Randomised trials with impact on clinical practice

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Adjuvant trial in melanoma patients comparing rIFN-α to rIFN-γ to Iscador to a control group after curative resection of high risk primary (≥3 MM) or regional lymphnode metastasis (EORTC 18871)

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Purpose: In 1987 the EORTC-MCG embarked on a prospectively randomized and controlled adjuvant trial to evaluate the effectiveness of low dose rIFN-α2 (1 MU) or rIFN-γ (0.2 mg) both s.c. qod for 12 months in comparison with an untreated control group. The *Association of Medical Oncology (AIO)*, branch of the *German Cancer Society*, added a fourth arm with Iscodor (s.c. tiw) and a two-monthly quality of life exploration for the same treatment period.

Methods: All randomized patients were followed for the time to progression and duration of survival. Quality control of the histopathology and data verification were secured according to the bylaws of the EORTC. An intention-to-treat analysis was performed.

Results: From 1987 to 1996, a total of 830 pts. were randomized to one of the 3 (EORTC) or 4 (AIO) treatment/observation arms and followed for a median of 5.5 years. A total of 513 relapses and 435 deaths have been reported. At 6 years, the disease-free interval (DFI) rate was 34% and the survival was 42%. The treatment comparisons stratified by the initial stage of disease at randomization yielded non-significant results, regarding either the DFI (logrank P = 0.64) or the duration of survival (logrank P = 0.72). In terms of DFI the relative risk estimates (95% confidence intervals) were: 0.9 (0.75, 1.18) for the comparison rIFN-α2 vs. control 1.0 (0.80, 1.26) for rIFN-γ vs. control, and 1.33 (0.93, 1.89) for Iscador vs. control.

Conclusions: These results show that the clinical benefits of low dose IFN (α or γ) and of Iscador are most likely not important. Therefore these should not be prescribed as adjuvant treatments in high risk malignant melanoma patients.

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QUASAR: A UKCCCR study of adjuvant chemotherapy (CT) for colorectal cancer

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QUASAR is a large, simple, pragmatic trial which aims to determine which colorectal cancer patients should receive adjuvant CT and which CT regimen to use. Patients with a clear indication for CT, and without metastases or other evident residual disease, were randomised to receive 5-fluorouracil (370 mg/m^2) with either high (250 mg fixed dose) or low dose (25 mg) L-folinic acid, and coupled with either levamisole or placebo. The CT could be given, by clinician's choice, either as six 5-day courses at 4-weekly intervals or as thirty once weekly doses. Patients for whom there is substantial uncertainty whether or not they should receive CT are randomised equally between CT and observation only – with CT considered only on recurrence.

The trial opened in May 1994 and has randomised 6180 patients from 170 centres in the UK and elsewhere. The CT comparisons closed in October 1997 with 4927 and 4863 randomised in the folinic acid dose and levamisole comparisons, respectively. So far, there have been 1390 deaths and 1591 recurrences reported. Survival was non-significantly worse with levamisole than placebo (odds ratio 1.10; 95% confidence interval 0.99 to 1.23; p = 0.07), and with high-dose compared to low-dose L-folinic acid (OR 1.07; CI 0.96 to 1.19; p = 0.20), precluding any worthwhile benefit from levamisole or high dose FA in these regimens. Updated results will be presented.

The uncertain indication randomisation continues with 1860 randomised towards a target of 2500. Patients allocated CT now all receive 5-FU with low-dose folinic acid. Because it is uniquely large the QUASAR study CT comparisons are uniquely reliable. With continued support, the QUASAR CT vs observation randomisation will also provide much more reliable evidence on the value of CT, in particular among Dukes B and rectal cancer patients.

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Long term results of immediate adjuvant hormonal therapy with goserelin in patients with locally advanced prostate cancer treated with radiotherapy – A phase III EORTC study

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Purpose: To increase the survival of patients with locally advanced prostate cancer by combining a conventional external irradiation and an adjuvant hormonotherapy initiated at the very start of the treatment.

Methods: In the period 1987–1995, 415 patients under 81, were randomly allocated between the combined approach and radiotherapy alone, followed by the same hormonotherapy in case of relapse. The median age was 71 years. In both arms, 50 Gy were delivered to the pelvis in 5 weeks, and 70 Gy in 7 weeks to the prostate. Hormonotherapy was given by a monthly subcutaneous injection of Zoladex^r 3.6 mg (goserelin) continued for a period of 3 years.

Results: With a median follow-up of 61 months, hormonotherapy has resulted in an increase of 5-year local control from 79 to 97% (P < 0.001) and clinical disease free survival from 40 percent to 75% (P < 0.001); this has led to a significant increase in 5-year overall survival from 62 percent to 78% (P < 0.001) in favor of the combined modality treatment.

Conclusion: These updated results confirm the previous data (Bolla M et al. N Engl Med 1997; 337: 295–300): adjuvant LHRH analogue (goserelin) started at the onset of external irradiation improves overall survival.

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Randomized trial of chemoprevention with vitamin A and N-acetylcysteine in patients with cancer of the upper and lower airways: The EUROSCAN study

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Purpose: Euroscan, the large-scale trial to assess the effects of Vitamin A and N-acetylcysteine in patients with early stage head and neck cancer or lung cancer after treatment with curative intent started in 1988.

Methods: The study has a 2 × 2 factorial design with the following treatments: 1) retinyl palmitate (300,000 IU daily during the first year and 150,000 IU daily in the second year), 2) NAC (600 mg daily during two years), 3) the combination of both and 4) no intervention.

Results: 2573 patients from 76 European institutes in 15 countries were randomized to one of the 4 treatment arms. 1065 (41.4%) presented with laryngeal cancer, 485 (18.8%) with oral cancer and 1023 (39.8%) with lung cancer. The median age at study entry was 61 years, 13.0% were females and 6.5% reported to never have smoked. Twenty three percent of the 1932 patients randomized to receive one of the interventions stopped treatment before completion of the planned 2 years. Toxicity was observed more often in the retinyl arms with 45% of the patients experiencing some degree of toxicity. After a median follow-up of 49 months, a total of 916 patients have been reported with a recurrence, a 2nd primary tumor (SPT) or/and death. The first event reported was a recurrence in 572 patients, a tobacco related 2nd tumor in 154 cases and a non-tobacco related 2nd tumor in 57 cases. Results by treatment in terms of duration of survival, disease free survival and 2nd tumors will be presented.