# Head and Neck Cancer

## Combination Therapy: Chemotherapy + Radiation Therapy

### Cetuximab – Radiation

<table>
<thead>
<tr>
<th>Cetuximab</th>
<th>400 mg/m²</th>
<th>IV</th>
<th>One dose on week 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>250 mg/m²</td>
<td>IV</td>
<td>Once a week of weeks 2 – 8</td>
</tr>
</tbody>
</table>

*Followed by*

| Radiation* | Various radiation schemas were used including: Once daily radiation for a total of 35 fractions – each of 2 Gy to a total dose of 70 Gy delivered over 7 weeks; Twice daily radiation schedule that included 60 – 64 fractions to a total dose of 72 – 76.8 Gy delivered over 6 – 6.5 weeks. A concomitant boost was also permitted administered in 42 fractions to a total dose of 72 Gy delivered over 6 weeks |

*Radiation to begin in week 2.

**NOTE:** Amifostine has been shown to be effective in reducing radiation-induced xerostomia. The most effective dose is 200 mg/m² IV over 3 – 5 minutes, administered at least 15 – 30 minutes prior to radiation three times weekly [Reference: Jellema AP, et al. *Cancer* 2006;107:544 – 53].


### Cisplatin – Hyperfractionated Radiation

<table>
<thead>
<tr>
<th>Cisplatin</th>
<th>20 mg/m²/day</th>
<th>IV</th>
<th>Days 1 – 5 (consecutive days) during week 1 and 5 or 6 of radiotherapy. Administer 1.5 hours before the afternoon radiotherapy session</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
<td>Hyperfractionated radiation of 1.2 Gy administered twice daily with an interfraction interval of 6 hours. Total radiation dose is 72 – 76.8 Gy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Routine pre- and post-hydration administered.

**NOTE:** Amifostine has been shown to be effective in reducing radiation-induced xerostomia. The most effective dose is 200 mg/m² IV over 3 – 5 minutes, administered at least 15 – 30 minutes prior to radiation three times weekly [Reference: Jellema AP, et al. *Cancer* 2006;107:544 – 53].

**CISPLATIN (WEEKLY) – HYPERFRACTIONATED RADIOTHERAPY**

**Cisplatin**  
40 mg/m² IV*  
Days 1, 8, 15, 22, 29 and 36

**Radiation**  
The primary tumor and bilateral draining lymphatics above the clavicle are to be treated with 5 fractions per week over 5.5 weeks (days 1 – 38) with a single fraction of 1.8 Gy (to a total dose of 50.4 Gy). Starting the 4th week of treatment, additional radiation therapy was administered as a concomitant boost (days 22 – 38). The boost volume covers the primary tumor and the involved neck nodes. The dose was 1.5 Gy/day up to 19.5 Gy, resulting in a total tumor dose of 69.9 Gy

*Administer over 30 minutes with adequate pre- and post-hydration.

NOTE: Amifostine has been shown to be effective in reducing radiation-induced xerostomia. The most effective dose is 200 mg/m² IV over 3 – 5 minutes, administered at least 15 – 30 minutes prior to radiation three times weekly [Reference: *Jellema AP, et al. Cancer* 2006;107:544 – 53].


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**CISPLATIN – RADIATION**

**Cisplatin**  
100 mg/m² IV*  
Days 1, 22 and 43 during radiation

**Radiation**  
70 Gy given in single, daily 2 Gy fractions

*Routine pre- and post-hydration required.

NOTE: Amifostine has been shown to be effective in reducing radiation-induced xerostomia. The most effective dose is 200 mg/m² IV over 3 – 5 minutes, administered at least 15 – 30 minutes prior to radiation three times weekly [Reference: *Jellema AP, et al. Cancer* 2006;107:544 – 53].


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**PACLITAXEL – CISPLATIN – RADIATION**

**Paclitaxel**†  
30 mg/m² IV  
Days 1, 8, 15, 22, 29, 36 and 43

**Cisplatin**  
20 mg/m² IV*  
Days 2, 9, 16, 23, 30, 37 and 44

**Radiation**  
70 Gy in 35 daily 2 Gy fractions delivered on Monday – Friday (for 5 weeks)

†Routine premedication administered; *Routine pre- and post-hydration required.

NOTE: Chemotherapy to be given prior to radiation on appropriate days. Amifostine has been shown to be effective in reducing radiation-induced xerostomia. The most effective dose is 200 mg/m² IV over 3 – 5 minutes, administered at least 15 – 30 minutes prior to radiation three times weekly [Reference: *Jellema AP, et al. Cancer* 2006;107:544 – 53].

**PACLITAXEL – CISPLATIN – 5–FLUOROURACIL – RADIATION (PCF)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Day(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel‡</td>
<td>175 mg/m²</td>
<td>IV</td>
<td>Day 1</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>100 mg/m²</td>
<td>IV**</td>
<td>Day 2</td>
</tr>
<tr>
<td>5–Fluorouracil</td>
<td>500 mg/m²/day</td>
<td>CIVI</td>
<td>Days 2 – 6</td>
</tr>
</tbody>
</table>

‡Routine premedication administered; *Administer over 3 hours; **Routine pre- and post-hydration required.

Repeat cycle every 3 weeks for 3 courses.

*Followed by*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Day(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>100 mg/m²</td>
<td>IV*</td>
<td>Days 1, 22 and 43</td>
</tr>
<tr>
<td>Radiation</td>
<td>70 Gy total dose administered in 35 fractions of 2Gy over a 7-week period. Nodal areas not clinically involved by tumor received a total dose of 50 Gy.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Routine pre– and post-hydration required.

NOTE: Amifostine has been shown to be effective in reducing radiation-induced xerostomia. The most effective dose is 200 mg/m² IV over 3 – 5 minutes, administered at least 15 – 30 minutes prior to radiation three times weekly [Reference: Jellema AP, et al. Cancer 2006;107:544 – 53].

### HEAD AND NECK CANCER
### ADJUVANT THERAPY

#### CISPLATIN – RADIATION

<table>
<thead>
<tr>
<th>Cisplatin</th>
<th>100 mg/m²</th>
<th>IV</th>
<th>Days 1, 22 and 43 during radiation therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation therapy</td>
<td>2 Gy/day Monday – Friday for 5 – 5.5 weeks to a total of 50 – 54 Gy. Close or positive margins received a 12 Gy boost (total 66 Gy) in 33 fractions over a period of 6.5 weeks.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Routine pre- and post-hydration required.

**NOTE:** Amifostine has been shown to be effective in reducing radiation-induced xerostomia. The most effective dose is 200 mg/m² IV over 3 – 5 minutes, administered at least 15 – 30 minutes prior to radiation three times weekly [Reference: Jellema AP, et al. Cancer 2006;107:544 – 53].

HEAD AND NECK CANCER
SYSTEMIC CHEMOTHERAPY

CARBOPLATIN – 5–FLUOROURACIL

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Route</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>300 mg/m²</td>
<td>IV*</td>
<td>Day 1</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>1000 mg/m²/day</td>
<td>CIVI**</td>
<td>Days 1 – 4</td>
</tr>
</tbody>
</table>

*Administer over 5 – 10 minutes; **Administer as a continuous 24–hour infusion.

Repeat cycle every 28 days.


CETUXIMAB

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Route</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>400 mg/m²</td>
<td>IV* #</td>
<td>Day 1, week 1</td>
</tr>
<tr>
<td>Cetuximab‡</td>
<td>250 mg/m²</td>
<td>IV**</td>
<td>Day 8 and then weekly thereafter</td>
</tr>
</tbody>
</table>

#A test dose of 20 mg was administered before the first dose of cetuximab; *Administer over 2 hours; **Administer over 1 hour.

Continue until disease progression or unacceptable toxicity.


CETUXIMAB – CISPLATIN

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Route</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab‡</td>
<td>400 mg/m²</td>
<td>IV* #</td>
<td>Day 1, week 1</td>
</tr>
<tr>
<td>Cetuximab‡</td>
<td>250 mg/m²</td>
<td>IV**</td>
<td>Day 8 and then weekly thereafter</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>75 – 100 mg/m²</td>
<td>IV**</td>
<td>Day 1</td>
</tr>
</tbody>
</table>

‡Patients were premedicated with dexamethasone 20 mg and diphenhydramine 50 mg IV 30 minutes before the cetuximab infusion; #A test dose of 20 mg was administered before the first dose of cetuximab, followed by an observation period of 30 minutes for signs of severe infusion reactions; *Administer over 2 hours; **Administer over 1 hour.

DOSE MODIFICATIONS: 1A delay of cetuximab therapy for 2 consecutive weeks was allowed for patients with grade 3 skin toxicity; 2Cetuximab was interrupted for up to 2 weeks in case of grade 3 skin reactions. If a grade 3 skin reaction occurred for the 2nd or 3rd time in the same patients, cetuximab doses were reduced to 200 and 150 mg/m², respectively. Recurrence of a grade 3 skin reaction despite 2 dose reductions warranted discontinuation of cetuximab.

Repeat cycle every 21 days

CISPLATIN – CAPECITABINE
Cisplatin 75 mg/m² IV* Day 1

Followed by

Capecitabine 1000 mg/m² BID PO Days 1 – 14

*Administer over 30 minutes with adequate pre- and post-hydration.

NOTE: Capecitabine available as 150 and 500 mg tablets.

Repeat cycle every 21 days for a maximum of 6 cycles.


CISPLATIN – 5-FLUOROURACIL
Cisplatin 100 mg/m² IV* Day 1
5-Fluorouracil 1000 mg/m²/day CIVI** Days 1 – 4

*Administer over 15 – 30 minutes with adequate pre- and post-hydration; **Administer as continuous 24-hour infusion daily.

Repeat cycle every 21 days.


DOCETAXEL – CARBOPLATIN
Docetaxel‡ 65 mg/m² IV* Day 1

Followed immediately by

Carboplatin AUC 6 IV** Day 1

‡Routine premedication administered; *Administer over 1 hour; **Administer over 30 minutes.

Repeat cycle every 21 days until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS: Docetaxel dose was reduced by 25% if ANC nadir was < 1 x 10⁹/L or the platelet count was between 50 – 100 x 10⁹/L. If the platelet count fell below 50 x 10⁹/L and/or the ANC fell below 0.5 x 10⁹/L, the dose of carboplatin was reduced to an AUC of 5 and Docetaxel was withheld. G-CSF was permitted in patients with Grade 3 or 4 neutropenia.

**DOCETAXEL – CISPLATIN**

Docetaxel‡ 75 mg/m² IV * Day 1

*Followed by*

Cisplatin 75 mg/m² IV ** Day 1

‡Routine premedication administered; *Administer over 1 hour; **Administer over 30 minutes with adequate pre- and post-hydration.

Repeat cycle every 21 days to a maximum of 12 months.


**DOCETAXEL – CISPLATIN – 5-FLUOROURACIL (DCF OR TPF)**

Docetaxel‡ 75 mg/m² IV * Day 1

*Followed by*

Cisplatin 75 mg/m² IV ** Day 1

Followed by

5-Fluorouracil 750 mg/m²/day CIVI Days 1 – 5

‡Routine premedication administered; *Administer over 1 hour; **Administer with adequate pre- and post-hydration.

Repeat cycle every 21 days for 3–4 cycles then proceed to definitive surgery or radiation therapy.


**PPF (PACLITAXEL – CISPLATIN – 5-FLUOROURACIL)**

Paclitaxel‡ 175 mg/m² IV * Day 1

Cisplatin 100 mg/m² IV ** Day 2

5-Fluorouracil 500 mg/m²/day CIVI *** Days 2 – 6

‡Routine premedication administered; *Administer over 3 hours; **Administer over 1 hour with adequate pre- and post-hydration; ***Administer as a continuous 24 hour infusion daily for 5 days.

Repeat cycle every 21 days to a maximum of 3 cycles, and then proceed to definitive radiation ± surgery.

### TIC (PACLITAXEL – IFOSFAMIDE – CARBOPLATIN)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel†</td>
<td>175 mg/m²</td>
<td>IV*</td>
<td>Day 1</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1000 mg/m²/day</td>
<td>IV**</td>
<td>Days 1 – 3</td>
</tr>
<tr>
<td>Mesna</td>
<td>200 mg/m²***</td>
<td>IV</td>
<td>Days 1 – 3</td>
</tr>
<tr>
<td>Mesna</td>
<td>400 mg/m²#</td>
<td>IV</td>
<td>Days 1 – 3</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC 6</td>
<td>IVº</td>
<td>Day 1</td>
</tr>
</tbody>
</table>

†Routine premedication administered; *Administer over 3 hours; **Administer over 2 hours; ***Administer this dose prior to each dose of ifosfamide; #Administer this dose after each dose of ifosfamide; ºAUC calculated using the Calvert formula.

NOTE: Consider definitive local treatment with radiation ± surgery after 4 cycles.

Repeat cycle every 21 – 28 days.


### TIP (PACLITAXEL – IFOSFAMIDE – CISPLATIN)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
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<tr>
<td>Paclitaxel†</td>
<td>175 mg/m²</td>
<td>IV*</td>
<td>Day 1</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1000 mg/m²/day</td>
<td>IV**</td>
<td>Days 1 – 3</td>
</tr>
<tr>
<td>Mesna</td>
<td>400 mg/m²/day***</td>
<td>IV</td>
<td>Days 1 – 3</td>
</tr>
<tr>
<td>Mesna</td>
<td>200 mg/m²/day#</td>
<td>IV</td>
<td>Days 1 – 3</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>60 mg/m²</td>
<td>IVº</td>
<td>Day 1</td>
</tr>
</tbody>
</table>

†Routine premedication administered; *Administer over 3 hours. Hydrate with at least 1000 mL saline over 3 hours prior to paclitaxel; **Administer over 2 hours; ***Administer this dose prior to each dose of ifosfamide; #Administer this dose after each dose of ifosfamide; ºPre– and post–hydration administered.

Repeat cycle every 21 – 28 days.

NASOPHARYNGEAL CANCER

CETUXIMAB – CARBOPLATIN

Cetuximab‡  400 mg/m² IV Day 1
Cetuximab‡  250 mg/m² IV Day 8 and weekly thereafter
Carboplatin  AUC 5** IV Day 1

‡Routine premedication administered; **AUC according to the Calvert Formula.

DOSE MODIFICATIONS: If a patient experienced Grade 3 skin toxicity, cetuximab therapy could be interrupted for up to 2 consecutive infusions with no change in the dose level. If toxicity resolved to grade 2 or less after up to 2 weeks of interruption, treatment could be resumed. On the 2nd and 3rd occurrence of Grade 3 skin toxicity, cetuximab therapy could be interrupted again for up to 2 consecutive weeks, with subsequent dose reductions to 200 and 150 mg/m² respectively. Patients had treatment discontinued if more than 2 consecutive infusions were withheld or if a 4th occurrence of grade 3 skin toxicity occurred. Cetuximab was not held for carboplatin–related toxicities.

Repeat cycle every 21 days to a maximum of 8 cycles.


CISPLATIN – 5–FLUOROURACIL – RADIATION (INTERGROUP STUDY 0099)
CHEMORADIOTHERAPY FIRST

Cisplatin  100 mg/m² IV* Days 1, 22 and 43

Concurrent with

Radiation  1.8 – 2 Gy fractions Monday to Friday for 35 to 39 fractions for a total dose of 70 Gy.

POSTRADIOTHERAPY: 4 WEEKS POST RADIATION THERAPY OR LAST DOSE OF CHEMOTHERAPY

Cisplatin  80 mg/m² IV* Day 1
5–Fluorouracil  1000 mg/m²/day CIVI Days 1 – 4

Repeat cycle every 28 days for 3 courses.

*Administer over 15 – 20 minutes with routine pre– and post–hydration.