EDUCATIONAL HIGHLIGHTS FROM DATA PRESENTED AT THE

43RD ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO)

EMERGING THERAPIES FOR BREAST CANCER NON-SMALL CELL LUNG CANCER HEAD AND NECK CANCER PROSTATE CANCER

JUNE 1–5, 2007, CHICAGO, IL, USA

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PART ONE:
CONSOLIDATING THE EVIDENCE FOR TAXANES IN THE MANAGEMENT OF EARLY BREAST CANCER

Adjuvant chemotherapy with combined regimens such as doxorubicin and cyclophosphamide, with or without a taxane, remains the cornerstone of chemotherapy for most early breast cancer patients. Various approaches have been taken to further improve results with chemotherapy, including the use of dose-dense regimens, selection of subpopulations of patients who may respond better to certain treatments, and the addition of biological agents. Recent data suggest that the addition of trastuzumab to taxane-containing regimens can improve disease-free survival and overall survival. At a satellite symposium at the 2007 ASCO Annual Meeting in Chicago, IL, Mark D. Pegram (Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA, USA) discussed the use of adjuvant chemotherapy in early breast cancer, and at other sessions the results of trials testing these various approaches to optimise chemotherapy were reported.

Adjuvant breast cancer therapy: analysing current treatment paradigm

Dr. Pegram gave a case-based presentation on the current treatment of women with early breast cancer during a satellite symposium entitled "Evolving Treatment Paradigms in Cancer Care."

Treating high-risk premenopausal early breast cancer

To illustrate the possible treatment options for high-risk patients with early breast cancer, Dr. Pegram questioned the audience as to how they would treat a premenopausal women who had undergone lumpectomy to remove a poorly differentiated, high-grade, ductal carcinoma, and who was node-negative, oestrogen and progesterone receptor (ER/PR)-negative, and positive for the human epidermal growth factor receptor (HER2).

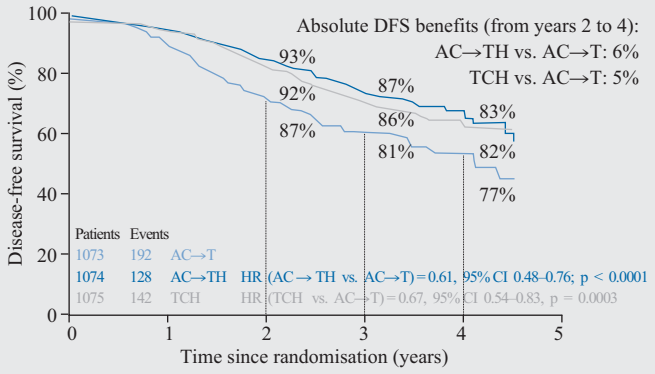
The two most common treatment regimens chosen by the audience for this patient were (1) anthracycline-based chemotherapy incorporating one year of trastuzumab and (2) non-anthracycline-based chemotherapy with one year of trastuzumab. Approximately half of oncologists from Europe or the US said they would prescribe a taxane in addition to an anthracycline-based regimen with trastuzumab for one year, while 24% of EU and 38% of US oncologists would prescribe a non-anthracycline-based regimen with trastuzumab.

The HERA trial confirmed the benefit of trastuzumab in patients with HER2-positive breast cancer [1], but there remain important questions that must be addressed to properly optimise trastuzumab use: Who are the ideal candidates for trastuzumab treatment; what is the optimal dosage of trastuzumab; should trastuzumab be given during or after chemotherapy; and which chemotherapy regimens work best in combination with trastuzumab?

Patients must overexpress HER2 to be eligible for trastuzumab; thus it is important to have high quality screening. Quality assurance results from the NSABP B-31 study suggested that the use of a central laboratory to confirm laboratory results was necessary and dramatically reduced the number of false positive results from 21% to 2% [2].

Dr. Pegram noted that the timing of trastuzumab therapy differs on either side of the Atlantic: in the US there is tendency for trastuzumab to be used in combination with chemotherapy, whereas therapy tends to be sequential in EU countries. Different chemotherapies show very different drug interactions with trastuzumab [3], so there is a clear rationale for determining the optimal timing of treatment.

Figure 1 **DISEASE-FREE SURVIVAL IN HER2-POSITIVE WOMEN TREATED WITH TRASTUZUMAB DURING OR AFTER CHEMOTHERAPY IN THE BCIRG 006 TRIAL: 2ND INTERIM ANALYSIS**



DFS = disease-free survival; AC→T = doxorubicin + cyclophosphamide followed by docetaxel alone; AC→TH = doxorubicin + cyclophosphamide followed by docetaxel + trastuzumab; TCH = docetaxel + carboplatin + trastuzumab; HR = hazard ratio

Source: Pegram M. Data presented at the 43rd Annual Meeting of the American Society of Clinical Oncology (ASCO). Chicago, IL, USA, 2007

Trastuzumab in combination with chemotherapy was first tested in the NCCTG N9831 study [4], which looked at adjuvant chemotherapy (doxorubicin plus cyclophosphamide, then paclitaxel) with concurrent vs. sequential trastuzumab. Although the data require further follow-up before firm conclusions can be drawn, the early evidence suggests that combined adjuvant chemotherapy with trastuzumab improves disease-free survival to a greater extent than sequential use (hazard ratio [HR] 0.64, p = 0.011). The BCIRG 006 study addressed the question of which combination(s) of adjuvant chemotherapy and trastuzumab is best to use in node-negative patients. This study compared doxorubicin plus cyclophosphamide followed by docetaxel with or without trastuzumab or a combined regimen of docetaxel plus

carboplatin plus trastuzumab in 3,222 patients. Data from the second interim analysis [5] showed that patients who received both docetaxel and trastuzumab had better disease-free survival than those who received doxorubicin plus cyclophosphamide plus docetaxel alone (Figure 1). This benefit was even higher in node-negative patients: there was a 68% risk reduction with doxorubicin plus cyclophosphamide followed by docetaxel plus trastuzumab vs. doxorubicin plus cyclophosphamide followed by docetaxel only (p = 0.0007). The risk reduction for disease-free survival was 53% with docetaxel plus carboplatin plus trastuzumab vs. doxorubicin plus cyclophosphamide followed by docetaxel (p = 0.01). In addition, the docetaxel plus carboplatin plus trastuzumab regimen was associated with fewer toxicities and less change in mean left ventricular ejection fraction.

The optimal duration of trastuzumab treatment was examined in the FinHer study, in which 1,010 patients were treated with either docetaxel or vinorelbine in combination with 5-fluoruracil (5-FU) plus epirubicin plus cyclophosphamide and trastuzumab in HER2-positive patients . The results showed higher disease-free survival rates with additional trastuzumab therapy given for up to four years. These data are yet to be confirmed, but "the FinHer study opens the door for future trial designs exploring short vs. long adjuvant trastuzumab," noted Dr. Pegram. The current standard in North America is to give trastuzumab for up to one year, he added.

In summary, for a high-risk HER-positive patient, it is important to confirm that the patient was indeed HER2-positive, and then the recommended dose of trastuzumab recommended is 6 mg/kg every three weeks for approximately one year. Evidence suggests a greater benefit if trastuzumab is used in combination with chemotherapy rather than after it. Non-anthracycline-containing regimens work just as well as, if not better than doxorubicin plus cyclophosphamide, with the benefit of being less (cardio-) toxic.

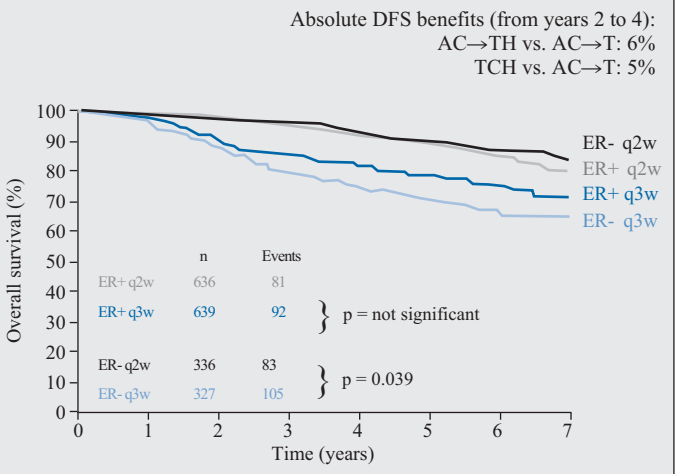
Dose-dense chemotherapy

In HER2-negative patients in whom trastuzumab is not an option, such as a woman who is node-positive and ER/PR-positive but HER2-negative, dose-dense chemotherapy may be considered. A survey of the audience showed that almost half of the US oncologists would favour dose-dense doxorubicin plus cyclophosphamide followed by paclitaxel; 25% would use 5-FU plus epirubicin plus cyclophosphamide for three cycles followed by three cycles of docetaxel. Nineteen per cent would use doxorubicin plus cyclophosphamide for four times every three weeks followed by weekly paclitaxel for 12 cycles. By comparison, half of all responding EU oncologists favoured 5-FU plus epirubicin plus cyclophosphamide for three cycles followed by docetaxel for three cycles. Twenty-seven per cent favoured docetaxel plus doxorubicin plus cyclophosphamide for six cycles.

The Intergroup/CALGB 9741 trial which compared dose-dense with sequential chemotherapy in node-positive or high-risk node-negative women with early breast cancer, observed no difference between the regimens in terms of disease-free survival [6]. "Dose-dense [chemotherapy] cannot be achieved, at least in a clinically meaningful fashion, simply by giving sequential chemotherapy in early stage breast cancer," said Dr. Pegram.

An exploratory subset analysis of the Intergroup/CALGB 9741 study [6], looking at the impact on overall survival of dose density based on hormone receptor status, showed absolutely no benefit of the dose-dense approach over the sequential chemotherapy in ER-positive patients in term of disease-free survival, although ER-negative patients clearly derived a significant benefit (Figure 2).

Figure 2 **OVERALL SURVIVAL BY ER STATUS AND DOSE DENSITY IN THE INTERGROUP/CALBG 9741 TRIAL**



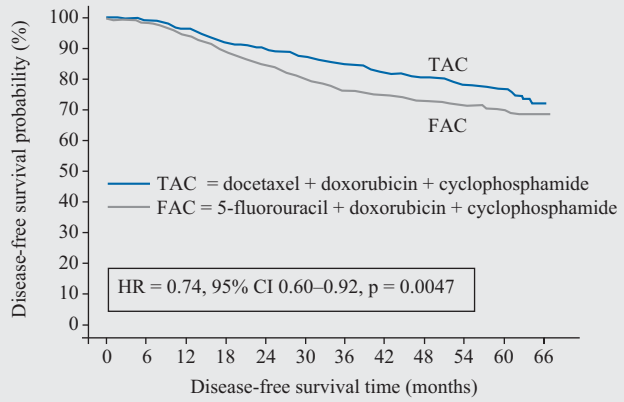
ER = oestrogen receptor

Source: Pegram M. Data presented at the 43rd Annual Meeting of the American Society of Clinical Oncology (ASCO). Chicago, IL, USA, 2007.

Haematologic toxicities associated with the dose-dense approaches can be ameliorated with granulocyte colony-stimulating factor, but Dr. Pegram noted that "unfortunately the Food and Drug Administration in the US has issued a black-box warning for the erythopoietins." There is also the potential for more neurotoxicity with the dose-dense approach. "If you are going to use a dose-dense approach, do so carefully and monitor closely and watch out for neurotoxicity," Dr. Pegram advised. What are the alternatives to dose-dense adjuvant chemotherapy regimens? In addition to sequential regimens there are combination regimens such as 5-FU (500 mg/m^2) plus doxorubicin (50 mg/m^2) plus cyclophosphamide (500 mg/m^2) and docetaxel (75 mg/m^2) plus doxorubicin (50 mg/m^2) plus cyclophosphamide (500 mg/m^2). Data from the TAX 316/ BCIRG 001 trial investigating these two regimens clearly show a benefit of the docetaxel-containing regimen over the one containing 5-FU in terms of both disease-free survival and overall survival (Figures 3 and 4). Indeed, after a median follow-up of 55 months and six cycles of chemotherapy, docetaxel plus doxorubicin plus cyclophosphamide compared with 5-FU plus doxorubicin plus cyclophosphamide significantly reduced the rate of relapse (p = 0.0047) by 26% and there was a 31% reduction in the risk of mortality; although nonsignificant, this

may change as "further analysis is planned as the data mature with time," said Dr. Pegram. While the docetaxel plus doxorubicin plus cyclophosphamide regimen is myelosuppressive, this can be managed with granulocyte colony-stimulating factor prophylaxis.

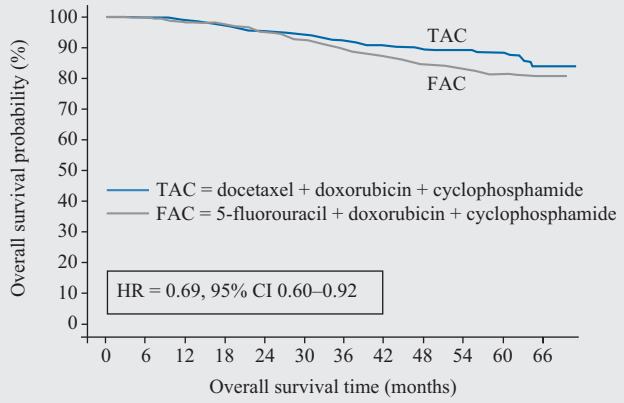
Figure 3 **SIGNIFICANTLY HIGHER DISEASE-FREE SURVIVAL RATE ACHIEVED WITH TAC THAN FAC IN THE TAX 316/BCIRG 001 TRIAL**



HR = hazard ratio

Source: Pegram M. Data presented at the 43rd Annual Meeting of the American Society of Clinical Oncology (ASCO). Chicago, IL, USA, 2007.

Figure 4 **TREND FOR BETTER OVERALL SURVIVAL WITH TAC THAN FAC IN THE TAX 316/BCIRG 001 TRIAL**



HR = hazard ratio

Source: Pegram M. Data presented at the 43rd Annual Meeting of the American Society of Clinical Oncology (ASCO). Chicago, IL, USA, 2007.

Results of Intergroup Trial E1199

Trials such as the Intergroup E1199 study are also investigating other sequences of adjuvant chemotherapy, including those comparing the taxanes. In an oral session, Jack A. Sparano (Albert Einstein College of Medicine and Breast Evaluation Center, Montefiore Medical Center, Bronx, NY, USA) presented the updated results of this phase III study of doxorubicin plus cyclophosphamide followed by either docetaxel or paclitaxel [7]. The analysis was based on 4,950 eligible patients (T1–3 and N1–2 or T2–3 and node-negative) who had altogether experienced 1,048 disease-free survival events with 686 deaths and a median follow-up of 63.8 months.

All patients in this trial received standard doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2) therapy every three weeks before being randomised to one of four treatment arms: (1) paclitaxel (175 mg/m^2) every three weeks for four cycles (maximum 700 mg/m^2); (2) weekly paclitaxel (80 mg/m^2) for 12 cycles (maximum 960 mg/m^2); (3) docetaxel (100 mg/m^2) every three weeks for four cycles (maximum 400 mg/m^2); (4) weekly docetaxel (35 mg/m^2) for 12 cycles (maximum 420 mg/m^2).

Two primary comparisons were undertaken. The first found no difference in disease-free survival between paclitaxel vs. docetaxel treatment (HR = 1.032, 95% CI 0.91–1.17; p = 0.61). The second primary comparison showed a nonsignificant trend towards better disease-free survival benefits with dosing every three weeks vs. every week (HR = 1.062, 95% CI 0.94–1.20; p = 0.33). However, primary comparisons appeared to be confounded by unanticipated interaction between taxane and schedule. All secondary comparisons were unplanned and, therefore, should be interpreted as exploratory. Rates of grade 2–4 neuropathy were highest in the weekly and three-weekly paclitaxel arms (27% and 20%, respectively). Docetaxel three-weekly was associated with more severe neutropenia, febrile neutropenia, and infection, but primary prophylaxis with growth factors was not used.

Does ER status influence docetaxel efficacy?

Several studies have suggested that the efficacy of adjuvant chemotherapy is less in women with ER-positive than in those with ER-negative disease. However, in the pre-operative setting, docetaxel and weekly paclitaxel have been shown to have substantial activity in patients with ER-positive breast cancer.

To investigate the effect of ER expression on docetaxel efficacy, Fabrice Andre (Breast Cancer Unit and Translational Research Unit, Institut Gustave Roussy, Villejuif, France) and coworkers performed a pooled analysis of the BCIRG 001 and FNCLCC PACS 01 trials [8–10]. Median follow-up was 55 months in BCIRG 001 and 59 months in PACS 01.

Overall, docetaxel significantly improved overall survival in both ER-negative patients (HR 0.69, 95% CI 0.52–0.94) and ER-positive patients (HR 0.70, 95% CI 0.54–0.91). Docetaxel similarly reduced risk of death by 30% in ER-positive and by 31% in ER-negative patients. Thus, there was no significant interaction between the efficacy of docetaxel and ER status concluded Dr. Andre.

This analysis also looked at the specific level of ER expression in patients with HR-positive disease, since this has been suggested to predict response to anthracyclines. The impact of docetaxel on disease-free survival and overall survival was not significantly different in patients with ER strongly positive tumours compared to those with ER weakly positive tumours, or even those with ER-negative tumours. In addition, docetaxel was associated with a significant reduction in the risk of relapse

(21%) and the risk of death (30%) in patients with node-positive and ER-positive breast cancer. Dr. Andre concluded by saying that "there was no strong evidence that the risk reduction provided by docetaxel is significantly lower in patients with ER-positive breast cancer."

BCIRG 007: First results of overall survival analysis

In a late-breaking abstract, Dr. Pegram presented the first overall survival analysis of the multicentre BCIRG 007 trial. This trial investigated the use of trastuzumab in combination with docetaxel with or without carboplatin as first-line therapy for women with HER2-positive metastatic breast cancer [11]. A total of 132 patients were treated with docetaxel plus carboplatin plus trastuzumab and 131 with docetaxel plus trastuzumab. There was no crossover from the docetaxel plus trastuzumab to the docetaxel plus carboplatin plus trastuzumab arm.

Similar baseline characteristics were reported with the exception of more patients receiving endocrine therapy in the docetaxel plus carboplatin plus trastuzumab arm (36.4%) than in the docetaxel plus trastuzumab arm (26.7%), even though fewer patients in this arm were ER/PR-positive (65.2% vs.72.5%).

Overall survival in the intent-to-treat population at a median follow-up of 39 months was not significantly different among the two treatment arms ($p = 0.65$). A total of 138 events occurred, 67 in the docetaxel plus trastuzumab arm and 71 in the docetaxel plus carboplatin plus trastuzumab arm. Dr. Pegram said that both regimens were effective in this patient population with an average time to progression of more than 10 months and overall survival of more than 36 months.

With the exception of nausea and vomiting, patients in the docetaxel plus trastuzumab arm experienced more non-haematological adverse events than those in the docetaxel plus carboplatin plus trastuzumab arm. There were more grade 3/4 haematological events with docetaxel plus carboplatin plus trastuzumab than with docetaxel plus trastuzumab, including asymptomatic thrombocytopenia (15.3% vs. 2.3 %, $p < 0.001$). Dr. Pegram noted that "in contrast to a previous study showing an advantage to addition of carboplatin to paclitaxel plus trastuzumab, this study failed to demonstrate enhanced efficacy of carboplatin in combination with docetaxel and trastuzumab."

Study acronyms

BCIRG 001, 006, 007	Breast Cancer International Research Group trials 001, 006, 007
CALGB 9741	Cancer and Leukemia Group B trial 9741
FinHer	Finland Herceptin study
FNCLCC PACS 01	Federation Nationale des Centres de Lutte contre le Cancer trial PACS 01
HERA	Herceptin Adjuvant trial
NCCTG N9831	North Central Cancer Treatment Group trial N9831
NSABP B-31	National Surgical Adjuvant Breast and Bowel Project trial B-31

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PART TWO:
EMERGING PARADIGMS IN THE TREATMENT OF NON-SMALL CELL LUNG CANCER

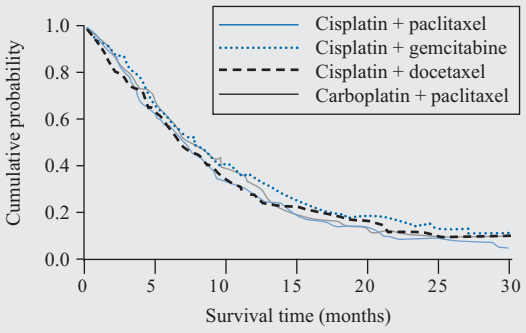
Lung cancer is the most common cause of cancer mortality in Europe, accounting for approximately one fifth (334,800) of all cancer deaths in 2006 [1]. While efforts at tobacco control have resulted in a declining death rate for men and levelling of the death rate for women, earlier treatment and more effective therapies are needed. Since the 1970s, chemotherapy regimens for non-small cell lung cancer (NSCLC) have gradually increased survival from two to four months with cisplatin to more than eight to ten months using docetaxel with cisplatin as first-line therapy. Newer agents, including gefitinib, erlotinib, pemetrexed, and bevacizumab, have the potential to increase survival when added to chemotherapy agents. At a satellite symposium at the 2007 ASCO Annual Meeting in Chicago, IL, USA, one presentation outlined the current direction that treatment of NSCLC is going. Some key abstracts at ASCO also illustrated these emerging concepts in lung cancer treatment.

Chemotherapy regimens for treatment of NSCLC

Edward S. Kim (University of Texas M.D. Anderson Cancer Center, Houston, TX, USA) opened a satellite symposium at this year's ASCO annual meeting entitled "*Evolving Treatment Paradigms in Cancer Care*," with a discussion of emerging treatment strategies for NSCLC.

Various platinum-based chemotherapy doublets have been tested in NSCLC with similar results. In ECOG 1594, patients with stage IIIB or IV NSCLC were randomised to paclitaxel plus cisplatin, cisplatin plus gemcitabine, docetaxel plus cisplatin, or paclitaxel plus carboplatin (Figure 1) [2]. After two years of follow-up, survival ranged from about 5–12% for cisplatin plus paclitaxel to about 7–15% for the other three combinations. However, none of the four regimens offered a significant advantage over the others in treatment of NSCLC.

Figure 1 **ECOG 1594 SURVIVAL BY TREATMENT GROUP**

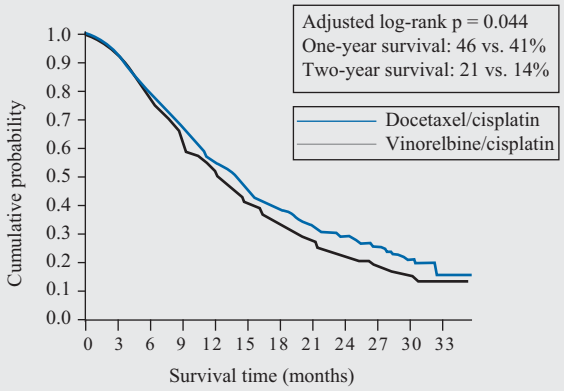


Source: Schiller JH, et al. New Engl J Med 2002;346:92-98.

The TAX 326 trial compared docetaxel (75 mg/m^2) plus cisplatin (75 mg/m^2) every three weeks (q3w) with vinorelbine (25 mg/m^2, days 1, 8, 15, 22) plus cisplatin (100 mg/m^2, day 1) every four weeks (q4w). The one-year survival rate was 46% for docetaxel plus cisplatin and 41% for vinorelbine plus cisplatin; the two-year survival rate was 21% for the docetaxel arm and 14% for the vinorelbine arm (Figure 2) [3].

The IALT is the largest lung cancer study ever done, randomising 1,867 patients with stage I–III NSCLC to observation or one of three cisplatin doses (80 mg/m^2 q3w for four cycles, 100 mg/m^2 q4w for three to four cycles, or 120 mg/m^2 q4w for three cycles) plus etoposide, vinorelbine, vinblastine, or vindesine [4]. The results showed a 4.1% five-year survival benefit with chemotherapy, similar to the 5% benefit shown in an earlier meta-analysis of the difference between cisplatin-based chemotherapy and no chemotherapy [5]. A Canadian study found a 15% survival benefit for cisplatin plus vinorelbine compared with observation in patients with resected stage IB/II NSCLC [6].

Figure 2 **TAX 326: SURVIVAL ON DOCETAXEL + CISPLATIN VS. VINORELBINE + CISPLATIN**



Source: Fossella FV, et al. J Clin Oncol 2003;21:3016–3024.

The CALGB 9633 trial compared paclitaxel (200 mg/m^2) plus carboplatin (AUC 6) (n = 173) with observation (n = 171) following resection in patients with stage IB NSCLC [7]. In 2004, an unplanned analysis found a 12% difference in four-year survival favouring the chemotherapy arm (hazard ratio [HR] = 0.62, p = 0.01). However, two years later there was no significant difference in survival between the two arms [8]. "We have to be careful what we extrapolate from these small studies," cautioned Dr. Kim.

Results of the phase III ANITA trial demonstrated that different subsets of patients respond differently to therapy [9]. Vinorelbine plus cisplatin was compared to observation in 840 patients with resected stage I–III NSCLC. The median survival in the

treatment arm was 65.8 months compared to 43.7 months in the observation arm. Five-year survival rates were higher in patients with stage II (52%) and stage IIIA (42%) NSCLC who received therapy, than in those with stage II (39%) and stage III (26%) disease who received no therapy. However, in patients with stage I NSCLC no survival difference was observed between the treatment arm (62%) and the observation arm (63%). "Clearly, we need to find better agents to build on these regimens, or find out which patients respond better to these drugs," said Dr. Kim.

Addition of targetted therapy to chemotherapy

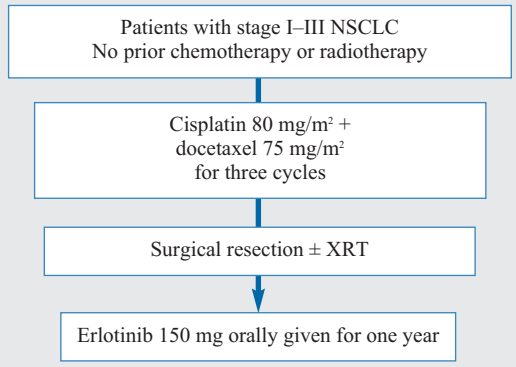
The addition of targetted therapies to standard chemotherapy for NSCLC can improve response in certain subsets of patients, noted Dr. Kim. Much has been learned about epidermal growth factor receptor (EGFR) inhibitors in NSCLC. Among those that are approved or in trials are gefitinib, erlotinib, lapatinib, cetuximab, panitumumab, and matuzumab. Vascular endothelial growth factor (VEGF) inhibitors in clinical trials for lung cancer include the monoclonal antibody bevacizumab and several multitargetted tyrosine kinase inhibitors (TKIs), including sunitinib and sorafenib.

Bevacizumab was shown to be effective when added to first-line chemotherapy in a large phase III ECOG trial [10]. A total of 878 patients with stage IIIB/IV NSCLC were randomised to six cycles of carboplatin plus paclitaxel with or without bevacizumab (15 mg/kg q3w). Addition of bevacizumab improved median survival to 12.3 months vs. 10.3 months in patients not receiving bevacizumab ($p = 0.003$). One-year survival rate was 51% in the bevacizumab group compared to 44% in the control group. Grade 3/4 toxicities that were significantly higher in the bevacizumab group included neutropenia ($p = 0.002$), hypertension ($p < 0.001$), and haemorrhage ($p < 0.001$). "This was the first study in lung cancer to add a third drug and show a benefit," said Dr. Kim.

Erlotinib was tested as second- or third-line therapy for NSCLC in the NCIC CTG BR.21 trial [11]. A total of 731 patients with NSCLC were randomised to either erlotinib 150 mg/day ($n = 488$) or placebo ($n = 243$). The erlotinib group had a 42.5% improvement in median survival (6.7 months) compared to the placebo group (4.7 months). The erlotinib group had significantly better one-year overall survival (OS) (31% vs. 21%) and six-month progression-free survival (PFS) (25% vs. 10%) than the placebo group ($p < 0.001$).

At M.D. Anderson Cancer Center (MDACC), Dr. Kim's group pioneered the addition of bevacizumab to erlotinib in a heavily pretreated population with advanced NSCLC. This combination produced a median OS of 12.6 months and an 18% response rate. PFS in patients treated with bevacizumab plus erlotinib was 4.4 months, similar to the 4.8 month PFS observed in patients treated with bevacizumab plus docetaxel [12]. The MDACC neoadjuvant trial in patients with stage I–III NSCLC currently uses a treatment protocol of cisplatin plus docetaxel followed by maintenance therapy with erlotinib (Figure 3).

Figure 3 **MDACC NEOADJUVANT TRIAL SCHEMA**



NSCLC = non-small cell lung cancer; XRT = chest radiation

Source: Kim ES. Data presented at the 43rd Annual Meeting of the American Society of Clinical Oncology (ASCO). Chicago, IL, USA, 2007.

Individualised therapy for NSCLC

According to Dr. Kim, the future of lung cancer treatment is in individualised therapy. Using the Lung Metagene Model to refine the assessment of risk and guide the use of adjuvant chemotherapy in patients with stage IA NSCLC, investigators retrospectively predicted which patients were at high risk of recurrence [13]. Patients with completely resected excision repair cross-complementation group 1 (ERCC1)-negative tumours appear to benefit from adjuvant cisplatin-based chemotherapy, whereas patients with ERCC1-positive tumours do not [14]. MDACC has developed a system called Biomarker-based Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE), for use in patients with NSCLC in second-line therapy or beyond. All patients are biopsied and tested for five biomarker groups, which are used to randomise them to one of four treatment groups: erlotinib, ZD6474, bexarotene plus erlotinib, or sorafenib. The information collected in these trials will be used to predict response to therapy. Since December 2006, over 70 patients have been enrolled and more than 50 have been treated.

"Future objectives in treating NSCLC include defining a high-risk population. We need better screening strategies and we need better patient-defined treatments," said Dr. Kim. "Chemotherapy and targetted therapy are both good armamentariums. We can look forward and build on them. We have to focus on performance status and quality of life. Tissue-based personalised medicine is the future."

EGFR inhibitor maintenance therapy for advanced NSCLC

Concurrent chemoradiotherapy is the standard of care for patients with unresectable stage III NSCLC, producing a median survival of 15 to 17 months. The SWOG 9504 phase II trial of platinum and etoposide with concurrent thoracic radiotherapy

(PE/TRT) followed by consolidation docetaxel produced a median survival of 26 months [15] with a 29% five-year survival rate [16], showing that the standard can be improved upon. Karen Kelly (University of Colorado Cancer Center, Aurora, CO, USA) presented an update of the SWOG 0023 phase III trial, which tested the hypothesis that maintenance therapy with gefitinib would improve patient outcomes following chemoradiotherapy and consolidation docetaxel [17].

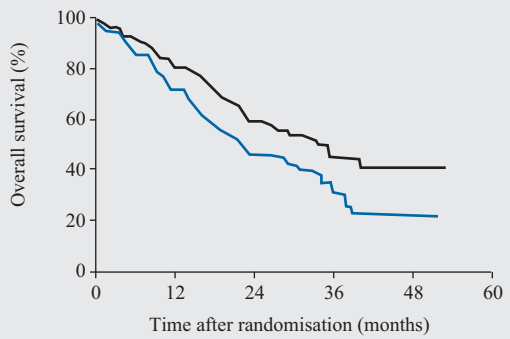
All patients received the core regimen of cisplatin (50 mg/m^2, given on days 1 and 8) plus etoposide (50 mg/m^2, given on days 1–5) every 28 days for two cycles with concurrent thoracic radiation, followed by three cycles of docetaxel (75 mg/m^2). The patients were randomised to maintenance therapy with gefitinib (500 mg/day, later amended to 250 mg/day due to toxicity) or placebo. In April 2005, an unplanned interim analysis showed that the p value for testing the alternative hypothesis of a 33% improvement with gefitinib was p = 0.0015, leading to closure of the trial at that time. The preliminary results, presented in 2005, showed that the median PFS was 11 months for gefitinib and 10 months for placebo. The median survival was 19 months for gefitinib compared with 29 months for placebo (p = 0.09) [18].

Dr. Kelly presented the updated results at a median follow-up time of 27 months [17]. Of the 571 eligible patients enrolled in the trial, 243 were randomised to gefitinib (n = 118) or placebo (n = 125) at the time of study closure. Most patients had objective responses to the core regimen. PFS from the time of randomisation was eight months for the gefitinib arm and 12 months for the placebo arm. OS was 23 months for gefitinib and 35 months for placebo (p = 0.01). The one-year OS rate was 73% for the gefitinib arm compared with 81% for the placebo arm (Figure 4). At two years, 46% of gefitinib patients had survived compared with 59% of placebo patients.

Figure 4 **OVERALL SURVIVAL IN SWOG 9504 AT A MEDIAN FOLLOW-UP OF 27 MONTHS**

	n	Events	Median (months)	One-year overall survival	Two-year overall survival
Gefitinib	118	71	23	73%	46%
Placebo	125	54	35	81%	59%

Hazard ratio 0.63 (95% CI 0.44–0.91), p = 0.013



Source: Kelly K, et al. J Clin Oncol 2007;25(Suppl.):7513.

The primary cause of death in both arms was lung cancer, accounting for 61 deaths (86%) in the gefitinib arm and 43 deaths (80%) in the placebo arm. Toxicity was responsible for two deaths (3%) in the gefitinib arm and no deaths in the placebo arm. Correlation of baseline characteristics and survival showed no statistical interaction between treatment and any of the baseline characteristics. The primary toxicity of the core regimen was grade 3/4 neutropenia; however, infection with neutropenia was rare.

Dr. Kelly concluded that maintenance gefitinib was safe and well tolerated but it produced an inferior survival compared to placebo. Although the reasons for this result remain unclear, the use of maintenance EGFR-TKIs in stage III NSCLC outside of clinical trials should be avoided. The core regimen of PE/TRT followed by docetaxel demonstrated a favourable survival in the treatment of unresectable stage III NSCLC in this large Intergroup study.

Bevacizumab in the treatment of advanced or recurrent NSCLC

Christian Manegold (Interdisciplinary Thoracic Oncology, Department of Surgery, Heidelberg University Medical Centre, Mannheim, Germany) reported the results of the randomised, controlled, multicentre international AVAiL phase III trial. This study compared two doses of bevacizumab in combination with cisplatin and gemcitabine vs. placebo with cisplatin and gemcitabine in previously untreated patients with advanced or recurrent nonsquamous NSCLC [19]. All patients were treated with cisplatin and gemcitabine and randomised to 7.5 or 15 mg/kg bevacizumab every three weeks or placebo. Bevacizumab was continued until disease progression.

The intent-to-treat (ITT) analysis reported a median PFS of 6.1 months for placebo (n = 347), 6.7 months for bevacizumab 7.5 mg/kg (n = 345), and 6.5 months for bevacizumab 15 mg/kg (n = 351). At 12 months, PFS was 9.7% for the placebo group, 14.1% for the bevacizumab 7.5 mg/kg group, and 14.1% for the bevacizumab 15 mg/kg group. However, 7% of patients had received nonprotocol therapy and a preplanned corrected analysis found a HR of 0.68 for the low-dose bevacizumab group vs. placebo (p = 0.0001) and a HR of 0.74 for the high-dose bevacizumab group vs. placebo (p = 0.0021).

Response rates were 20% in the placebo group, 34% in the low-dose bevacizumab group (p < 0.0001 vs. placebo), and 30% in the high-dose bevacizumab group (p = 0.0017 vs. placebo). Median duration of response was 4.7 months for placebo, 6.1 months for low-dose bevacizumab, and 6.1 months for high-dose bevacizumab.

Dr. Manegold concluded that AVAiL is the second phase III trial showing benefit from bevacizumab therapy in advanced NSCLC in terms of PFS and response rate. Cisplatin and gemcitabine in combination with bevacizumab were well tolerated with low rates of severe haemoptysis and pulmonary haemorrhage.

Prognostic factors for overall survival in patients with stage III NSCLC

Stage III NSCLC is a heterogeneous disease with varying outcomes observed in patients with similar clinical stages. Foluso O. Ademuyiwa (Section of Hematology/Oncology, Department of Medicine, University of Chicago, IL, USA) presented an analysis of patient variables associated with overall survival from patients enrolled in a phase III trial of chemoradiation therapy for stage III NSCLC [20]. Patients were treated with cisplatin plus etoposide and concurrent radiation therapy, followed by randomisation to either docetaxel (75 mg/m^2 q3w for three cycles) or observation. Characteristics were compared between treatment groups using the t-test and Fisher's exact test. Median survival times were compared using log rank and Wilcoxon tests and univariate analysis of prognostic factors was performed.

The analysis showed that haemoglobin values ≥12 were associated with median survival of 21.5 months compared with 16.8 months in patients with lower haemoglobin ($p = 0.012$). Forced Expiratory Volume in 1 second (FEV1) > 2 L was associated with a 21.5 month median survival compared with 18.9 month median survival in patients with FEV1 < 2 L ($p = 0.021$). Survival was not significantly influenced by age, sex, use of PET scan in staging, body mass index (BMI), stage (IIIA or IIIB), ECOG performance status (PS), race, or smoking status.

Dr. Ademuyiwa concluded that higher haemoglobin values and FEV1 > 2 L are independent prognostic factors for overall survival in patients with stage III NSCLC. These factors may be useful for predicting more favourable outcomes in this population. Overall prognostic assessment and treatment decisions should be individualised by considering specific patient pretreatment characteristics that affect survival.

Study acronyms

ANITA trial	Adjuvant Navelbine International Trialist Association trial
AVAiL trial	Avastin in Lung trial
CALGB 9633	Cancer and Leukemia Group B trial 9633
ECOG 1595	Eastern Collaborative Oncology Group trial 1594
IALT	International Adjuvant Lung Cancer Trial
MDACC trial	M.D. Anderson Cancer Center trial
NCIC CTG BR.21 trial	National Cancer Institute of Canada Clinical Trials Group trial BR.21
SWOG 9504 trial	Southwest Oncology Group trial 9504

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PART THREE:
IMPROVING TREATMENT OPTIONS FOR PATIENTS WITH ADVANCED PROSTATE CANCER

Until recently, chemotherapy had a minimal role in the treatment of patients with prostate cancer. In the 1980s several large randomised trials tested cytotoxic therapy for advanced prostate cancer, using agents such as cyclophosphamide, dacarbazine, vincristine, and 5-fluorouracil (5-FU). However, the median survival obtained with these drugs was only in the range of 20 to 40 weeks [1]. The best treatment options for these patients remained hormone therapy and steroids for many years. This situation changed in 2004 with the approval of docetaxel, which in combination with steroids is the standard of care in first-line therapy of hormone refractory prostate cancer (HRPC). Updated data from the landmark TAX 327 study that looked at docetaxel and prednisone in HRPC were presented at the 2007 ASCO Annual Meeting in Chicago, IL. In addition, new analyses of this study identified potential prognostic markers that predict survival and response to therapy, and hold the promise of eventually enabling the individualisation of therapy based on patient characteristics.

First-line therapy for advanced prostate cancer

In 1996, the combination of mitoxantrone plus prednisone was investigated for the treatment of 161 patients with HRPC [2]. The primary end point was palliative response defined as a two-point decrease in pain. A palliative response was achieved by 29% of patients on mitoxantrone and prednisone compared with 12% of those on prednisone alone ($p = 0.01$). The median duration of palliation was 43 weeks in patients who received chemotherapy compared with 18 weeks in those who did not ($p < 0.0001$). There was no difference in overall survival (OS); however, this trial was not powered to detect a survival difference.

Dominik R. Berthold (Department of Medical Oncology and Hematology, Princess Margaret Hospital, Toronto, ON, Canada), presented an update of the TAX 327 trial [3], designed to compare docetaxel plus prednisone with mitoxantrone plus prednisone in patients with HRPC. A total of 1,006 men were accrued from 2000 to 2002 and randomised to docetaxel (75 mg/m^2) plus prednisone (10 mg/day) every three weeks (q3w); docetaxel (30 mg/m^2) plus prednisone weekly; or mitoxantrone (12 mg/m^2) plus prednisone. The primary analysis was conducted in 2003. Eligible patients had progressive prostate cancer despite primary androgen deprivation, Karnofsky performance status ≥60%, no previous cytotoxic therapy except estramustine, and no other major medical conditions. Patients were evaluated for prostate specific antigen (PSA), pain, and quality of life (QOL) at baseline and every three weeks during treatment.

At the primary analysis, patients receiving docetaxel q3w had significantly longer survival than patients in the mitoxantrone arm [4]. Weekly docetaxel provided no significant survival benefit. Patients in the docetaxel q3w arm had better palliation and a higher PSA response. At the time of this analysis, 557 patients had died.

At the updated analysis in January 2007, 310 additional deaths were reported, for a total of 867 deaths. Comparison of the nitial and updated analyses shows that the docetaxel q3w patients had a median survival of 18.9 months in 2003 and 19.2 months in 2007 (Figure 1). The mitoxantrone arm had a median survival of 16.5 months in 2003 and 16.3 months in 2007. The difference between the two arms was statistically significant in both the original and updated analyses ($p = 0.009$ and $p = 0.004$, respectively).

Figure 1 **COMPARISON OF INITIAL AND UPDATED ANALYSIS**

	Docetaxel q3w (n = 335)	Docetaxel weekly (n = 334)	Mitoxantrone (n = 337)
Original data 2003			
n (%) dead	166 (50%)	190 (57%)	201 (60%)
Median survival*	18.9 (17.0–21.2)	17.4 (15.7–19.0)	16.5 (14.4–18.6)
Hazard ratio*	0.76 (0.62–0.94)	0.91 (0.75–1.11)	
p value	0.009	0.36	
Updated data 2007			
n (%) dead	285 (85.1%)	285 (85.4%)	297 (88.1%)
Median survival*	19.2 (17.5–21.3)	17.8 (16.2–19.2)	16.3 (14.3–17.9)
Hazard ratio*	0.79 (0.67–0.93)	0.87 (0.74–1.02)	
p value	0.004	0.09	

* 95% confidence interval indicated
q3w = every three weeks

Source: Berthold DR, et al. J Clin Oncol 2007;25(Suppl.):5005.

The three-year survival rate was 17.9% (n = 335) for the docetaxel q3w arm, 16.7% for the docetaxel weekly arm (n = 334), and 13.7% for the mitoxantrone arm (n = 337). Subgroup survival analysis by age, baseline PSA, presence or absence of pain, and functional assessment of cancer therapy-prostate (FACT-P) showed the survival benefit was consistent across all subgroups.

"The updated survival analysis confirms the previously reported results," concluded Dr. Berthold. "The similar hazard ratios among the analysed subgroups are evidence for robust data. Therefore, docetaxel given every three weeks plus prednisone remains the preferred treatment option for most patients with metastatic HRPC. Prolonged survival is

extremely important for these patients and docetaxel is the only chemotherapeutic agent to demonstrate a survival benefit in this setting," he added.

Impact of bone pain on survival in patients with HRPC treated with chemotherapy

The TAX 327 study established docetaxel every three weeks plus prednisone as front-line therapy for patients with metastatic HRPC [3,4]. However, the timing of initiation of chemotherapy remains controversial. Many physicians and patients wait until symptoms appear to start docetaxel. "Docetaxel is the reference therapy in this disease but it is associated with toxicity. Many of these patients have comorbidities and they are older so it often is preferable to delay treatment," said presenter Stéphane Oudard (Department of Medical Oncology, Georges Pompidou European Hospital, Paris, France). "In this study we wanted to answer the question of whether we should start chemotherapy as soon as possible in asymptomatic patients," continued Dr. Oudard.

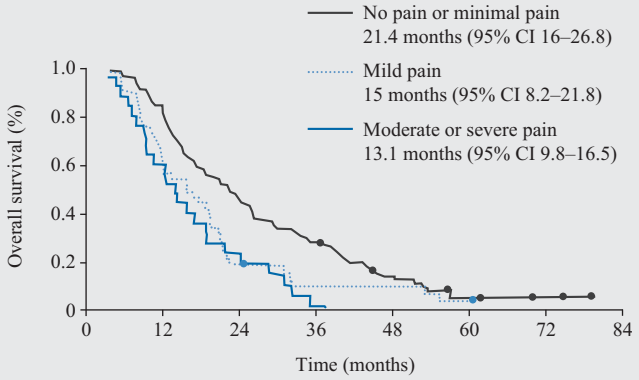
The primary end point was to explore the impact of bone pain on OS [5]. The secondary end point was to evaluate the relationship between PSA doubling time (PSA-DT) and survival of patients with minimal or no pain. This was a retrospective analysis of an institutional database of consecutive chemo-naïve patients with metastatic HRPC. The patients were treated with docetaxel (70–75 mg/m^2) or mitoxantrone (12 mg/m^2) every three weeks and prednisone (10 mg/day). Baseline bone pain was evaluated as no pain or minimal pain, mild pain, or moderate to severe pain.

"We found that presence of bone pain is associated with shorter survival and absence of bone pain is associated with longer survival. So, it is a prognostic factor," said Dr. Oudard. At the start of therapy, 79 patients had no or minimal pain (docetaxel n = 52, mitoxantrone n = 27); 41 patients had mild pain (docetaxel n = 29, mitoxantrone n = 12); and 25 patients had moderate or severe pain (docetaxel n = 16, mitoxantrone n = 9). Patients with no or minimal pain had an OS of 21.4 months compared with 15 months for patients with mild pain and 13.1 months for those with moderate or severe pain (Figure 2). One-year and three-year median OS were 75% and 29% in patients with no or minimal pain, 56% and 11% in patients with mild pain, and 52% and 4% in patients with moderate or severe pain (p = 0.002).

A difference in survival was observed according to PSA-DT in all three bone pain categories. In patients with no or minimal pain, median OS was 16.5 months in those with PSA-DT < 45 days and 32.5 months in those with PSA-DT ≥ 45 days. In patients with mild pain, median OS was 11.2 months in those with PSA-DT < 45 days and 18.4 months in those with PSA-DT ≥ 45 days. In patients with moderate or severe pain, median OS was 8.3 months in those with PSA-DT < 45 days and 16.1 months in those with PSA-DT ≥ 45 days.

These results suggest that patients with HRPC with minimal or no bone pain can have better survival with docetaxel-based therapy. The OS benefit was even higher for asymptomatic patients with longer PSA-DTs. "This is an aggressive disease and we should start chemotherapy as soon as possible," said Dr. Oudard. "We need prospective studies to randomise asymptomatic patients to starting chemotherapy when symptoms begin versus starting chemotherapy up front before symptoms appear."

Figure 2 **OVERALL SURVIVAL ACCORDING TO BONE PAIN INTENSITY**



p = 0.001 (log-rank test, stratified by treatment)

Source: Oudard S, et al. J Clin Oncol 2007;25(Suppl.):5149.

A prognostic model for predicting overall survival in patients with HRPC

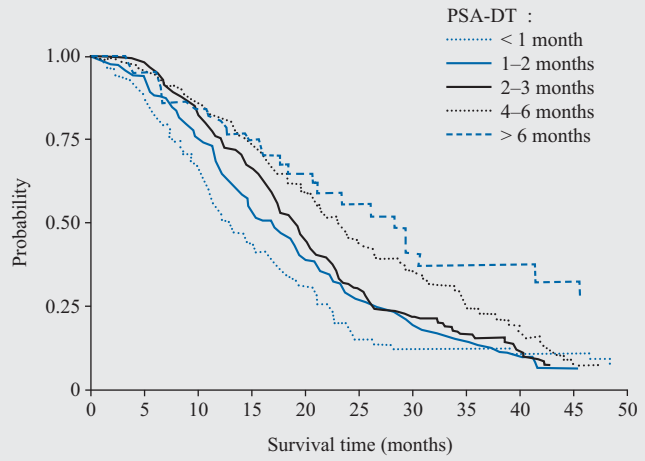
Prognostic nomograms used in metastatic HRPC were developed prior to the use of docetaxel and may not be generalisable to the current treatment setting. The purpose of the study, presented by Mario Eisenberger (Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD, USA), was to develop a multivariate prognostic model and nomogram based on prospectively collected baseline clinical variables prior to initiation of chemotherapy in the TAX 327 trial [6].

Of the 1,006 men with metastatic HRPC randomised to docetaxel or mitoxantrone in study TAX 327, 686 patients had baseline data that included PSA kinetics. A total of 518 deaths were recorded at the time of this analysis. A multivariate Cox model and nomogram were developed to predict survival at one, two, and five years. All significant variables at the p = 0.05 level or based on prior information were included in the multivariate analysis.

Ten independent prognostic factors were identified in multivariate analysis: liver metastases (hazard ratio [HR] 1.64, p = 0.023), number of metastatic sites (>2 vs. ≤2, HR 1.58, p = 0.001), pain at baseline (HR 1.46, p < 0.0001), Karnosfky performance status (≤70 vs. ≥80, HR 1.42, p = 0.011), progression type (measurable disease, HR 1.40, p = 0.002, bone scan progression, HR 1.28, p = 0.014), baseline PSA-DT (<55 vs. ≥55 days, HR 1.20, p = 0.048), every unit rise in baseline log PSA (HR 1.17, p < 0.0001), tumour grade Gleason (≥8 vs. ≤7) or WHO (3–4 vs. 2–3, HR 1.18, p = 0.076), every unit rise in alkaline phosphatase, IU/L (HR 1.26, p < 0.001),

and every unit rise in haemoglobin, g/dL (HR 1.10, p = 0.006). Using a PSA-DT less than one month as a reference, a decreasing risk of death was observed as PSA-DT lengthened, with a relative hazard of 0.79, 0.69, 0.53, and 0.37 for patients with a PSA-DT of one to two months, two to three months, three to six months, and more than six months, respectively (p < 0.001 for trend; Figure 3). A nomogram to predict one-, two-, and five-year survival probability in patients with progressive HRPC was constructed using data derived from this study.

Figure 3 **OVERALL SURVIVAL BY PSA-DT**



Log-rank p < 0.0001
PSA-DT = prostate-specific antigen doubling time

Source: Eisenberger M, et al. J Clin Oncol 2007;25(Suppl.):5058.

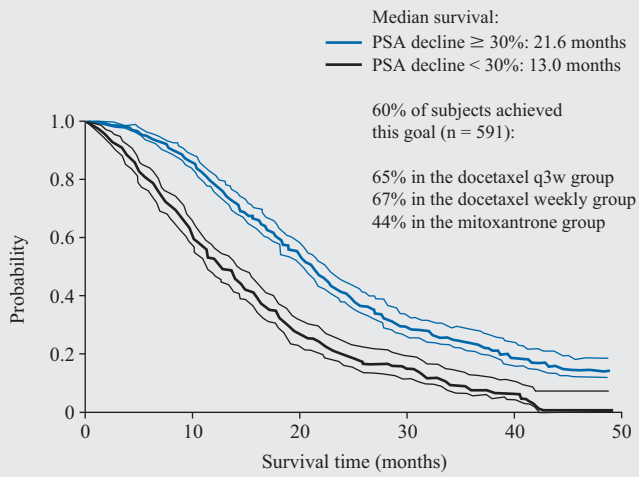
The investigators concluded that each of the 10 identified prognostic factors was an independent multivariate predictor of OS at five years. The most significant predictors of mortality in this database were the presence of liver metastases, metastatic tumour burden, and clinically significant pain. These factors have not been included in previous nomograms. PSA kinetics have emerged as an independent prognostic factor in HRPC. Large-scale prospective phase III trials are essential to validate the nomogram developed in this study.

PSA decline as a surrogate for overall survival in HRPC

Andrew J. Armstrong (Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD, USA) explained that a surrogate is an intermediate end point between treatment and true end point — which should be survival. Defining a surrogate is challenging, and depends on the treatment analysed, including mechanism and end point in question. Reliable surrogate end points for survival in phase III trials of men with HRPC are needed to improve palliative care and avoid unnecessary treatment, to optimise therapy for responding patients, and to accelerate the development of new therapies. Data analysis of the TAX 327 trial was presented by Dr. Armstrong [7]. The objective was to systematically evaluate a range of posttreatment PSA declines, alterations in PSA kinetics, and pain response for surrogacy of OS associated with three-weekly docetaxel therapy. The study also aimed to evaluate the degree of surrogacy of the intermediate end point by studying the Prentice Criteria for surrogacy using Cox proportional hazards models and calculating the proportion of treatment effect explained (PTE) by each surrogate marker [8].

A total of 943 patients from all three treatment groups (docetaxel q3w, docetaxel weekly, and mitoxantrone q3w) were evaluable for PSA kinetic response. The median PSA was 114 ng/mL and the median PSA-DT was 57 days; the values were similar across treatment groups. A 30% or greater PSA decline with therapy was identified as the optimal cut-off that correlated with OS, based on the highest PTE point estimate (0.66, 95% CI 0.23–1.0), with 1.0 being a perfect surrogate. Survival curves show that 60% of the patients (n = 591) achieved a ≥30% decline in PSA. Median survival for patients with a ≥30% PSA decline was 21.6 months compared to 13.0 months for those with a ≤30% PSA decline (p < 0.001). PSA decline ≥30% was achieved by 65% of patients in the docetaxel q3w group, 67% in the docetaxel weekly group, and 44% in the mitoxantrone group (Figure 4).

Figure 4 **SURROGATE EFFECT FOR ≥30% PSA DECLINE**



Hazard ratio 0.50 (95% CI 0.43–0.58; p < 0.001)

PSA = prostate-specific antigen; q3w = every three weeks

Source: Armstrong AJ, et al. J Clin Oncol 2007;25(Suppl.):5009.

Median survival increased as PSA decline increased. Median survival in the 12% of patients with PSA normalisation (33.3 months) was more than double that of patients whose PSA did not normalise (15.8 months).

Pain response was identified in 29% of 466 evaluable patients. The median survival for patients with a pain response was 18.6 months vs. 12.5 months in those with no pain response (HR 0.60 for OS; PTE = 0.64).

The investigators concluded that a ≥30% PSA decline within three months of therapy initiation represents the optimal surrogate in TAX 327 for OS, confirming the SWOG9916 analysis. A PTE of 66% explained by this level of decline is consistent with a moderate surrogate effect. Other measures of

PSA or pain response had independent prognostic significance but did not achieve a higher degree of surrogacy. “PSA declines represent a continuum of prognosis; however, any cut-off is not biologically based nor fully predictive of survival benefits with chemotherapy,” concluded Dr. Armstrong. “Thus, we feel that overall survival should remain the primary end point for phase III HRPC trials at this time.”

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PART FOUR: EMERGING THERAPIES FOR HEAD AND NECK CANCER

Treatment options for squamous cell cancer of the head and neck (SCCHN) have been limited, with poor responses and five-year survival advantage ranging from 1% to 8% [1]. Persistent, recurrent, and new local-regional disease were the major causes of death prior to development of adequate chemoradiotherapy and enhanced radiation techniques. With improved local-regional control, distant metastases are emerging as a more frequent cause of treatment failure in locally advanced SCCHN. Radiation therapy and concurrent single-agent cisplatin have been the treatment standard for SCCHN. In attempts to improve efficacy, trials have tested combinations of cisplatin with docetaxel and 5-fluorouracil (5-FU), and compared various combinations of induction therapy and/or chemoradiotherapy. Additionally, recent trials have added targetted therapies to regimens for first- and second-line therapy. While not currently a standard component of chemotherapy regimens for SCCHN, recent trials have had promising results with the addition of docetaxel to regimens.

Redefining the role of induction chemotherapy in head and neck cancer

At a satellite symposium entitled "*Evolving Treatment Paradigms in Cancer Care*," Marshall R. Posner (Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA) discussed past and current research on induction and sequential therapy for SCCHN. According to Dr. Posner, induction therapy often is not considered an option for SCCHN because it has an insignificant effect on survival. As shown in a 2002 meta-analysis, survival only improved 2% with induction chemotherapy, compared to 8% with chemoradiotherapy ($p < 0.0001$) [1]. However, the meta-analysis also showed that a platinum plus 5-FU regimen improves survival by 5% ($p = 0.01$).

The Studio phase III trial was one of the original studies that demonstrated the effectiveness of platinum plus 5-FU [2]. The patients were randomised to chemotherapy (platinum plus 5-FU) or no chemotherapy followed by surgery (if resectable) and radiation therapy. Results showed that the group with resectable tumours in the surgery arm had slightly better survival. "Although survival was lower in the chemotherapy arm, surgery may have increased the risk of local-regional recurrence," said Dr. Posner. Ten-year results showed a doubling of survival, improved local-regional control, and reduced distant metastases in the patients with unresectable tumours treated with platinum plus 5-FU compared to those treated with radiation therapy alone [3].

According to Dr. Posner, the period after initial chemotherapy is the critical time to begin the next treatment. "Any delay results in a rapid and substantial increase in tumour repopulation and growth," he said. "For that reason, the sequence of treatment should be from chemotherapy directly to chemoradiotherapy without surgery, which leaves an enhanced tumour growth environment." The choice of chemoradiotherapy regimen can be based on response and toxicity experienced with induction therapy. Further, a weekly regimen provides more regional sensitisation and may be more biologically effective and less toxic than high-dose pulsed therapy.

Comparison of induction chemotherapy and chemoradiotherapy

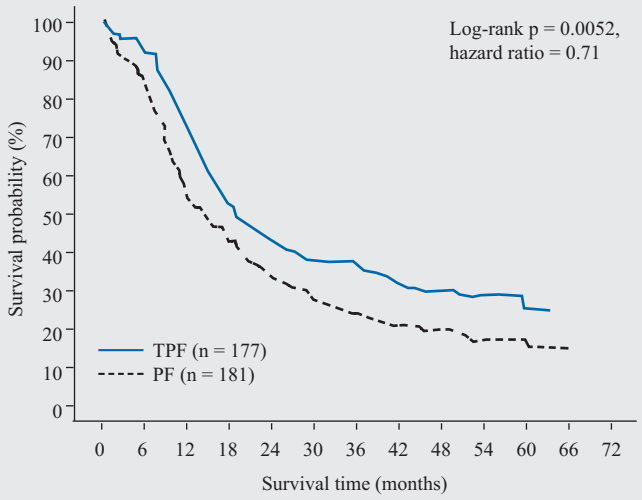
The Calais chemoradiotherapy regimen uses high-dose pulsed carboplatin and 5-FU with once-daily radiation therapy [4]. In patients with oropharyngeal cancer, the Calais regimen was associated with a 6% improvement in five-year survival ($p = 0.05$) [5]. A more aggressive carboplatin plus 5-FU schedule in patients with oropharyngeal cancer produced a 26% five-year survival rate compared with 13% in the boost-radiation therapy only group ($p < 0.008$). Toxicity in the chemotherapy group was high, with 68% grade 3/4 mucositis and a 50% rate of oesophageal stenosis [6–9].

The INT-026 study established bolus cisplatin as the standard of care in the US [10] based on a three-year overall survival of 37% vs. 27% for cisplatin vs. cisplatin plus fluorouracil added to surgery and radiotherapy and 23% for radiotherapy alone. However, distant metastases were not reduced. The RTOG 91-11 trial randomised 547 patients with stage III/IV SCCHN to radiotherapy plus induction therapy, radiotherapy plus concomitant therapy, or radiotherapy alone [11,12]. At the five-year update, laryngectomy-free survival was equivalent in the induction (44.6%) and chemoradiotherapy (46.6%) arms and significantly improved over radiation therapy alone (33.9%, $p < 0.011$). Overall survival was slightly better in the cisplatin plus fluorouracil arm.

The GORTEC 2000-01 trial compared four cycles of docetaxel (75 mg/m^2 day 1) plus cisplatin (75 mg/m^2 day 1) plus 5-FU (750 mg given on days 1–5) with three cycles of cisplatin (100 mg/m^2 day 1) plus 5-FU (1000 mg given on days 1–5) in resectable larynx and hypopharynx cancer [13]. At 30 months median follow-up, of the 220 patients randomised overall survival was somewhat better in the docetaxel plus cisplatin plus 5-FU arm than in the cisplatin plus 5-FU arm, but this difference was not statistically significant. However, larynx preservation rate was significantly better in the docetaxel-treated arm, as preservation rate in patients treated with docetaxel plus cisplatin plus 5-FU was 63.2% vs. 41.4% for those treated with cisplatin plus 5-FU ($p = 0.036$).

The European TAX 323 phase III trial tested docetaxel plus cisplatin plus 5-FU vs. cisplatin plus 5-FU followed by radiotherapy in patients with unresectable SCCHN, using the same regimen as in the GORTEC trial [14]. Overall survival was markedly improved in the docetaxel plus cisplatin plus 5-FU arm (n = 177), with a 29% reduction in the hazard of death vs. the cisplatin plus 5-FU arm (n = 181; p = 0.0052). Treatment with docetaxel plus cisplatin plus 5-FU was associated with less toxicity than with cisplatin plus 5-FU, with lower rates of stomatitis, nausea, and toxicity-related death (Figure 1).

Figure 1 **OVERALL SURVIVAL IN TAX 323**



TPF:	177	163	127	91	74	64	60	43	26	16	7	
PF:	181	150	98	77	57	47	39	33	25	15	8	4

TPF = docetaxel + cisplatin + 5-fluorouracil;
PF = cisplatin + 5-fluorouracil

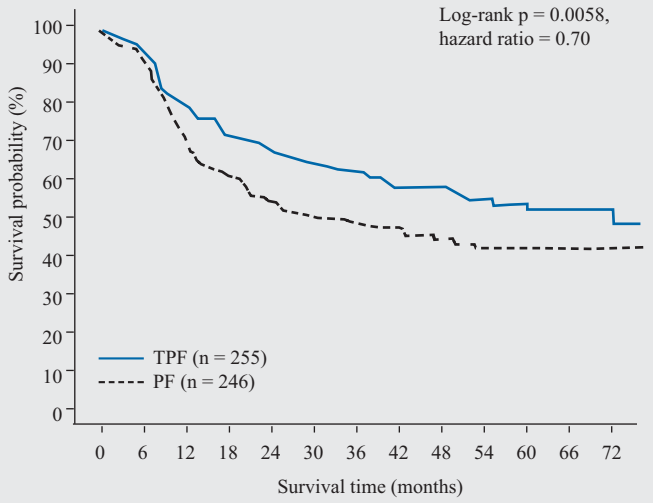
Source: Remenar E, et al. J Clin Oncol 2006;24(Suppl.):5516.

Meta-analyses of induction chemotherapy trials show that cisplatin plus 5-FU produces a 5% improvement in five-year survival ($p < 0.01$) [1]. Treatment with docetaxel plus cisplatin plus 5-FU is more effective than with cisplatin plus 5-FU. After induction chemotherapy and radiation therapy, failure is frequently local-regional (30%), with few distant metastases [15]. Chemoradiotherapy yields a significant 8% improvement in five-year survival [1]. Less local-regional failure occurs than with induction chemotherapy, but there are relatively more distant metastases [5,10,16,17].

Sequential therapy for SCCHN

Dr. Posner reported on the TAX 324 phase III trial, which assessed sequential combined-modality therapy in patients with SCCHN. Patients were randomised to three cycles of induction docetaxel plus cisplatin plus 5-FU or cisplatin plus 5-FU, followed by assessment of clinical and pathologic response. All patients then received immediate carboplatin and daily radiation therapy, followed by surgery. At a median follow-up of 42 months, the median survival in the docetaxel plus cisplatin plus 5-FU arm (n = 255) was 70.6 months vs. 30.1 months for the cisplatin plus 5-FU (n = 246). The three-year overall survival was 62% for docetaxel plus cisplatin plus 5-FU vs. 48% for cisplatin plus 5-FU (hazard ratio [HR] 0.70, p = 0.0058; Figure 2). Three-year progression-free survival was significantly better with docetaxel plus cisplatin plus 5-FU (49%) than with cisplatin plus 5-FU (37%; HR 0.71, p = 0.004).

Figure 2 **OVERALL SURVIVAL IN TAX 324**



TPF:	255	234	196	176	163	136	105	72	52	45	37	20	11	
PF:	246	223	169	146	130	107	85	57	36	32	28	10	7	1

TPF = docetaxel + cisplatin + 5-fluorouracil
PF = cisplatin + 5-fluorouracil

Source: Posner M. Data presented at the 43rd Annual Meeting of the American Society of Clinical Oncology (ASCO). Chicago, IL, USA, 2007.

Grade 3/4 neutropenia and febrile neutropenia were increased by treatment with docetaxel plus cisplatin plus 5-FU (84% and 12%, respectively) vs. treatment with cisplatin plus 5-FU (56% and 7%, respectively). However, there were twice as many treatment delays and greater dose reductions in the cisplatin plus 5-FU arm than in the docetaxel plus cisplatin plus 5-FU arm. "This was entirely due to prolonged neutropenia from platinum and 5-FU," said Dr. Posner. The toxicity of chemoradiotherapy was not enhanced by prior docetaxel induction therapy.

The local-regional failure rate was 31% with docetaxel plus cisplatin plus 5-FU vs. 38% with cisplatin plus 5-FU (p = 0.03). Distant metastases occurred in 5% of patients receiving docetaxel plus cisplatin plus 5-FU compared with 9% of patients receiving cisplatin plus 5-FU (p = 0.18).

Dr. Posner concluded that treatment with docetaxel plus cisplatin plus 5-FU significantly improves survival compared to cisplatin plus 5-FU. "Induction chemotherapy and sequential therapy with docetaxel plus cisplatin plus 5-FU are tolerable and safe and represent new, acceptable standards of care for locally advanced SCCHN," said Dr. Posner. "Phase III trials are needed to determine if sequential therapy or aggressive chemoradiotherapy is best."

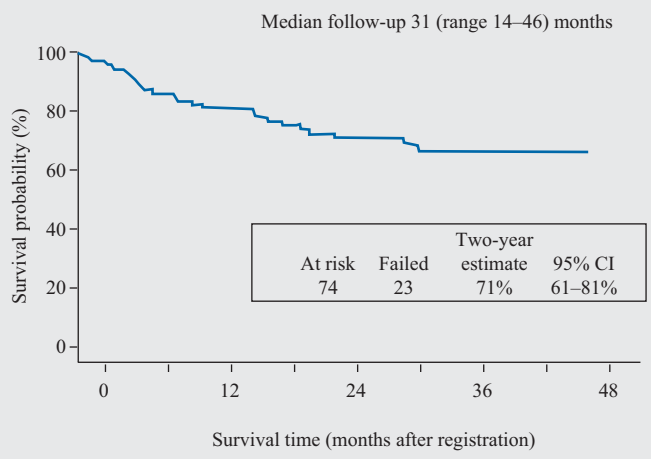
Induction therapy followed by chemoradiotherapy in locally advanced SCCHN

The SWOG S0216 phase II trial investigators hypothesised that optimal nonoperative therapy might consist of induction taxane-containing chemotherapy; accelerated fractionation/ concomitant boost (AF/CB) radiation therapy; and concomitant cisplatin chemotherapy [18]. This trial, presented by David J. Adelstein (Cleveland Clinic Taussig Cancer Center, Cleveland, OH, USA), aimed to assess overall response, complete response, and toxicities in patients with advanced SCCHN using this multimodality treatment approach. Patients with previously untreated stage III/IV, nonmetastatic SCCHN received induction therapy with docetaxel (75 mg/m^2, intravenously given on day 1) plus cisplatin (100 mg/m^2, intravenously given on day 1) plus 5-FU (1,000 mg/m^2 given intravenously over 24 hours for four days) every 21 days for two cycles. Following induction, patients received radiation therapy (72 Gy AF/CB) and cisplatin (100 mg/m^2 intravenously given) every 21 days for two cycles.

Of 74 patients who began treatment, 62 completed induction therapy and began chemoradiotherapy, and 50 completed all therapy. Toxicity from the induction regimen was significant, including grade 3/4 neutropenia in 59% of patients, and two deaths. "Overall, 85% of patients experienced at least one toxicity ≥grade 3 during induction," said Dr. Adelstein. Acute toxicity during chemoradiotherapy was significant, including grade 3/4 mucositis in 48% and grade 3/4 neutropenia in 31% of patients, and two additional deaths. Most patients (91%) experienced at least one grade 3/4 toxicity.

An unconfirmed complete response rate in both the primary site and the neck was observed after induction therapy in 7% of patients. After all therapy, the best response for both the primary site and the neck was 30%. With a median follow-up of 31 months, the estimated two-year progression-free survival was 66% (95% CI 55–77%). Most treatment failures were local-regional. The two-year projected estimate of overall survival was 71% (95% CI 61–81%; Figure 3).

Figure 3 **OVERALL SURVIVAL IN THE S0216 TRIAL**



Source: Adelstein J, et al. J Clin Oncol 2007;25(Suppl.):6014.

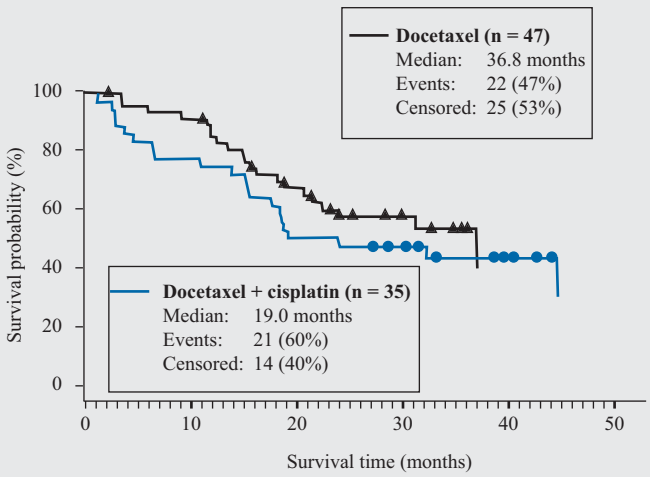
"Although this toxicity strains the limits of acceptability for a cooperative group trial, the regimens proved feasible and could be completed in 68% of patients. The 66% progression-free survival was encouraging. Careful study of this kind of sequential treatment will be required before it can be adopted as a treatment standard," said Dr. Adelstein.

Concomitant chemotherapy and radiation therapy for SCCHN

Thierry Bouillet (Department of Medical Oncology and Radiotherapy, Hôpital des Peupliers, Paris, France) presented results of the TAX 20006 phase II study of concomitant docetaxel with or without cisplatin and radiotherapy for first-line treatment of locally advanced SCCHN [19]. The study objectives were objective response rate, time to progression, overall survival, and safety. Patients were randomised to docetaxel (20 mg/m^2 per week, given on day 1, for seven cycles) with or without cisplatin (20 mg/m^2 given on days 1–3, every three weeks, for three cycles) and concomitant radiation therapy.

Efficacy was assessed eight weeks after the end of radiotherapy. The docetaxel plus cisplatin arm was prematurely discontinued due to overall response rate <76%, as planned by protocol. The response rate with docetaxel (n = 44) was 90.7% vs. 70.0% with docetaxel plus cisplatin (n = 30). The median overall survival with docetaxel was 36.8 months vs. 19.0 months with docetaxel plus cisplatin (Figure 4). The main toxicities with docetaxel were mucositis and skin toxicity.

Figure 4 **OVERALL SURVIVAL IN THE TAX 20006 STUDY**



Source: Bouillet T, et al. J Clin Oncol 2007;25(Suppl.):6047.

The investigators concluded that the addition of weekly docetaxel to conventional radiation therapy showed good efficacy and is feasible with expected adverse events.

Targetted therapy for locally advanced SCCHN

Vascular endothelial growth factor (VEGF) expression is increased in SCCHN. The anti-VEGF monoclonal antibody, bevacizumab, may enhance the effect of concurrent radiation therapy and docetaxel in the treatment of SCCHN. Therefore, a phase II trial reported by Panos Savvides (CASE Medical Center University Hospital, Case Western Reserve University School of Medicine, Cleveland, OH, USA), was designed to establish the efficacy and toxicity of this combination in patients with locally advanced SCCHN [20]. Patients with previously untreated stage III/IVB SCCHN received once-daily radiation, weekly docetaxel (20 mg/m^2 per week for the duration of radiation) and biweekly bevacizumab (5 mg/kg per two weeks) during and for up to one year following radiation. After a nine-month median follow-up, 9 of 10 patients were in complete response and one developed metastases. The worst toxicities were grade 3 dermatitis (40%), mucositis (20%), infections (20%), and dehydration (20%).

The investigators concluded that these preliminary data suggest that the addition of bevacizumab to concurrent radiation and docetaxel is feasible, safe, and active.

Second-line chemotherapy for recurrent/metastatic SCCHN

Relapse or distant metastasis of SCCHN has a poor prognosis with less than one year survival. Although taxanes are widely used for palliative therapy in this setting, there is no standard treatment. Haralabos Koussis (Department of Medical Oncology, Instituto Oncologico Veneto, Padova, Italy) presented results of treatment with weekly docetaxel (35 mg/m^2 for three of four weeks) in 24 patients with recurrent metastatic SCCHN [21]. Primary end points were response rate, duration of response, time to progression and toxicity evaluation. No patients achieved a complete response but six had partial responses with a mean duration of 3.4 months. Six patients had stable disease and 12 had disease progression. Time to progression was 3.2 months. Four patients had grade 3/4 haematologic toxicity and three had grade 4 mucositis. These results suggest that weekly docetaxel is active and tolerable as second-line therapy in this population.

Targetted therapy for recurrent/metastatic SCCHN

Interrupting the epidermal growth factor receptor (EGFR) signalling pathway has shown promise in a variety of cancers and preclinical data have demonstrated possible synergy with platinums and taxanes. Treatment options for patients with recurrent/metastatic SCCHN are limited. The addition of docetaxel to the cisplatin regimen showed promising results with respect to response rate and median survival [22]. Erlotinib, an EGFR tyrosine kinase inhibitor, had a 4.3% response rate as single agent in SCCHN [23]. The possible synergy and efficacy was investigated in a study presented by Edward S. Kim (University of Texas M.D. Anderson Cancer Center, Houston, TX, USA). In this open-label study patients with recurrent/ metastatic SCCHN were assigned to erlotinib in combination with docetaxel and cisplatin [23]. Patients (n = 48) were treated with up to six cycles of cisplatin (75 mg/m^2 every three weeks) plus docetaxel (60 mg/m^2 every three weeks) plus erlotinib (100 mg orally given daily) and continued on erlotinib until disease progression. After the first six patients did not experience any toxicity worse than grade 2, the docetaxel dose was increased to 75 mg/m^2 and erlotinib to 150 mg.

The most common grade 3/4 toxicity was neutropenia (64%), but the febrile neutropenia rate was only 10%. Anaemia, diarrhoea, nausea, dehydration, and skin toxicity were the predominant nonhaematologic toxicities. A complete response was achieved by 8%, a partial response by 58%, and stable disease by 25% of patients. The overall response rate was 66% and the disease control rate was 91%. Only three patients progressed after two cycles of treatment. Progression-free survival was six months and overall survival was 11 months, with a one-year survival rate of 48%.

“This is the first report of the EGFR tyrosine kinase inhibitor erlotinib combined with chemotherapy in incurable head and neck cancer,” said Dr. Kim. “There is encouraging efficacy. A proposed phase II randomised study of docetaxel plus cisplatin vs. docetaxel plus cisplatin plus erlotinib is under consideration. We should also consider testing a combination like this in the neoadjuvant or induction settings.”

Study acronyms

GORTEC 2000-01 trial	Groupe d’Oncologie Radiothérapie Tête et Cou (Radiotherapy Oncology Group for Head and Neck) trial 2000-01
INT-026 study	Intergroup study 026
RTOG 91-11 trial	Radiation Therapy Oncology Group trial 92-11
SWOG S0216 trial	Southwestern Oncology Group trial S0216

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