

EVIDENCE WATCH

A review and assessment of recent clinical trial data

Oncology Exchange provides overviews of important clinical trial data presented at the 40th Annual Meeting of the American Society of Clinical Oncology (ASCO), held in New Orleans, LA, June 5–9, 2004, and at the 9th Congress of the European Haematology Association (EHA), in Geneva, Switzerland, June 10–13, 2004. Leading Canadian experts offer commentary and clinical interpretations.

Head and neck cancer

STANDARD CISPLATIN/INFUSIONAL 5-FLUOROURACIL (PF) VS DOCETAXEL (T) PLUS PF (TPF) AS NEOADJUVANT CHEMOTHERAPY FOR NONRESECTABLE LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (LA-SCCHN): A PHASE III TRIAL OF THE EORTC HEAD AND NECK CANCER GROUP (EORTC #24971). (ASCO)

Investigators: J. B. Vermorken et al.

This Phase 3 study compared the efficacy of paclitaxel (T) added to the induction (neoadjuvant) chemotherapy regimen of cisplatin + 5-fluorouracil (PF) in 358 patients with nonresectable locally advanced squamous cell carcinoma of the head and neck. Participants in the PF therapy arm (n = 181) received cisplatin 100 mg/m² on day 1, then 5-fluorouracil 1000 mg/m² by continuous infusion on days 1–5 every 21 days. In the TPF arm (n = 177) patients received 75 mg/m² paclitaxel on day 1 and their

dosages of cisplatin and 5-fluorouracil were reduced to 75 mg/m² and 750 mg/m² respectively. Treatment was planned to continue for 4 cycles unless disease progressed, toxicity was excessive or the patient elected to discontinue therapy. Participants in both arms received various types of radiotherapy (RT) according to a defined protocol during weeks 4–7, unless their disease progressed after cycle 1 or 2 of chemotherapy. Some had surgery, either before or after RT.

After median followup of 32 months, the patients in the TPF arm had significantly better progression-free survival (hazard ratio [HR] 0.72; 95% CI 0.56–0.91; P = 0.006), overall survival (HR 0.73; 95% CI 0.57–0.94; P = 0.016) and response rate (67.8% vs 53.6%; P = 0.007). Further, these patients had less Grade 3–4 nausea (0.6% vs 7.3%), vomiting (0.6% vs 5.0%) and stomatitis (4.6% vs 11.2%) and fewer toxic deaths (2.3% vs 5.5%), compared to patients receiving PF only.

COMMENTARY: Samy El-Sayed, MBBCh, FRCR, FRCPC, Associate Professor, University of Ottawa and Senior staff, Radiation Oncology, Ottawa Regional Cancer Centre

The basic hypothesis of this Phase 3 study was to test whether adding a taxane to a cisplatin and 5-fluorouracil (PF) regimen is advantageous in the neoadjuvant treatment of patients with head and neck cancer. The study results showed that adding the taxane significantly improved outcome and reduced toxicity in 358 patients with nonresectable locally advanced squamous cell carcinoma of the head and neck. The doses of PF were reduced in the experimental arm.

While the study concludes that the hypothesis is proven, it has important flaws. The report implies that cisplatin + 5-fluorouracil as induction (or neoadjuvant) chemotherapy is a standard of care, which is far from being true. PF is indeed the most commonly used regimen in this setting, but the neoadjuvant chemotherapy approach itself remains experimental and so far has not been shown to improve local

control or survival outcome. Thus, although new chemotherapy regimens may prove more effective than older ones, they need to be tested in randomized trials against the standard treatment approaches of surgery plus radiotherapy or concomitant chemo- and radiotherapy. Further, the study allowed a variety of locoregional treatments, which may have affected outcome, so careful examination of the data will be needed when the detailed analysis is made available.

Nonetheless, the fact that adding a taxane to a combination treatment has resulted in a survival advantage is certainly of interest and warrants further investigation. This study is one of several in head and neck cancer which prove the superiority of PTF to TF but do not show a local control or survival advantage for adding neoadjuvant chemotherapy to local treatment. For now I would not advise a change of practice.

CETUXIMAB PROLONGS SURVIVAL IN PATIENTS WITH LOCOREGIONALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK: A PHASE III STUDY OF HIGH DOSE RADIATION THERAPY WITH OR WITHOUT CETUXIMAB. (ASCO)

Investigators: J. A. Bonner et al.

This was a Phase 3 trial investigating the impact of combining cetuximab with high-dose radiation on locoregional disease and survival. The 424 participants, who had locoregionally advanced squamous cell carcinoma of the oropharynx, hypopharynx or larynx, were stratified by Karnofsky score (60–80 vs 90–100, presence or absence of nodal disease, tumour stage (1–3 vs 4), radiation fractionation regimen (1/day vs 2/day vs concomitant boost). They were randomized to receive either radiation alone for 6–7 weeks (n = 213) or radiation + cetuximab. Median duration of followup was 38 months. Median survival as determined by Kaplan-Meier

estimates was 28 months for RT only vs 54 months for RT + cetuximab, and 3-year survival was 44% vs 57% (Table 1) (P = 0.02 for both). Incidence of mucositis was similar in both groups,

but the patients receiving cetuximab had more Grade 3–4 infusion reactions (3% vs 0%, P = 0.50) and skin reactions (34% vs 18%, P = 0.0003) than those treated with RT alone.

TABLE 1. Survival outcomes in patients with locally advanced squamous cell carcinoma of the head and neck, treated with cetuximab + RT vs RT alone

	Cetuximab + RT (n = 211)	RT only (n = 213)	P-value (log-rank test)
median survival	54 months	28 months	0.02
3-year survival	57%	44%	0.02

COMMENTARY: Samy El-Sayed, MBBCh, FRCR, FRCPC, Associate Professor, University of Ottawa and Senior staff, Radiation Oncology, Ottawa Regional Cancer Centre

This study is an important milestone in the development of more specific therapy and perhaps less toxic treatment for patients with locally advanced squamous cell carcinoma of the head and neck region (LA-SCCHN). It is a Phase 3 trial investigating the impact of combining cetuximab (an anti-EGFR agent) with high-dose radiation on locoregional disease and survival in 424 participants. The results are impressive and the size of the benefit equals that of adding more toxic chemotherapy to radiation.

Patients with LA-SCCHN now have many treatment options. One choice is concomitant chemoradiotherapy, which is fairly toxic. Alternatively, radical surgery followed by radiotherapy ± chemotherapy is an option, which can be rather mutilating. This study now presents a third option of adding an anti-EGFR agent to radiotherapy — apparently much less toxic than the first 2 options while just as effective.

Ideally a direct Phase 3 trial would examine the outcomes obtained with each of these approaches. In the absence of such a comparison, however, these results strongly support the use of the combination of radiotherapy and anti-EGFR in patients with locally advanced disease.

A more difficult question is: for which population of patients will this treatment become a standard of care? Further information and more detailed analysis is required, particularly regarding the baseline characteristics of the study population. As the study was completed in the era of concomitant chemoradiotherapy but included a radiotherapy-only arm — felt to be inferior treatment for many patients — probably only patients who were ineligible for concomitant chemoradiotherapy were enrolled. Nonetheless, the results are very exciting and stimulating, and practice patterns will likely change within the next few months as further analysis becomes available.

Chronic lymphocytic leukemia

ZAP-70 PROTEIN TYROSINE KINASE IS AN INDEPENDENT MARKER OF DISEASE PROGRESSION IN B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA. (EHA)

Investigators: Poeta DG et al.

This study analyzed the value of a tyrosine kinase required for T cell signalling — zeta-associated protein-70 (ZAP-70) — as well as the cell-surface

CD38 antigen, as prognostic indicators in 183 B-CLL patients and as predictors of IgVH mutational status, in 77 patients. Flow cytometry was used to detect

ZAP-70 and CD38 with a cutoff value of 20% for both markers. With regard to modified Rai stage, 64 had low stage, 116 intermediate stage and 3 high stage.

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Sixty-three patients were positive for ZAP-70 (34.4%) and 33 were positive for CD38 (18%).

In 77 patients there was a significant correlation between the presence of IgVH mutations and ZAP-70 positivity. Of 19 patients without IgVH mutations 16 (84%) were ZAP-70-positive, while 49 of 58 patients (84%) with mutations were ZAP-70-negative ($P = 0.00001$). The correlations between ZAP-70 values and soluble CD23 levels (another marker of disease progression) and between ZAP-70 and CD38 were also significant. There was no correlation between IgVH status and CD38 status, with 48 of 58 (83%) of IgVH -mutation-positive patients being CD38-negative and 7 of 19 (37%) non-mutated patients being CD38-positive ($P = 0.1$, not significant).

In 58 patients treated with fludarabine, ZAP-70-positive patients appeared to be

drug-resistant, having a lower complete response rate than seen with ZAP-70-negative patients (16% vs 63%, $P = 0.006$). As shown in **Table 2**, ZAP-70-positive patients also had shorter 10-year overall survival (OS) (80% vs 96%; $P = 0.019$) and progression-free survival (PFS) (14% vs 71%; $P < 0.00001$). In addition, CD38-positive patients had a shorter 10-year OS (78% vs 92%, $P = 0.035$)

and PFS (16% vs 56%, $P = 0.00004$) than CD38-negative patients. Patients positive for both ZAP-70 and CD38 had the lowest PFS. Multivariate analysis showed that the ZAP-70 status was a better predictor of PFS than Rai stage. The authors concluded that measurement of ZAP-70 by flow cytometry correlated with unmutated IgVH gene status and predicted short PFS and OS.

TABLE 2. Survival at 10 years in B-CLL patients according to ZAP-70 and CD38 status

Markers	OS (P-value)	PFS (P-value)
ZAP-70+	80%	14%
ZAP-70-	96% ($P = 0.019$)	71% ($P < 0.00001$)
CD38+	78%	16%
CD38-	92% ($P = 0.035$)	56% ($P = 0.00004$)

COMMENTARY: James Johnston, MB, BCh, FRCPC, Professor of Internal Medicine, University of Manitoba and Senior Investigator, The Genomic Centre for Cancer Research and Diagnosis, Manitoba Institute of Cell Biology, Winnipeg

The prognosis for chronic lymphocytic leukemia (CLL) is highly variable and while clinical staging may predict survival within groups of patients, it does not predict the likelihood of disease progression or drug resistance for the individual patient. With the evolution of new and more effective therapies for CLL interest has grown in developing new prognostic markers which would allow clinical trials to evaluate specific therapies according to the patients' risk stratification.¹ Probably the 2 most important areas are in classifying patients according to molecular genetics and according to the presence or absence of mutations of the IgVH gene.¹ When measured by fluorescent in situ hybridization (FISH), the one-quarter of patients with a deletion of 11q or 17p have the worst prognosis. Additionally, multiple studies have shown that the one-half of CLL patients with mutations of the IgVH gene have improved survival compared to patients without mutations.¹ Further, those without mutations are more likely to have deletions of 11q or 17p, although multivariate analyses show these deletions to be independent risk factors.² Gene sequencing is time-consuming and expensive, however, and not available in routine laboratories, leading to the evaluation of CD38 and ZAP-70 as surrogate markers for mutational status. These markers can be detected by flow cytometry and could be routinely assessed at the time of diagnosis.

This present abstract by Del Poeta et al has investigated a large number of patients and supports the findings of other studies indicating the important roles of ZAP-70 and CD38 for prognosis in CLL. Although it was previously suggested that ZAP-70 status only correlates with survival in Binet stage A

patients, the present report indicates that the ZAP-70 status may predict for PFS and OS in all CLL patients.³ Further, others have shown that in newly diagnosed patients the time to treatment is shorter for those who are ZAP-70-positive.^{4,5} Rassenti et al⁴ found the median time from diagnosis to treatment for ZAP-70-negative patients to be 9.2 years and for those who are ZAP-70-positive to be 2.9 years. Importantly, this study and that of Rassenti et al⁴ both found an 80% correlation between the presence or absence of mutations of the IgVH gene and ZAP-70 negativity or positivity, respectively. This contrasts with 2 other studies which found a much higher correlation between ZAP-70 status and mutational status.^{3,4} The discrepancy may be related to differences in the number and type of patients studied, as the correlation between IgVH status and ZAP-70 status is much closer in patients with early-stage disease.^{5,6}

The question thus remains as to whether both ZAP-70 and IgVH need to be measured, an issue not addressed by Del Poeta et al. Rassenti et al⁴ demonstrated that obtaining both variables supplies additional information — with ZAP-70-positive patients with unmutated IgVH genes having the shortest time from diagnosis to requiring treatment and those who were ZAP-70-negative with mutated IgVH genes having the longest time. This report implies that the reason for the more aggressive course of ZAP-70-positive patients may be at least partly related to drug-resistance. It also suggests that additional prognostic information is obtained when the CD38 status is calculated along with the ZAP-70 status — although this finding contrasts with a previous report.⁵

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In summary, ZAP-70 status, IgVH gene status and CD38 status all appear to be useful prognostic measures in CLL. Along with molecular genetic analysis by FISH, measures of all 3 are now being routinely incorporated into clinical trials for this disease. The results of these ongoing studies will determine which of these markers should be routinely assessed in CLL to provide more accurate prognosis and to guide therapy. Finally, ongoing studies are investigating why ZAP-70 is elevated in some CLL patients and whether it is directly responsible for the poor prognosis of these patients.

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