**Paclitaxel and gemcitabine vs. paclitaxel and pegylated liposomal doxorubicin in advanced non-nasopharyngeal head and neck cancer: an efficacy and cost analysis randomized study conducted by the Hellenic Cooperative Oncology Group**


**Record Status**
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

**Health technology**
The study compared two treatment options for patients with head and neck cancer (HNC).

Group A patients underwent treatment with gemcitabine, 1,000 mg/m² dissolved in 500 mL 0.9% sodium chloride and administered over 30 minutes on days 1 and 8. On day 1 this was followed immediately by paclitaxel, 175 mg/m² over 3-hour infusion, with standard premedication. The treatment was administered every 3 weeks.

Group B patients underwent treatment with pegylated liposomal doxorubicin, 40 mg/m² dissolved in 250 mL 5% dextrose, administered by infusion over 1 hour infusion on day 1. This was immediately followed by paclitaxel as in Group A. The treatment cycle was repeated every 4 weeks.

It was reported that the antiemetics used were ondansentron and dexamethasone.

**Type of intervention**
Treatment.

**Economic study type**
Cost-effectiveness analysis.

**Study population**
The study population comprised adult patients (age 18 years) who fulfilled the following inclusion criteria:

- histological or cytologically documented locally advanced or recurrent/ metastatic non-nasopharyngeal squamous cell carcinoma of the head and neck region;
- a performance status 2 or less on the Eastern Cooperative Oncology Group scale;
- a life expectancy of at least 12 weeks;
- adequate bone marrow, hepatic and renal function; and
- adequate cardiovascular, pulmonary and nutritional status to tolerate protocol treatment.

Patients with a history of the following were excluded:

- prior or synchronous cancer, except for completely excised non-melanoma skin cancer or curatively resected in situ cervical cancer;
- serious infection or other serious underlying medical condition which impeded the patient from receiving protocol.
treatment;

motor or sensory neuropathy, Grade II or higher, according to World Health Organization criteria;

atrial or ventricular arrhythmias and/or congestive heart failure, even if medically controlled; and

patients who had received chemotherapy for advanced disease.

Setting
The setting was hospital. The economic study was carried out in Greece.

Dates to which data relate
Patients were recruited between November 1999 and November 2004. The resource use data were collected during the effectiveness trial, while the cost data were based on actual data from the year 2005.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations showed that a sample of at least 253 patients was required to give 80% power for the detection of a 3-month difference in 6-month baseline median survival, using a two-sided test and assuming a 5% withdrawal rate. The accrual goal was not reached even though recruitment was continued for one year longer than originally planned. At the interim analysis an administrative decision was made to end the study due to the poor accrual rate. At this time 176 patients had already been accrued. Four patients were excluded because of inadequate medical records, and 6 did not meet the inclusion criteria (5 received other than protocol treatment and 1 patient had a second primary tumour at study entry). Overall, 166 eligible patients were included in the study, of which 85 were assigned to group A and 81 to group B. It was reported that one patient assigned to group B received group A treatment.

Study design
The study was a randomised multi-centre Phase III trial. The patients were followed up after the third and sixth treatment cycle and every 3 months after completion of treatment until disease progression. Patient stratification was conducted according to history of induction chemotherapy or concomitant chemoradiotherapy. Patients were also stratified according to the performance status (PS: 0+1 versus 2). It was reported that, overall, 92 patients discontinued treatment (47 in group A and 45 in group B). The reasons for discontinuation were death, treatment toxicity, disease progression and refusal to continue with the treatment. In addition, one patient in group B was transferred to a different hospital.

Analysis of effectiveness
The analysis was conducted on an intention to treat basis. The patient groups were shown to be comparable in terms of their baseline demographic and clinical characteristics. The primary health outcome used in the analysis was patient survival. The secondary health outcomes comprised time to progression (TTP), time to treatment failure (TTF), the overall response rate (ORR) and rates of acute severe toxicities. TTP and survival curves were estimated using the Kaplan-Meier method. A log rank test was used to compare time to event distributions.
**Effectiveness results**

Median survival was 8.6 months (range: 0.07 to 63.08) in group A and 11.05 months (range: 0.62 to 59.64) in group B, (p=0.25).

The estimated survival rate at 1 year was 35% (95% confidence interval, CI: 24.8% to 45.2%) in group A versus 47% (95% CI: 36.3% to 58.3%) in group B.

At 2 years, the estimated survival rate was 18% (95% CI: 9.4% to 26.6%) in group A versus 20% (95% CI: 10.5% to 28.9%) in group B.

At 3 years, the estimated survival rate was 12% (95% CI: 4% to 20%) in group A versus 14% (95% CI: 5.3% to 22.5%) in group B.

Median TTP was 4.4 months in group A (range: 0.07% to 63.08%) and 6 months in group B (range: 0.62% to 59.64%), (p=0.09).

The ORR did not differ between the two groups. (p=0.21)

Median TTF was 2.95 months (range: 0.01 to 63.08) in group A and 3.84 months (range: 0.01 to 59.64) in group B, (p=0.14).

**Clinical conclusions**

The analysis demonstrated that there were no significant differences in response rate, time to disease progression and survival between the two treatment options.

**Measure of benefits used in the economic analysis**

The authors did not derive a summary measure of benefit in the economic analysis. As the effectiveness analysis demonstrated equal effectiveness for the two treatment regimes, a cost-minimisation analysis was performed.

**Direct costs**

The health care resources and costs included in the analysis were for chemotherapy and concomitant drugs, diagnostic and laboratory tests, hospitalisations, treatment of adverse events and follow-up visits. The costs and the quantities of resources used were not reported separately. The resource use data were based on actual data collected alongside the effectiveness study, whilst the cost data were based on actual data derived from a hospital database. All costs were reported for the year 2005.

**Statistical analysis of costs**

The cost results were summarised using descriptive statistics.

**Indirect Costs**

The indirect costs were not included in the analysis.

**Currency**

Euros (EUR).

**Sensitivity analysis**

To investigate uncertainty surrounding the cost data, a bootstrap analysis was performed.
Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The mean total treatment cost were EUR 7,419 (range: 1,044 to 13,826; 95% CI: 6,688 to 8,150) in group A and EUR 11,068 (range: 2,350 to 19,362; 95% CI: 10,038 to 12,098) in group B.

The cost-difference, which was mainly attributed to chemotherapy costs, was statistically significant (mean EUR 3,649; 95% CI: 2,386 to 4,912; p<0.001).

Synthesis of costs and benefits
The costs and benefits were not combined.

Authors' conclusions
Although the two treatment options did not differ in relation to survival, the combination of paclitaxel and gemcitabine incurred significantly less costs to the Greek National Health Service than the combination of paclitaxel and pegylated liposomal doxorubicin for the treatment of non-nasopharyngeal head and neck cancer (HNC).

CRD COMMENTARY - Selection of comparators
The choice of the comparators was explicitly justified. The authors focused on treatment options that were not platinum-based, the effectiveness of which had been demonstrated in previous conducted Phase I and II trials. You should decide if these are widely used technologies in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a multi-centre randomised controlled trial which, together with the statistical analysis performed, was appropriate to account for potential biases and confounding factors. Although the study sample was representative of the study population and the patient groups were shown to be comparable at analysis, power calculations demonstrated that the sample size was not sufficient to detect estimated differences. However, methods of randomisation, length of the study and the loss to follow-up were all reported, suggesting that the internal validity of the study was good.

Validity of estimate of measure of benefit
As the effectiveness analysis demonstrated that the two treatments were equally effective, only costs were assessed further. A cost-minimisation analysis was therefore performed.

Validity of estimate of costs
The cost analysis was conducted from the perspective of the Greek National Health System. Although it appears that all the relevant cost categories have been included in the analysis, the unit costs and the resource quantities were not reported separately. This will hinder the analysis from being reworked for other settings.

Other issues
Only indirect comparisons with published studies were possible, as former studies did not refer to the same comparators. The issue of the generalisability of the results to other settings was not directly addressed. The authors do not appear to have presented their results selectively. The study considered patients with advanced non-nasopharyngeal HNC and this was reflected in the authors' conclusions. The authors acknowledged a number of limitations to their study. First, the ORR did not comprise a primary outcome. Second, the estimated results should be treated with caution as imaging techniques were not used in the assessment of patients as indicated. Third, some patients with non-
measurable disease were enrolled. In addition, the impact of the treatment on the patients’ quality of life was not evaluated given the lack of a valuation tool in the Greek language for HNC patients.

**Implications of the study**
The authors did not make explicit recommendations for changes in policy or practice. However, they called for a Phase III randomised trial directly comparing each of the treatment options with standard chemotherapy.

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**Other publications of related interest**
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**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
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