotherapy (Table 3).3,26,27 These trials consistently have shown

| Table 3. Combination vs Single-Agent Chemotherapy for Metastatic Disease |
|--------------------------|------------------|-----------------|-----------------|
| Study                  | Patients, \( n \) | Agents              | Response Rate, % | Mean Survival, mo |
| Jacobs et al26          | 245              | Cisplatin and 5-FU | 32*<sup>1</sup> | 5.5               |
|                        |                  | Cisplatin          | 17              | 5                 |
|                        |                  | 5-FU               | 13              | 6.1               |
| Forastiere et al3       | 277              | Cisplatin and 5-FU | 32†<sup>2</sup> | 6.6               |
|                        |                  | Carboplatin and 5-FU | 21              | 5                 |
|                        |                  | Methotrexate       | 10              | 5.6               |
| Clavel et al27         | 382              | Cisplatin, methotrexate, bleomycin, and vincristine | 34‡<sup>3</sup> | 7                 |
|                        |                  | Cisplatin and 5-FU | 31§<sup>4</sup> | 7                 |
|                        |                  | Cisplatin          | 15              | 7                 |

*\( P = .035 \); †\( P < .001 \); ‡\( P < .001 \); §\( P = .003 \).

5-FU = 5-fluorouracil.

Data from Forastiere et al3; Jacobs et al26; and Clavel et al27.
increased response rates for combination regimens but have not shown a survival benefit. However, on the basis of the increase in response rates and manageable toxicity, combination therapy with a platinum analog plus another drug, such as bleomycin, 5-FU, methotrexate, and/or vincristine in various combinations, has become the standard of care for metastatic disease. In the study by Forastiere et al, carboplatin was found to be comparable to cisplatin in terms of overall survival but resulted in a lower response rate than cisplatin. The trial by Clavel et al showed that giving more than 2 traditional chemotherapeutic agents produced no better results than giving 2 traditional chemotherapeutic agents in terms of overall survival and response rates.

**Epidermal Growth Factor Receptor Blockade**

A newer approach to treating cancer is to block EGFRs. Peptide growth factors activate signaling pathways, which control cell proliferation and death in normal and malignant cells. The epidermal growth factor was one of the first growth factors to be identified and has a pivotal role in the regulation of normal cell growth and differentiation. The EGFR autocrine pathway contributes to several processes that are important in cancer development and progression, including cell proliferation, apoptosis, angiogenesis, and metastatic spread. The key role the EGFR plays in cancer has led to an extensive search for selective inhibitors of the EGFR signaling pathway. A variety of approaches are currently being used to target the EGFR.

**Cetuximab**

The most promising strategies in clinical development include producing monoclonal antibodies to prevent ligand binding and creating small-molecule inhibitors of tyrosine kinase enzymatic activity to inhibit autophosphorylation and downstream intracellular signaling. Cetuximab is a chimeric human-murine monoclonal IgG1 antibody that has been the first anti-EGFR–targeted therapy to receive clinical evaluation in patients with cancer in phase II and III studies when given alone or with conventional therapies, such as radiotherapy and chemotherapy. In March 2006, cetuximab was approved by the US Food and Drug Administration for use in combination with radiation therapy to treat patients with squamous cell HNCA that cannot be removed by surgery. Cetuximab also was approved for use in patients with metastatic HNCA that have already failed traditional chemotherapy.

In a phase III study of patients with locoregionally advanced squamous cell carcinoma of the head and neck, high-dose radiotherapy was compared to high-dose radiotherapy plus cetuximab. After a median follow-up of 45 months, the median durations of locoregional control (LRC) were 24.4 months for radiotherapy plus cetuximab and 14.9 months for radiotherapy only (log-rank \( P = .005 \)). Adding cetuximab to radiotherapy reduced the risk of locoregional failure by 32% (hazard ratio = 0.68). At 2 years, 50% of the patients in the radiotherapy plus cetuximab arm and 41% of those in the radiotherapy only arm had LRC. The median duration of survival was 49 months for combination therapy and 29 months for radiotherapy only (median follow-up, 45 months). A 26% reduction in the risk of mortality also was noted for combination therapy compared to radiotherapy only (hazard ratio = 0.74, log-rank \( P = .03 \)). The 3-year survival rates were 56% for combination therapy and 45% for radiotherapy only. Except for acne-like rashes and infusion reactions, the incidence of grade 3 or 4 adverse effects did not differ between the treatment arms.

Reports of several phase II trials of cetuximab alone or with chemotherapy in patients with refractory or recurrent HNCA have been published (Table 4).

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Patients, n</th>
<th>Response Rate, %</th>
<th>Median Survival, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical controls*</td>
<td>151</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>Platinum-based chemotherapy + cetuximab</td>
<td>96</td>
<td>10</td>
<td>6.1</td>
</tr>
<tr>
<td>Cisplatin + cetuximab</td>
<td>132</td>
<td>SD, 18</td>
<td>SD, 11.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD/1, 20</td>
<td>PD/1, 6.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD/2, 6</td>
<td>PD/2, 4.3</td>
</tr>
<tr>
<td>Cetuximab monotherapy</td>
<td>103</td>
<td>16.5</td>
<td>5.8</td>
</tr>
</tbody>
</table>

*Historical controls had disease that was refractory to platinum-analog chemotherapy.

PD/1 = patients with progressive disease who received cetuximab and cisplatin; PD/2 = patients in whom progressive disease developed within 90 days after platinum-analog therapy and who were then given cetuximab; SD = stable disease.

Data from Leon et al; Baselga et al; Herbst et al; and Trigo et al.
Results of these trials have been compared to those obtained in patients who have not responded to platinum-analog therapy and who therefore serve as historical controls to underscore their dismal prognosis and the need for novel therapies.\textsuperscript{31} Baselga et al treated 96 patients with cetuximab followed by platinum-analog chemotherapy at the same dose and schedule, after which progressive disease (PD) was documented before entry into the study.\textsuperscript{32} The response rate in the intent-to-treat population was 10\%, and the disease control rate, which included CR, PR, and stable disease (SD), was 53\%. The median time to progression was 85 days, and the median duration of survival was 183 days. Treatment was well tolerated. The most common cetuximab-related adverse events were skin reactions, particularly an acne-like rash.

In a study by Herbst et al, 132 patients with HNCA received 2 3-week cycles of treatment with cisplatin/paclitaxel or cisplatin/5-FU.\textsuperscript{33} Patients with a CR or PR continued to receive standard therapy. Seventy-six patients with SD ($n = 51$) or those with PD in arm 1 (PD/1; $n = 25$) received combination therapy with cetuximab and cisplatin. The protocol was subsequently amended to enroll patients who had developed PD within 90 days after platinum-analog therapy (PD – arm 2 [PD/2]; $n = 54$). The results showed that 5 patients (20\%) in PD/1, 3 patients (6\%) in PD/2, and 9 patients (18\%) with SD achieved an objective response. Median duration of response was 4.2 months in the PD/1 group, 4.1 months in the PD/2 group, and 7.4 months in the SD group; median duration of overall survival was 183 days. Rash (in 79\%) and diarrhea (in 37\%) were the most common drug-related adverse effects, although their severity was mild to moderate in most cases. In a phase II study of 47 patients with advanced HNCA, patients were given gefitinib 500 mg daily in combination with other therapy or as monotherapy.\textsuperscript{36} The observed response rate was 10.6\%, and the disease control rate was 53\%. Median time to progression was 3.4 months, and median duration of survival was 8.1 months. The only grade 3 adverse effect was diarrhea, which occurred in 3 patients. More studies are needed to assess the results of using these agents with traditional therapies in patients with HNCA.

**CONCLUSIONS**

Progress has been and continues to be made in the treatment of HNCA. However, current outcomes are unacceptable, particularly in advanced disease, and therefore, a need exists for novel approaches to disease management that combine traditional agents with the newer agents currently being developed. Despite promising results of randomized studies and meta-analyses, optimism must be balanced with realism because survival rates remain low. In early-stage disease, progress in surgical techniques and imaging has enabled more accurate resection. The objective now is to maintain a favorable efficacy-toxicity ratio for treat-
ment and to reduce the incidence of second primary tumors, which are often the major cause of relapse.

In patients with advanced HNCA, survival improves when chemotherapy is combined with radiotherapy compared to when radiotherapy is given alone. As in this instance, we continue to hone our therapeutic skills, albeit painstakingly slowly.

The immediate aim of treatment for advanced HNCA should be to increase survival, LRC, and organ preservation and to reduce the formation of distant metastases and the incidence of severe, acute, treatment-related adverse side effects, particularly mucositis. In addition, the use of neoadjuvant chemotherapy, which has so far failed to meet expectations, merits further investigation in well-defined, controlled trials. The outlook for patients with recurrent/metastatic disease remains poor, particularly for those patients whose disease progresses when treated with platinum-based therapies. For these patients, the goal is to improve response rates to chemotherapy and, whenever possible, to prolong survival without compromising quality of life.

In the search for treatments that improve outcomes in various cancers, targeted molecular therapies, such as cetuximab, erlotinib, and gefitinib, are in the investigational stages. Clinical experience with cetuximab plus radiotherapy for locally advanced disease and cetuximab plus chemotherapy for recurrent/metastatic disease indicates that these combination therapies show promise. Studies in which cisplatin-refractory disease was treated with cetuximab alone or with cisplatin plus cetuximab have produced encouraging results. The ability of targeted therapies to increase the therapeutic index of current conventional therapies without increasing their toxicities indicates that these agents have a key role to play in future practice and merit further investigation when used with other, more established therapies.

REFERENCES


