Advanced head and neck cancers

Transatlantic collaboration shows results

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Concurrent postoperative administration of cisplatin (Platinol) and radiotherapy has been established by two separate studies to be the treatment of choice in people with advanced head and neck cancer who have undergone surgery.

Taken together, the results of the European Organisation for Research and Treatment of Cancer (EORTC) study and the US Radiation Therapy Oncology Group (RTOG) study, both published in the May 6 issue of the *New England Journal of Medicine* (vol 350, pp 1945–1952 and 1937–1944, respectively), showed benefits from the concurrent therapies compared to radiotherapy alone. This treatment was already the established therapeutic option for tumours that had spread locally, but which were not considered operable.

But while both studies were positive – showing enhanced disease-free survival at five years in the EORTC group and enhanced two-year local and regional control in the RTOG group – only the EORTC study demonstrated significant increases in survival. "These are puzzling discrepancies, that require further investigation," said Professor Jacques Bernier, principal investigator of the EORTC study and director of the Department of Radio-Oncology at the Oncology Institute of Southern Switzerland, Bellinzona.

Squamous cell cancer of the head and neck is the sixth most common cancer worldwide, with a lifetime risk of 2% for men, and 0.6% for women. There are approximately 76,000 new cases of oral-cavity, pharyngeal and laryngeal cancer diagnosed each year in Western Europe. "Patients often have a genetic predisposition to head and neck cancer which favours malignant transformation if they come into contact with tobacco and alcohol," said Professor Bernier.

Professor Jacques Bernier, principal investigator of the EORTC trial, is keen to find an explanation for discrepancies between the results of the two trials

Early disease is generally treated with either radiotherapy or surgery, which have a similar likelihood of controlling tumours. But for patients with locally advanced disease – i.e. disease that has spread locally from its site of origin, but not to distant sites in the body – treatment is more complex, requiring surgery with postoperative radiotherapy. Unfortunately such patients still show a particularly high rate of local recurrence. When two or more regional lymph nodes are involved, or there is extra capsular spread of disease or microscopically involved mucosal margins of resection, there are particularly high rates of local recurrence (27–61%), distant metastases (18–21%) and a high risk of death, with a five-year survival rate of 27–34%, indicating the need for development of additional treatments.

Such statistics have led investigators to look at different ways of delivering chemotherapy, including induction chemotherapy (consisting of several courses of chemotherapy before radiotherapy); sequential chemotherapy (where chemotherapy is administered at a different time from radiotherapy); concurrent chemotherapy (where chemotherapy is given at the same time as radiotherapy) and adjuvant chemotherapy (administered after patients have been rendered disease free). Studies looking at delivering sequential chemotherapy postoperatively have revealed little in the way of benefit. Most noteworthy, the

Inter-group study 0034, published in the *Journal of Clinical Oncology* in 1990 (vol 8, pp 838–847), showed that the sequential addition of cisplatin and fluorouracil to radiotherapy reduced the incidence of nodal and distant failure, but produced no effect on survival.

However, other studies suggested that for patients with inoperable head and neck cancers, chemotherapy was beneficial when delivered at the same time as radiotherapy. The RTOG 88-24 study, published in 1997, which gave cisplatin in a single high dose (100mg/m^2) on days 1, 22 and 43 of radiotherapy (*Int J Radiat Oncol Biol Phys* vol 37, pp 777–782), showed improved local control and increased survival. Whilst severe toxicity occurred in 20% of cases treated with adjuvant chemo-radiation, 48% of patients remained alive at three years and 81% had locoregional control of disease.

A study published in 1996 showed benefits from combining postoperative radiotherapy with weekly cisplatin infusions for locally advanced head and neck cancers (*Int J Radiat Oncol Biol Phys*, vol 36, pp 999–1004). Another, published in 1993, found improved outcomes combining postoperative radiotherapy with Mitomycin C (*Int J Radiat Oncol Biol Phys*, vol 27, pp 241–250). In both these studies, disease-free survival was increased for patients in the combined therapy arm compared to those in the control arm, who just received radiotherapy.

This was the background against which the recently published EORTC and RTOG trials were started, in 1994 and 1995 respectively. Both were much larger than the earlier studies and both aimed to establish whether adding cisplatin concurrently to postoperative radiotherapy improved outcomes for patients with high-risk resected head and neck cancers. The focus on cisplatin was due to its presumed effect of "radiosensitising" cells – i.e. rendering cells more vulnerable to the toxic effects of radiation when administered concurrently – which was expected to yield a greater benefit than the sum of the benefits of radiotherapy and chemotherapy considered separately. (The interaction between cisplatin and ionizing radiation is not fully understood, but may be achieved by the synchronisation and redistribution of tumour cells into the more sensitive G2-M phase of the cell cycle, or by the cisplatin creating abnormal ridges within DNA that inhibits its capacity to spontaneously repair after radiotherapy.)

Protocols and patients

The EORTC trial involved patients with stage III or IV head and neck cancers. After undergoing surgery, 167 patients were randomly assigned to receive radiotherapy alone (66 Gy over a period of six weeks) and 167 to receive the same radiotherapy regimen combined with 100 mg/m^2 cisplatin on days 1,22 and 43 of the radiotherapy regimen. The study, which had a median duration of follow-up of 60 months, was designed to detect an absolute increase of 15% in disease-free survival. The RTOG trial, which followed exactly the same treatment protocol in a similar patient population, assigned 210 patients to postoperative radiotherapy and 206 to combined therapy, with a median duration of follow-up of 45.9 months. The trial was designed to detect an absolute increase of 15% in the two-year rate of local and regional control.

The eligibility criteria for the two trials differed, but overall patients had to be in good general condition to receive chemotherapy and to have a previously untreated, histologically proven squamous cell carcinoma arising from the oral cavity, oropharynx, larynx or hypopharynx. The cancer had to be classed as stage III or IV, or had to show high-risk characteristics such as histologic evidence of invasion of two or more regional lymph nodes, extracapsular extension of nodal disease or microscopically involved mucosal margins. "Cancers of the nasopharynx were excluded from the studies because it was felt they had a different natural history from the other head and neck cancers (with faster metastasis) and would skew results," said Dr Bernier. All patients had undergone surgery with curative intent and those with distant metastases were excluded from the study.

"In both studies cisplatin was selected because it was considered the best agent at the time to increase the control without increasing the toxicity", said Dr Bernier. "Although 5-FU, for example, is very effective, it has the disadvantage of increasing mucosal reactivity to radiotherapy and can result in patients needing parental feeding and severely adverse effects on quality of life."

Positive results

Both studies yielded positive results. In the EORTC trial, after an average of approximately five years, progression-free survival was 47% in the group of patients treated with cisplatin plus radiation, compared with only 36% in the group of patients treated with radiation alone. The overall survival rates at five years were 53% for patients treated with cisplatin and radiation therapy, compared with only 40% for patients treated with radiation alone. Severe side effects (grade 3 or higher) occurred in 41% of patients treated with combination therapy, compared with only 21% of patients treated with radiation alone. But severe mucosal adverse effects were similar in the two groups.

In the RTOG trial, after approximately 46 months cancer-free survival was 22% higher in the patients treated with radiation and chemotherapy, compared

to those treated with radiation alone. However, overall survival was similar. Cancer recurrences at or near the site of origin occurred in 18% of patients treated with combined therapy, compared to 28% of patients treated with radiation alone at approximately two years following treatment. Severe side-effects occurred in 34% of patients treated with radiation alone, compared with 77% of patients treated with chemotherapy and radiation therapy, and in this study four patient deaths were directly attributable to treatment.

"The magnitude of a 13–15% difference in survival observed in the EORTC trial was both much higher than the RTOG trial and higher than we'd been expecting, suggesting there are additional mechanisms in play that we've yet to determine," said Dr Bernier, who wants to find out why the beneficial effect was so much higher than in the RTOG trial. Differences in the presentation of morbidity data make comparisons of the two trials difficult. There are, however, suggestions that differences in overall survival found between the two trials might be attributable to differences in the types of patients recruited to each study, since they did not use identical eligibility criteria.

Another theory, put forward by Dr Jay S. Cooper, principal investigator of the RTOG trial and head of Radiation Oncology at Maimonides Medical Center in New York City, is that over time an effect on overall survival may still be seen in the RTOG trial. "If you don't find a mathematically statistically significant change, it doesn't mean one doesn't exist," he said. It is also possible, he suggests, that certain lifestyle issues that contributed to the cancer (such as heavy drinking and smoking) caused other problems, such as heart disease. "Even if you do a better job of controlling tumours, it may not translate immediately into better survival, because they'll still die of other things," he said.

Investigators from EORTC and RTOG hoped to review differences between the two trials when they met at the Sixth International Conference on Head and Neck Cancer in August. "We plan to screen for variations in patient selection and treatment density across the two trials to see if these could account for the differences in magnitude," said Dr Bernier.

Despite the positive findings, neither trial showed any reductions in distant metastases, and disease still recurred locally in 30% of patients, demonstrating that further improvements are still needed. One way forward, suggested Dr Bernier, may be to give chemotherapy immediately after surgery. "We'd keep the chemo as used in this study, but also give a weekly cycle of chemotherapy seven to ten days after surgery until the beginning of radiotherapy."

Toxicity concerns

Issues remain concerning toxicity, and future clinical trials evaluating agents not associated with such a high rate of side-effects are warranted. One novel targeted therapeutic approach under investigation is the agent Erbitux (cetuximab), which is a monoclonal antibody designed to bind to EGFR, a protein involved in the growth and replication of cells that is often over-expressed in cancer cells.

This binding action is believed to prevent or reduce the replication of the cancer cells, resulting in anti-cancer responses. In a trial presented by the Erbitux Head and Neck Study Group at the 40th Annual Meeting of the American Society of Clinical Oncology in June, 417 patients with locally advanced head and neck cancer were randomised to receive Erbitux plus high-dose radiation, or high-dose radiation alone (Abstract 5507). Three-year overall survival was 57% for patients treated with Erbitux plus radiation, compared with only 44% for those treated with radiation alone. The median survival increased from 28 months in the standard arm to 54 months in the experimental group. The only notable side-effect associated with Erbitux was skin rash.

Next steps

Advances are also needed in radiotherapy. In an editorial which appeared in the May issue of the *New England Journal of Medicine*, alongside the EORTC and RTOG trial results (vol 350, pp 1997–1998), Michele Saunders, from the Academic Department of Oncology at University College London, and Ana Rojas, from Mount Vernon Hospital, Middlesex, UK, suggest that the next obvious step towards further improving outcomes would be to identify a more effective radiotherapy regimen. "The radiobiology of radiotherapy as the sole agent in the treatment of squamous cell cancer of the head and neck is well understood, but the optimal dose, time frame and regimen of fractionation in a multidisciplinary setting are not." Two recent phase III trials indicate that use of a shorter than conventional overall treatment time for post-operative radiotherapy could improve tumour control and survival.

Dr Bernier believes the two studies make a convincing case for the standard use of the concurrent combined therapy, at least in the age group 70 and under. "This transatlantic collaboration justifies the fact that most countries now consider the combination of high doses of cisplatin and radiotherapy to be the new algorithm in the decision making process for locally advanced head and neck carcinomas treated with primary surgery," he said.