



EVIDENCE WATCH

A review and assessment of recent clinical trial data

Oncology Exchange provides overviews of important clinical trial data presented at the 42ND Annual Meeting of the American Society of Clinical Oncology (ASCO), held June 2–6, 2006 in Atlanta, Georgia. Leading Canadian experts offer commentary and clinical interpretations.

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Lung cancer

ADJUVANT CHEMOTHERAPY IN STAGE IB NON-SMALL CELL LUNG CANCER (NSCLC): UPDATE OF CANCER AND LEUKEMIA GROUP B (CALGB) PROTOCOL 9633. ASCO 2006, ABSTRACT 7007.

Investigators: G.M. Strauss et al.

TRIAL SUMMARY: The CALGB (The Cancer and Leukemia Group B) trial 9633 randomized 344 postsurgical patients with Stage IB non small-cell lung cancer (NSCLC) to receive either 4 cycles of adjuvant chemotherapy (paclitaxel 200 mg/m² + carboplatin AUC 6 every 3 weeks) or observation only. Because accrual was slower than expected, lengthening the period of observation for each patient, the target enrollment was reduced from 500 to 384 patients. Preliminary results reported in 2004 showed statistically significant improvement in disease-free survival (DFS) and overall survival (OS), the primary endpoint. At this report at median followup of 54 months, DFS was better in the group receiving adjuvant chemotherapy, with a hazard ratio

(HR) of 0.074, 90% 2-sided confidence interval (CI) of 0.57 to 0.96 and $p = 0.10$. A non-significant trend in OS favoured adjuvant chemotherapy (HR 0.80, CI 0.60–1.07, $p = 0.10$). Three-year survival was significantly better in the chemotherapy group (79% vs 70%, $p = 0.45$), while 5-year survival, so far, does not differ significantly (60% vs 57%, $p = 0.32$). Followup continues, as only 131 of the 150 deaths needed for final analysis have occurred. The authors concluded that this updated data no longer demonstrates an OS advantage for adjuvant chemotherapy in the subset of NSCLC patients with Stage IB disease, but note that the redesigned study had less power than originally planned.

LUNG ADJUVANT CISPLATIN EVALUATION (LACE): A POOLED ANALYSIS OF FIVE RANDOMIZED CLINICAL TRIALS INCLUDING 4,584 PATIENTS. ASCO 2006, ABSTRACT 7008.

Investigators: J.P. Pignon et al.

TRIAL SUMMARY: The Lung Adjuvant Cisplatin Evaluation (LACE) study combined data from the 5 largest trials conducted after the 1995 meta-analysis of cisplatin-based chemotherapy given after complete resection of tumours in patients

with NSCLC, reported in the British Medical Journal.¹ The trials were ALPI (Adjuvant Lung Project Italy), ANITA (Adjuvant Navelbine International Trialist Association), BLT (Big Lung Trial), IALT (International Adjuvant Lung Cancer

LANDMARKS

Trial) and JBR.10, a trial of the National Cancer Institute of Canada Clinical Trial Group (NCIC-CTG). At followup of 5.1 years, the overall hazard ratio for death was 0.89 (95% CI 0.82–0.96, $p < 0.005$), which translates into a 4.2% absolute benefit of cisplatin-based chemotherapy at 5 years.

The benefit varied with stage ($p = 0.046$), as shown in **Table 1**. Sex, age, planned radiotherapy and planned total dose of cisplatin did not cause significant variation in chemotherapy effect, nor did use of other drugs including vinorelbine, etoposide and vinca alkaloids. The authors concluded that adjuvant cisplatin-based chemotherapy improves survival in patients with NSCLC, and that the benefit is greatest in patients with Stages II and III disease.

TABLE 1. Overall survival benefit of adjuvant cisplatin for NSCLC patients by disease stage in the LACE combined analysis of ALP, ANITA, BLT, IALT and JBR10 trials

Disease stage	hazard ratio	95% CI
Stage IA	1.41	0.96–2.09
Stage IB	0.93	0.78–1.10
Stage II	0.83	0.73–0.95
Stage III	0.83	0.73–0.95

ADJUVANT CHEMOTHERAPY IN ELDERLY PATIENTS: AN ANALYSIS OF NATIONAL CANCER INSTITUTE OF CANADA CLINICAL TRIALS GROUP AND INTERGROUP BR.10. ASCO 2006, ABSTRACT 7009.

Investigators: C. Pepe et al.

TRIAL SUMMARY: This retrospective analysis of the influence of age on outcomes in the NCIC-CTG BR.10 trial compared pretreatment characteristics and survival benefit derived from adjuvant chemotherapy by patients older and younger than age 65. In 327 “young” and 155 “elderly” patients, baseline prognostic factors according to age were similar, with the exception of histology (adenocarcinoma in 58% of young vs 43% of elderly, squamous 32% young vs 49% elderly, $p = 0.001$) and performance status, with a score of 0 in 53% young vs 41% elderly ($p = 0.01$). Univariate analysis of OS showed a non-significant trend favouring the young (HR 0.77, 95% CI 0.58–1.04, $p = 0.084$), as did multivariate analysis (HR 0.75, 95% CI 0.56–1.01, $p = 0.059$). Patients older than 65 receiving adjuvant chemotherapy had significantly better OS compared to those on observation only (HR 0.61, 95% CI 0.38–0.98, $p = 0.04$). Patients older than 75 years had significantly shorter survival than those aged 66–74 (HR 1.95, 95% CI 1.11–3.41, $p = 0.02$).

In an evaluation of chemotherapy administration in 63 elderly and 150 young patients, mean dose intensities of vinorelbine and cisplatin were lower in the elderly than in the young: vinorelbine 13.2 vs 9.9 mg/m² per week ($p = 0.0004$) and cisplatin 18.0 vs 14.1 ($p = 0.006$). As well, the elderly received significantly fewer doses of adjuvant chemotherapy and fewer elderly patients completed treatment. No significant differences in toxicities, granulocyte colony stimulating factor (G-CSF) use or hospitalization were noted other than more myalgias and mood alteration in the elderly. Non-malignancy-related deaths occurred in 6 of 126 deaths (4.8%) in the young vs 12 of 71 (16.9%) in the elderly ($p = 0.008$). The authors concluded that NSCLC patients older than age 65 should be offered adjuvant chemotherapy, as they derive an OS benefit despite receiving fewer and/or lower doses, with acceptable toxicity, but that further study is needed of those above 75 years old.

COMMENTARY: Nevin Murray, MD, FRCPC, Clinical Professor of Medicine, University of British Columbia, BC Cancer Agency, Vancouver, BC.

Development of effective adjuvant chemotherapy for resected NSCLC has been a struggle. Early efforts dating from the late 1960s and 1970s demonstrated significantly detrimental effects of alkylating agents.¹ A 1995 meta-analysis¹ showed a 4% to 5% survival advantage with cisplatin-based regimens, but since the statistical significance of the effect was borderline, adjuvant chemotherapy did not become the standard of care. Several Phase III studies performed after the meta-analysis, including ECOG 3590 (Eastern Cooperative Oncology Group, Intergroup Trial 0115),² the BLT³ and ALPI,⁴ also failed to show a significant benefit with adjuvant chemotherapy. Then in 2003, the positive results from the IALT were reported.⁵ Because this was the largest trial of adjuvant chemotherapy for resected NSCLC, with 1867 patients, it was influential in rekindling interest in adjuvant chemotherapy for this disease. However, the survival benefit

was modest showing a statistically significant 4% survival advantage at 5 years with the addition of 4 cycles of cisplatin-based chemotherapy after complete resection of Stage I–III NSCLC (HR 0.86). In subset analyses there was no significant benefit for patients with Stage IB disease or for those more than 65 years old.

Two additional positive adjuvant trials were reported in 2004.⁶ The NCIC-CTG BR.10 trial randomized 482 patients with completely resected Stage IB–II NSCLC to receive 4 cycles of cisplatin + vinorelbine vs observation, reporting a 15% survival advantage at 5 years. The trial was stratified by stage, and subset analysis showed no benefit in patients with Stage IB disease. At the same 2004 meeting of the American Society of Clinical Oncology (ASCO), however, the CALGB trial 9633 of 344 patients with resected Stage IB NSCLC did report a survival advantage

for those receiving adjuvant carboplatin + paclitaxel chemotherapy vs observation.⁷ This was the only adjuvant trial to use a carboplatin-based regimen; the trial was closed early when the first interim analysis showed a 12% survival gain at 4 years (HR 0.62).

The presentation of the ANITA (Adjuvant Navelbine International Trialist Association) study⁸ at the 2005 ASCO meeting provided further confirmation on the efficacy of adjuvant chemotherapy for resected NSCLC. This trial of 840 patients, nearly equally balanced between Stages IB and IIIA, found a 9% survival advantage at 5 years (HR 0.79) with 4 cycles of adjuvant cisplatin + vinorelbine. Again, subset analysis found no benefit for the patients with Stage IB disease.

These positive studies established adjuvant chemotherapy as the standard of care for completely resected Stage II–IIIA NSCLC, and CALGB 9633 kept open the possibility of a role for adjuvant chemotherapy in Stage IB disease. After all, the IB pessimism of IALT, BR10 and ANITA trials were only subset analyses. It was “open season” for adjuvant chemotherapy for Stages IB–IIIA resected NSCLC.

SOME RESERVATIONS

The NSCLC adjuvant chemotherapy results reported at ASCO 2006 and summarized above have tempered the 2005 level of enthusiasm. An update of CALGB 9633 showed that with further followup the hazard ratio of 0.8 for overall survival was no longer statistically significant (p = 0.1). A statistically significant survival advantage is still observed at 2 and 3 years, but the difference at 5 years was 59% vs 57% (p = 0.375). An unplanned subset analysis of tumours greater than 4 cm, however, appeared to show a significant survival benefit.

Pignon et al’s individual patient meta-analysis of the large adjuvant trials conducted since the 1995 meta-analysis included 5 studies and 4584 patients. Because individual patient data were updated, examination of subsets is possible. This study found a 5.5% survival advantage at 5 years (HR 0.84, p < 0.001) for adjuvant cisplatin therapy overall, thus underlining the need to power adjuvant trials for this range of benefit. Subset analysis of Stage IB disease (excluding CALGB 9633 because it was not cisplatin-based) trended toward benefit (HR 0.93) but failed to reach statistical significance (95% CI 0.78–1.10). The impact of adjuvant chemotherapy was most favourable for vinorelbine + cisplatin within a regimen intending to deliver more than 300 mg/m² of cisplatin.

Pepe et al retrospectively analyzed the NCIC-CTG BR.10 results according to age older or younger than 65 years. Patients between 65 and 75 years appeared to benefit (HR 0.61, 95% CI 0.38–0.98, p = 0.04) despite having greater attenuation of delivered chemotherapy doses. Patients over 75 years had significantly shorter survival (HR 1.95, 95% CI 1.11–3.41, p = 0.02).

LESSONS LEARNED AND FURTHER QUESTIONS

Taken together, this information should enhance our confidence that adjuvant chemotherapy benefits NSCLC patients with positive lymph nodes whose tumours have

been completely resected. Real doubts persist, however, about the efficacy of adjuvant chemotherapy in node-negative disease. The meta-analysis showed that the relative risk of death with adjuvant chemotherapy was 1.41 (0.96–2.09) in Stage IA — a disturbing trend to a detrimental effect. The benefit for Stage IB disease is uncertain indeed and if an effect exists at all, it appears to be only 2% to 3% at 5 years.

The situation in lung cancer is similar to that in resected colorectal cancer where adjuvant chemotherapy clearly benefits the node-positive and is equivocal for node-negative patients. Perhaps there is a difference in the biology of chemosensitivity for node-positive vs node negative-disease. North American and European investigators should consider clinical trials for Stage I patients with uracil-tegafur-based chemotherapy as described by investigators in Japan⁹ (combining tegafur, a prodrug of fluorouracil and uracil, which inhibits enzymatic degradation of fluorouracil). After all, the lungs are embryologically part of the gastrointestinal tract modified for gas exchange.

With respect to patient age, the subset analysis of BR.10 reassures us that the hale and hearty elderly patient similar to those randomized on the trial may benefit from adjuvant chemotherapy. Such patients may not be representative of the general group of resected NSCLC patients older than 65 years, however.

Cisplatin + vinorelbine has the best evidence for efficacy, and the cisplatin should be dosed fairly stiffly aiming for a cumulative dose of at least 300 mg/m². This requires a creatinine clearance of ≥ 60 cc per minute. There are serious doubts that a carboplatin-based regimen can be substituted for those with impaired renal function — we clearly need more data. The number of patients in the lung databases is pathetic compared to the 75,000 in breast cancer meta-analyses. The next generation of trials should incorporate molecular predictors of prognosis¹⁰ and new agents. The next North American intergroup trial under consideration will include bevacizumab added to chemotherapy.

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Breast cancer prevention

THE STUDY OF TAMOXIFEN AND RALOXIFENE (STAR): INITIAL FINDINGS FROM THE NSABP P-2 BREAST CANCER PREVENTION STUDY. 2006 ASCO, ABSTRACT LBA5.

Investigators: D.L. Wickerham et al.

TRIAL SUMMARY: The randomized, double-blind STAR (study of tamoxifen and raloxifene) trial compared the effects of raloxifene 60 mg per day vs tamoxifen 20 mg per day in postmenopausal women at risk of developing invasive breast cancer. Almost 20,000 women (n = 19,747), with a 5-year predicted risk of breast cancer of at least 1.66% as determined by the modified Gail model, were enrolled between 1999 and 2004. Their mean age was 58 years, mean breast cancer risk was 4.03%, and average time in the study was 47 months.

With 163 cases of invasive breast cancer in women taking tamoxifen and 167 in those taking raloxifene, no dif-

ference was seen between the 2 groups (relative risk [RR] 1.02, 95% CI 0.82–1.27). Women in the raloxifene group had a 40% lower risk of invasive uterine malignancies (RR 0.62, 95% CI 0.35–1.08) although this did not reach statistical significance, while those in the tamoxifen group had lower risk of non-invasive breast cancer (RR 1.40, 95% CI 0.98–2.00). No significant differences were seen regarding other cancers or for death, cardiac events or osteoporotic fractures. Women taking raloxifene had fewer thromboembolic events, including deep vein thromboses and pulmonary emboli, compared to those taking tamoxifen (RR 0.76, p = 0.01).

COMMENTARY: Debjani Grenier, MD, FRCPC, Medical Oncologist, CancerCare Manitoba, St. Boniface General Hospital; Assistant Professor, University of Manitoba, Winnipeg MB.

Estrogen plays a key role in the pathogenesis of breast cancer. Four randomized-controlled trials involving 28,000 women have evaluated the effect of tamoxifen on the incidence of invasive breast cancer in women at high risk of developing the disease. The largest of these was the Breast Cancer Prevention Trial, conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), that included more than 13,000 women.¹ Compared with placebo, tamoxifen significantly lowered the relative risk of invasive and noninvasive breast cancers by almost 50%. A meta-analysis of other tamoxifen prevention studies showed similar risk reduction in breast cancers.²

Raloxifene, like tamoxifen, is a selective estrogen receptor modulator (SERM), and is indicated for the prevention and treatment of osteoporosis. In earlier studies in women with osteoporosis, raloxifene also reduced breast cancer incidence but was not associated with uterine carcinoma.³ At this year's ASCO, investigators presented the results of NSABP's second breast cancer prevention trial. The largest of all such trials, it has median followup of 3.9 years.⁴ Eligible women had to be postmenopausal and have at least a 5-year predicted breast cancer risk of 1.66% based on the Gail Model (modified version).⁵ The incidence of invasive breast cancer was the same in the tamoxifen and raloxifene-treated groups. Fewer non-invasive breast cancers occurred in the tamoxifen group, but the difference was not statistically significant. This latter observation is not easily explained given the known stepwise progression of breast carcinogenesis from noninvasive to invasive cancer. Given the small number of events (57 cases of noninvasive cancers in the tamoxifen group and 80 cases in the raloxifene group), it could be a statistical aberration.

Women on raloxifene experienced significantly fewer thromboembolic events and cataracts, and a nonsignificant reduction in the incidence of uterine cancers. Of note, significantly fewer cases of uterine hyperplasia and hysterectomies

were seen among women taking raloxifene who were not diagnosed with uterine carcinoma. The quality of life sub-study⁶ found no significant differences in patient-reported outcomes for physical and mental health and depression. Women in the tamoxifen group reported better sexual function but more gynecologic problems, vasomotor symptoms, leg cramps and bladder control problems whereas those taking raloxifene reported more musculoskeletal problems, dyspareunia and weight gain. Interestingly, approximately 30% of women had discontinued study therapy in both arms at the time of analysis.

CLINICAL IMPLICATIONS

From these results, one can surmise that raloxifene has efficacy similar to tamoxifen in reducing breast cancer incidence in high-risk postmenopausal women and that it is associated with a lower incidence of thromboembolic events and possibly also uterine events. Premenopausal women were unfortunately not included in this trial, so it remains unclear whether the same observations about raloxifene apply to this population. One should also keep in mind that there is no evidence for raloxifene benefit in women with a history of invasive breast cancer or ductal carcinoma in situ. Although it may be attractive to prescribe raloxifene for osteoporosis therapy in women with known breast cancer, this is not recommended given the paucity of data in this particular situation. In addition there may be a potential drug interaction in those women taking an aromatase inhibitor (AI) as adjuvant endocrine therapy. A previous study of SERM and AI adjuvant therapy showed that the combination was inferior to an AI alone in terms of efficacy.⁷ Also, despite the potential benefits of raloxifene, toxicities raise concerns, especially in healthy women.

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The AIs are another group of drugs being investigated as possible prevention agents. The NSABP are planning the “STELLAR” trial, a study of raloxifene vs letrozole. Other prevention trials underway are the International Breast Cancer Intervention II (IBIS-2) trial of anastrozole vs placebo and the NCIC-CTG MAP3 trial of exemestane vs placebo in postmenopausal women at high risk of developing breast cancer.

For now, women considered at high risk for the disease should have counselling about the potential benefits and toxicities of tamoxifen and (in postmenopausal women) raloxifene, and then decide which drug, if any, is best for them. Development of decision aids may be useful in this regard. Meanwhile, the search for the optimal breast cancer prevention drug continues at a rapid pace.

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Head and neck cancer

LONG-TERM RESULTS OF INTERGROUP RTOG 91-11: A PHASE III TRIAL TO PRESERVE THE LARYNX—INDUCTION CISPLATIN/5-FU AND RADIATION THERAPY VERSUS CONCURRENT CISPLATIN AND RADIATION THERAPY VERSUS RADIATION THERAPY. ASCO 2006, ABSTRACT 5517.

Investigators: A.A. Forastiere et al.

TRIAL SUMMARY: The RTOG 91-11 trial randomized 515 patients with resectable Stage III–IV cancer of the glottic or supraglottic larynx to 3 groups: induction cisplatin + fluorouracil, followed by radiotherapy if they responded (I+RT, n = 173); concurrent cisplatin 100 mg/m² q 21 days for 3 cycles + radiotherapy (CRT, n = 171); or radiotherapy alone (R, n = 171). Patients had laryngectomy if they had a partial response to cisplatin + fluorouracil, if disease was persistent or recurrent, or if they had laryngeal dysfunction.

At 5 years, with median followup for surviving patients of 6.9 years, significantly more patients in the I+RT (44.6%) and CRT (46.6%) groups were alive without laryngectomy compared to those receiving radiotherapy alone (33.9%, p = 0.011 for both chemotherapies). Disease-free survival was best in the groups receiving I+RT (38.6%, p = 0.016) and CRT (39%, p = 0.0058), vs 27.3 in the radiotherapy-alone group. Overall survival was similar in all groups in the first 5 years, at 59.2% for I+RT, 54.6% for CRT and 53.5% for radiotherapy, but beyond 5 years fewer patients receiving I+RT had died (p = ns). **Table 2** shows these and other endpoints reported.

TABLE 2. Outcomes in patients with cancer of the glottic or supraglottic larynx in RTOG 91-11 at 5 years (median followup of survivors 6.9 years)

	induction cisplatin + fluorouracil + radiotherapy (I+RT)	concurrent cisplatin + radiotherapy (CRT)	radiotherapy alone (R)
disease-free survival	38.6% p = 0.016 vs R	39% p = 0.0058 vs R	27.3%
overall survival	59.2%	54.6%	53.5%
laryngectomy-free survival	44.6% p = 0.011 vs R	46.6% p = 0.11 vs R	33.9%
preserved larynx	70.5% p = 0.0029 vs CRT	83.6%	65.7% p = 0.00017 vs CRT
locoregional control	54.9% p = 0.0018 vs CRT	68.8%	51% p = 0.0005 vs CRT
distant metastases	14.3%	13.2%	22.3%

COMMENTARY: Denis Soulières, MD, MSc, FRCPC, Hematologist and Medical Oncologist, CHUM-Hôpital Notre-Dame, Montréal, QC

In the last few years, many published experiences of concurrent chemoradiation therapy (CRT) demonstrated improved survival and organ preservation compared to radiation therapy alone and established concurrent CRT as a new standard of therapy for patients with locally advanced Stages III, IV-A and IV-B head & neck cancer. No trial to date has compared

concurrent CRT to surgery +/- RT, however. Clinical guidelines published in Ontario and Quebec established concurrent CRT as a chief option for most patients.^{1,2} Most studies and meta-analyses demonstrating an OS advantage, however, included mainly patients with primary oropharynx tumours,^{3,4} and subgroup analysis of survival data is lacking.

In this trial in a defined and restricted population, the primary endpoint was survival without laryngectomy. A schedule of induction chemotherapy followed by radiation (I+RT) in patients with significant tumour regression had previously been shown to provide adequate organ preservation without jeopardizing survival.⁵ In this followup, survival at 5 years was similar, but many non cancer-related deaths occurred in the concurrent CRT group after 5 years. This significantly reduced the proportion of concurrent CRT patients who were alive beyond 5 years to a rate close to that reported for patients treated with RT alone. Although not reaching statistical significance, the I+RT arm showed a numerical advantage in survival and no excess in death rate.

CONCURRENT CRT STILL THE STANDARD?

This followup data calls into question previous recommendations on the best therapy to improve survival and laryngectomy-free survival in laryngeal cancer patients.⁶ In clinical practice, organ preservation should not be obtained at the expense of a possible reduction in survival. Moreover, recent data on chemotherapy regimens like CPF (cisplatin + docetaxel + fluorouracil) compared to CP (cisplatin + fluorouracil) demonstrate that an increase in tumour response rates and complete responses translates into an OS advantage.⁷⁻⁹ The utilisation of more potent and potentially more toxic chemotherapy regimens was shown to be feasible and generally safe in the induction phase. Concurrent CRT with more potent chemotherapy agents leads to significantly more side effects and a possible reduction in the radiation dose or intensity.¹⁰ Targeted therapy + RT was demonstrated to be superior to RT alone with tolerable side effects, but was not compared to CRT.¹⁰ Phase III trials are currently underway and/or in planning to evaluate chemotherapy + targeted epidermal growth factor receptor (EGFR) inhibition + RT compared to standard CP + RT.

In view of potentially more effective induction chemotherapy regimens, the data presented by Forastiere at ASCO 2006 raises the question of whether or not concurrent CRT regimens remain the best option for patients with locally advanced cancer of the larynx. Further studies are needed to evaluate different scenarios: high response-rate induction chemotherapy followed by radiation therapy with or without concurrent chemotherapy vs concomitant chemotherapy and radiation. Meanwhile, local experience, clinical judgment and interdisciplinary consultation amongst surgeon, radiation oncologist and medical oncologist remain the major factors that should guide clinicians in the therapeutic options offered to patients.

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Gastric cancer

RANDOMISED MULTICENTRE PHASE III STUDY COMPARING CAPECITABINE WITH FLUOROURACIL AND OXALIPLATIN WITH CISPLATIN IN PATIENTS WITH ADVANCED OESOPHAGOGASTRIC (OG) CANCER: THE REAL 2 TRIAL. ASCO 2006, ABSTRACT LBA4017.

Investigators: D. Cunningham et al.

TRIAL SUMMARY: With overall survival as the primary endpoint, the REAL 2 trial aimed to show non-inferiority of capecitabine to fluorouracil and of oxaliplatin to cisplatin in patients with previously untreated cancer of the esophagus, esophageal-gastric junction or stomach. The 1002 patients were randomized to 8 cycles of treatment with 1 of 4 regimens: epirubicin mg/m² intravenously (IV) every 3 weeks, cisplatin 60 mg/m² IV every 3 weeks + fluorouracil 200 mg/m² IV daily (ECF); epirubicin, oxaliplatin 130 mg/m² + fluorouracil (EOF); epirubicin + cisplatin + capecitabine 625 mg/m² twice daily PO (ECX) or epirubicin + oxaliplatin + capecitabine (EOX).

The median age of participants was 63 (range 22–83), 81% were male, 40% had gastric primary tumours, 89% had performance status of 0–1, 77% had metastatic disease, 88% had adenocarcinoma and 52% had poorly differentiated tumours. At median followup of 17.1 months 850 events had occurred. **Table 3** (page 26) shows overall survival and rates of Grade 3–4 toxicities of patients receiving the 4 regimens. The authors concluded that in triplet regimens used for the treatment of advanced esophageal-gastric cancer, capecitabine can replace fluorouracil and oxaliplatin can replace cisplatin.

TABLE 3. Overall survival and rates of Grade 3–4 toxicities of patients with advanced esophageal-gastric cancer in the REAL 2 trial

	ECF: epirubicin + cisplatin + fluorouracil (n = 263)	EOF: epirubicin + oxaliplatin + fluorouracil (n = 245)	ECX: epirubicin + cisplatin + capecitabine (n = 250)	EOX: epirubicin + oxaliplatin + capecitabine (n = 244)
1-year overall survival (95% CI)	37.7% (31.8% to 43.6%)	40.4% (34.2% to 46.5%)	40.8% (34.7% to 46.9%)	46.8% (40.4% to 52.9%)
Median overall survival	9.9 months	9.3 months	9.9 months	11.2 months
Hazard ratio (95% CI)	1	0.95 (0.79–1.15)	0.92 (0.76–1.11)	0.80 (0.65–0.97)*
Complete + partial response (95% CI)	40.7% (34.5% to 46.8%)	46.4% (40.0% to 52.8%)	42.4% (36.1% to 48.8%)	47.9% (41.5% to 54.3%)
Grade 3–4 non-hematologic toxicity	36%	42%	33%	45%
Grade 3–4 neutropenia	42%	30%	51%	28%

* p = 0.025 in comparison with ECF

COMMENTARY: Christian Kollmannsberger MD, Medical Oncologist, Vancouver Cancer Centre, BC Cancer Agency, Vancouver, BC.

The prognosis for people with gastroesophageal cancer (GEC) remains very unfavourable.¹ Patients still do poorly despite recent advances in therapy. The most active chemotherapy regimens are epirubicin + cisplatin + fluorouracil (ECF), docetaxel + cisplatin, fluorouracil (DCF) and irinotecan + fluorouracil. Within randomized Phase III trials these provide response rates of approximately 40% and median survival rates of about 9 months.^{2–5} No randomized study has reported median survival beyond 1 year, however. Survival rates in GEC compare poorly with the 20 months achieved in advanced colorectal cancer (CRC), despite similar response rates. In contrast to GEC, a number of new agents are now routinely used in the treatment of colorectal cancer including oxaliplatin, irinotecan, capecitabine and bevacizumab.

A NON-INFERIORITY RCT

The REAL 2 trial is the first large randomized study in gastric cancer to include capecitabine and oxaliplatin. The primary endpoint of this well-conducted non-inferiority study was OS between the 4 treatment arms. With 1002 patients enrolled, patient characteristics were well balanced in all 4 treatment groups. Approximately 10% of participants in each group had squamous cell carcinoma and approximately 20% had only locally advanced disease. The results achieved for the ECF regimen confirm those from previous studies and consolidate ECF’s status as a reference regimen for the treatment of metastatic GEC.^{2,6} Response rates with the 4 regimens were 40.7% (ECF), 46.4% (EOF), 42.4% (ECX) and 47.9% (EOX). Median survival times were, respectively, 9.9, 9.3, 9.9 and 11.2 months. For the first time ever in a randomized Phase III trial in this malignancy, a treatment regimen achieved median survival of more than 10 months (EOX, 11.2 months). This study was designed, however, as a non-inferiority trial of capecitabine vs infusional fluorouracil and oxaliplatin vs cisplatin. It met the primary endpoint, demonstrating that capecitabine is not inferior to fluorouracil

and oxaliplatin not inferior to cisplatin. Should we therefore use the “modern” EOX regimen as a new standard instead of ECF?

If a trial demonstrates non-inferiority, the experimental regimen should have a significant advantage over the standard regimen in order to serve as the new standard of care — such as lower toxicity, being easier to use, providing clinically meaningful better progression-free survival or quality of life, or being less expensive. In REAL-2, toxicities in the 3 experimental arms were not clearly less than in the standard ECF arm. All-cause 60-day mortality as well as hematologic Grade 3–4 toxicities were similar. The frequency of Grade 3–4 non-hematologic toxicities was also similar, although the pattern of toxicities was different. Significantly more Grade 3–4 neurotoxicity was observed with oxaliplatin as compared to cisplatin-based regimens (EOF 8.4%, EOX 4.4% vs ECF 0.4%, ECX 1.7%) whereas cisplatin-based regimens caused more thromboembolic events (ECF 18.1%, ECX 14.1% vs EOF 8.5%, EOX 8.4%). Capecitabine-containing regimens are easier to use than protracted infusion fluorouracil regimens, but all the tested regimens still contained infusional components. Further, no differences in quality of life scores (p > 0.01) were observed between arms for any change from baseline to 12 weeks, indicating that carrying an infusion pump did not significantly impact quality of life. Progression-free survival, between 6 and 7 months, was similar for all 4 regimens. Moreover, when looking simply at drug costs, capecitabine- and oxaliplatin-containing regimens are considerably more expensive than fluorouracil- and cisplatin-based regimens. Based on these results, capecitabine and/or oxaliplatin-containing regimens will be another treatment option in our armamentarium for the treatment of esophagogastric cancers, but should not be considered the new standard of care for all patients. Thus for those with renal insufficiency, auditory impairment or any other contraindications for

cisplatin, oxaliplatin is now a valuable alternative to cisplatin. If prolonged fluorouracil infusions are chosen, capecitabine is an alternative to fluorouracil.

Where do we go from here? Other new regimens tested within randomized Phase III trials in recent years are docetaxel + cisplatin + fluorouracil and fluorouracil + irinotecan.^{4,5} Both appear to have efficacy similar, but not superior, to the ECF regimen and are alternatives to ECF. Whether these different regimens are cross-resistant or can potentially be applied sequentially in patients with performance status remains to be tested in formal trials. It is hoped that molecular-targeted therapies will have a major impact in the treatment of this disease. First results of early studies are promising, but randomized trials are needed in order to define the role of these agents. The exploration of new treatment options including targeted therapies may

also allow us to develop effective second-line or even third-line chemotherapy similar to colorectal cancer and thus improve the poor prognosis of these patients.

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Rectal cancer

ROUTINE SHORT COURSE PRE-OP RADIOTHERAPY OR SELECTIVE POST-OP CHEMORADIOTHERAPY FOR RESECTABLE RECTAL CANCER? PRELIMINARY RESULTS OF THE MRC CR07 RANDOMISED TRIAL. ASCO 2006, ABSTRACT 3511.

Investigators: D. Sebag-Montefiore et al.

TRIAL SUMMARY: The Medical Research Council (MRC) CR07 trial compared results of 2 radiotherapy/chemoradiotherapy regimens combined with total mesorectal excision (TME) in 1350 patients with operable, non-metastatic rectal adenocarcinoma. Enrolled patients, who were recruited between March 1998 and August 2005, were randomized to receive either routine preoperative short-course radiotherapy (25 Gy in 5 fractions) (PRE) or — if their tumour came within 1 mm or less of the circumferential resection margin (CRM) — postoperative chemoradiotherapy (45 Gy in 25 fractions) + fluorouracil chemotherapy (POST). At 3 years' median followup, 96% of the PRE group had received the allocated treatment. In the POST group, 12% of 676 patients were CRM-positive and 71% of them received postoperative chemoradiotherapy. Adjuvant chemotherapy was offered as per local policy. Of the node-positive patients with a positive CRM, 72% of the PRE and 87% of the POST group received adjuvant chemotherapy. For node-negative, CRM-positive participants, 38% of the PRE and 41% of POST patients received adjuvant chemotherapy.

The incidence of anastomotic leaks was 8% vs 7% and 60-day mortality was 2.7% vs 3.1% in the PRE and POST arms respectively. At the time of analysis 23 PRE patients vs 61 POST had confirmed local recurrence, 98 vs 106 had distant metastases, and 115 vs 146 had died. The overall local recurrence rates were 6.5% for tumours of the lower rectal third, 5.8% in the middle third and 7.4% in the upper third. As shown in **Table 4**, the 3-year rates for local recurrence, the primary endpoint, were 4.7% in the PRE group vs 11.1% in the POST group (HR 2.47, 95%

TABLE 4. Local recurrence rates at 3 years in MRC CR07 trial of rectal cancer patients receiving short-course preoperative radiotherapy vs selective postoperative chemoradiotherapy

	PRE	POST	HR (95% CI)
Overall recurrence	4.7%	11.1%	2.47 (1.61–3.79)
CRM-negative	3%	10%	2.91 (1.74–4.88)
CRM-positive	16%	23%	1.56 (0.60–4.04)
lower third	6%	10%	2.0 (0.97–4.15)
middle third	5%	10%	2.14 (1.14–4.0)
upper third	1%	16%	4.94 (1.79–13.64)
Stage I	0%	3%	12.19 (1.64–90.41)
Stage II	2%	8%	3.47 (1.29–9.35)
Stage III	9%	17%	2.02 (1.20–3.42)

CI 1.61–3.79). Rates of DFS were 79.5% vs 74.9% (HR 1.31, 95% CI 1.02–1.67) and of OS, 80.8% vs 78.7% (HR 1.25, 95% CI 0.98–1.59). Several subgroup analyses were performed, also shown in **Table 4**. The authors concluded that routine short-course preoperative radiotherapy significantly reduces local recurrence and improves DFS at 3 years compared to this selective postoperative chemoradiotherapy approach.

continued on page 30

LOCAL RECURRENCE AFTER RECTAL CANCER RESECTION IS STRONGLY RELATED TO THE PLANE OF SURGICAL DISSECTION AND IS FURTHER REDUCED BY PRE-OPERATIVE SHORT COURSE RADIOTHERAPY. PRELIMINARY RESULTS OF THE MEDICAL RESEARCH COUNCIL (MRC) CR07 TRIAL. ASCO 2006, ABSTRACT 3512.

Investigators: P. Quirke et al.

TRIAL SUMMARY: In the MRC CR07 trial, as described above, a prospective pathological assessment of the quality of resection was performed according to specific criteria. Of the 1350 patients enrolled, 1232 were prospectively assessed for CRM and 1119 for plane of surgery. At 3 years, in the 12% of resected specimens with CRM involvement (tumour ≤ 1 mm), local recurrence was 18%, DFS was 50% and OS was 57%. In the CRM-negative patients (89%), local recurrence was 7%, DFS was 81% and OS was 84%.

Three surgical planes were described which graded the quality of the resection specimen. The goal of TME is to remove the mesorectal envelope intact without cutting

through the fat down to the muscularis. Overall, 53% of specimens were optimal with an intact mesorectum, in 34% the mesorectum was largely intact and in 13% it was not. The CRM-positive rates for the 3 groups were 9%, 12% and 19%, respectively. The corresponding 3-year local recurrence rates were 4%, 8% and 15% ($p = 0.0019$). Rates of local recurrence and DFS favoured short-course preoperative radiotherapy over selective postoperative chemoradiotherapy for all grades of surgical quality. The authors concluded that short-course preoperative radiotherapy combined with good quality surgery almost completely eliminates local recurrence of operable rectal cancer.

COMMENTARY: Dr. John Hay, MB BChir, FRCPC, FRCR, Clinical Professor, Department of Surgery, Division of Radiation Oncology, UBC; Radiation Oncologist, British Columbia Cancer Agency, Vancouver Cancer Centre.

This trial must be viewed in the context of the studies that preceded it. In 1986 Quirke et al¹ showed that a detailed analysis of the circumferential (radial) resection margin (CRM) predicted most of the pelvic recurrences of rectal carcinoma — many patients with positive margins developed a recurrence whereas most of those without did not. This observation ultimately led to the design of the MRC trial. At the same time a few surgeons were reporting very low pelvic recurrence rates with surgical techniques that paid particular attention to achieving as wide a radial margin as possible, known as total mesorectal excision (TME).²

In 1997 the Swedish Rectal Cancer Trial³ reported that short-course preoperative pelvic radiotherapy (25 Gy given in 5 daily fractions completed within 10 days of surgery) significantly reduced the risk of pelvic recurrence and improved survival after non-TME resection when compared to surgery alone. The Dutch Rectal Cancer Group⁴ compared TME to TME plus short-course preoperative radiation. Their trial accrued patients between January 1996 and December 1999 and showed a benefit for preoperative treatment. Meanwhile, the United Kingdom MRC — later joined by the NCIC-CTG — started to accrue patients to the trial reported above. The major differences between this and the Dutch trial are that postoperative chemoradiation was mandated for those with a positive CRM and that adjuvant chemotherapy was allowed, so some Stage II and most Stage III patients received it. The other relevant trial, reported by the German Rectal Cancer Study Group,⁵ compared preoperative with postoperative chemoradiation in patients with T3 or T4 or node-positive rectal cancer. This showed reduced long-term toxicity, reduced local recurrence (from 13% to 6% at 5 years) and higher rates of sphincter preservation in the preoperative treatment arm.

The 2 arms in the MRC trial were well balanced for the usual prognostic variables such as age, sex, performance status, distance of the tumour from the anal verge and type of resection performed. It confirmed the findings of the Dutch trial that preoperative radiotherapy did not significantly increase the risk of anastomotic leaks or perioperative mortality. It differed from the Dutch trial in that preoperative treatment in MRC CR07 benefited those with all tumour stages (and not just T3) and also those with tumours in the upper third of the rectum. Preoperative was more effective than postoperative treatment in overcoming the effect of a positive CRM, although the local recurrence rate of 16% in the PRE arm is still higher than desirable. One major criticism is that the postoperative radiation dose of 45 Gy may be inadequate to control residual disease. The German trial used a postoperative dose of 54 Gy and most of their patients had a clear CRM.

A key part of the trial was the quality control provided by the pathologist for surgical technique and the resulting improvements: the proportions of optimal specimens rose and poor specimens fell during the trial. This was reflected in the rate of CRM positivity which fell rapidly from $> 20\%$ to approximately 10% during the first 3 years of the trial.

CLINICAL IMPLICATIONS

So how does this trial affect the management of resectable rectal cancer? It emphasizes the importance of good surgical technique and highlights the role of the pathologist in providing assessment for quality control. It supports the routine use of short-course preoperative radiotherapy, with appropriate use of postoperative chemotherapy, in patients with resectable tumours of the upper two-thirds of the rectum. This held for all TNM stages although the absolute benefit for Stage I disease was only 3%.

The situation in the lower third is less clear. Short-course treatment does reduce pelvic recurrence, but offers no significant benefit in improving the rate of sphincter-sparing surgery. The Dutch group⁶ have reported an unacceptably high rate of CRM positivity (30%) after abdominoperineal resection (APR) for lower-third tumours; they suggested a change in surgical technique and increased use of preoperative chemoradiation in this group of patients. A recent report from BC⁷ has shown similarly high rates of CRM positivity in patients having an APR for lower-third tumours. So a good case can be made for preoperative chemoradiation for all lower-third tumours, both to increase the rate of sphincter preservation and to improve local control. Preoperative chemoradiation remains the standard of care for patients with clinically locally advanced tumours at all levels or for those in whom appropriate pre-

operative imaging suggests that the tumour or adjacent nodes may not be resectable with clear margins.

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Multiple myeloma

SUPERIORITY OF MELPHALAN-PREDNISONE (MP) + THALIDOMIDE (THAL) OVER MP AND AUTOLOGOUS STEM CELL TRANSPLANTATION IN THE TREATMENT OF NEWLY DIAGNOSED ELDERLY PATIENTS WITH MULTIPLE MYELOMA. ASCO 2006, ABSTRACT 1.

Investigators: T. Facon et al.

TRIAL SUMMARY: The Intergroupe Francophone du Myelome IFM99-02 study investigated the impact of adding thalidomide to frontline therapy with melphalan + prednisone (MP) compared to MP alone and to tandem autologous stem cell transplant in elderly patients (age 65–75 years) with newly diagnosed multiple myeloma (MM). The 3 treatment arms consisted of MP for 12 cycles (arm 1), melphalan + prednisone + thalidomide (MPT) for 12 cycles (arm 2), and vincristine, doxorubicin and dexamethasone (VAD) for 2 cycles followed by stem cell mobilization with cyclophosphamide and G-CSF support, followed by tandem autologous stem cell transplant with reduced-dose melphalan (100 mg/m²) for conditioning (arm 3).

At 12 months, the MPT regimen resulted in higher response rates: ≥ partial response (PR) 81%, with 16% complete response (CR), compared to MP (≥ PR 40%, with 2% CR) and to tandem autologous transplant arm (≥ PR 73%, with 17% CR). By the time of this third planned interim analysis, with median followup of 32.2 months and 447 of the planned 476 patients enrolled, the higher response rates with the MPT regimen translated into superior median PFS of 27.6 months

TABLE 5. Results of IFM96-01 at median followup of 32.2 months

Endpoint	MP + thalidomide (n = 124)	MP (n = 191)	MP + autologous transplant (n = 121)
progression-free survival	27.6 months	17.1 months (p < 0.001*)	19.4 months (p = 0.001*)
overall survival	53.6 months	32.2 (p = 0.001*)	38.6 (p = 0.004*)

* vs MP + thalidomide

and OS of 53.6 compared to MP (PFS 17.1 and OS 32.2 months) and tandem transplant (PFS 19.4 and OS 38.6 months) (Table 5). In view of the clear superiority of the MPT arm, enrollment was terminated. The authors concluded that the MPT regimen could be the reference treatment for elderly patients with newly diagnosed multiple myeloma.

COMMENTARY: Nizar Bahlis, MD, Medical Oncologist, Assistant Professor, University of Calgary, Division of Hematology and Bone Marrow Transplantation.

At the 2006 ASCO annual meeting the Intergroupe Francophone du Myelome presented results of their IFM99-02 study, which showed that adding thalidomide to standard therapy with melphalan and prednisone in elderly multiple

myeloma patients (aged 65–75 years) provided statistically significant PFS and OS benefits, as shown in Table 5.

The Italian Multiple Myeloma Network GIMEMA recently reported similar results.¹ Elderly patients with

LANDMARKS

newly diagnosed MM were randomized to receive 6 cycles of MP or 6 cycles of MPT, with thalidomide continuing until disease progression or relapse. Similar to the IFM99-02, the addition of thalidomide resulted in superior response rates ($p < 0.0001$) and longer event-free survival (EFS) ($p = 0.0006$). Combined complete or partial response rates were 76.0% for MPT and 47.6% for MP alone (absolute difference 28.3%, 95% CI 16.5–39.1), and the complete and near-complete response rates were 27.9% and 7.2% for the MPT and MP arms, respectively (near-complete response, a subcategory of partial response, requires disappearance of myeloma protein in serum and urine, with positive immunofixation). Two-year EFS rates were 54% for MPT and 27% for MP ($p = 0.0006$). Three-year survival rates were 80% for MPT and 64% for MP (HR for MPT 0.68, 95% CI 0.38–1.22, $p = 0.19$). During the first 9 months after randomization, no survival difference was noted between the 2 groups, likely because of higher treatment-related deaths with MPT. Thereafter, the 3-year survival rate was 89% in patients receiving MPT and 70% in those treated with MP ($p = 0.03$). The analysis of overall survival, however, included data from 27 patients (21% in the MP group who had disease progression and subsequently crossed over to receive thalidomide. This crossover may have also contributed to the lack of statistical significance in the OS analysis.

IMPORTANT DIFFERENCES IN TRIAL DESIGN

These two studies present compelling data in favour of adopting the MPT regimen as a standard frontline therapy for elderly patients with multiple myeloma. They may even provide the clinical evidence of efficacy required for approval of thalidomide by Health Canada. It is important, however, to emphasize that although the IFM99-02 and GIMEMA studies demonstrate the superiority of the MPT regimen, treatment duration was different in the 2 studies. MPT was administered for 12 cycles in the IFM99-02 vs 6 cycles in the GIMEMA study, and while thalidomide was discontinued after 12 cycles in IFM99-02, it was continued until disease progression in the GIMEMA study. One could argue that the Italian study investigates the impact of thalidomide maintenance rather than frontline treatment, raising the question of optimal dosing and duration of thalidomide to be used in this patient population.


TOXICITY CONCERNS

Finally it is important to emphasize that the addition of thalidomide to MP in the IFM99-02 study resulted in significant toxicity. Incidence of Grade 3 and 4 toxicities was higher, in particular thrombosis (MPT 12% vs MP 4%, $p = 0.03$), neutropenia (MPT 26% vs MP 48%, $p < 0.05$) and neuropathy (MPT 6% vs MP 0%, $p < 0.001$). The risk of thromboembolism was also higher with MPT in the GIMEMA study as well (MPT 12% vs MP 2%, $p = 0.001$). This led to the introduction of mandatory prophylaxis with low molecular-weight heparin in the MPT arm, which provided efficient reduction in the thrombosis risk.

THE NEW STANDARD FOR ELDERLY MM PATIENTS?

So where do we go from here? While the data is compelling, a few questions still need to be answered before MPT is fully adopted for newly diagnosed myeloma patients over the age of 65:

- Is MPT superior to standard dose conditioning with melphalan 200 mg/m² and stem cell rescue? This question clearly implies that a subpopulation of elderly patients is eligible for high-dose therapy with melphalan conditioning at 200 mg/m².
- What is the optimal duration and dose of thalidomide?
- How will thalidomide compare with other new biological agents such as lenalidomide and bortezomib² in this patient population?
- What is the optimal type and duration of thrombosis prophylaxis?

Clearly the treatment of multiple myeloma has entered a new era in the last decade and after several years of status quo we are privileged to have access to regimens that positively impact patient survival. The difficult tasks ahead are to identify the specific subgroups of patients who do or do not benefit from the new available treatments, and to balance the excitement about their efficacy with potential side effects and quality of life issues. 

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Disclosure

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