3-month versus 6-month adjuvant chemotherapy for patients with high-risk stage II and III colorectal cancer: 3-year follow-up of the SCOT non-inferiority RCT

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Scientific summary

SCOT RCT: 3-year follow-up

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Scientific summary

Background

Patients with high-risk stage II or stage III colorectal cancer usually undergo surgical resection, followed by 6-month adjuvant chemotherapy. Administration of an oxaliplatin and fluoropyrimidine-based adjuvant chemotherapy regimen improves disease-free survival but is associated with a problematic toxicity profile; in particular, dose-dependent, cumulative peripheral neuropathy is a key toxicity that can persist long term despite the treatment for colorectal cancer having been curative. The toxicity of oxaliplatin and fluoropyrimidine regimens is cumulative, so reducing adjuvant treatment duration could ameliorate such effects; however, whether or not shortening the duration of adjuvant treatment could compromise its efficacy is debated.

The cost of colorectal cancer treatment in the year after diagnosis is considerably higher than that of treating other common cancers. Three-month adjuvant chemotherapy could be anticipated to be more cost-effective than the current standard 6-month treatment, provided that efficacy is maintained.

The Short Course Oncology Therapy (SCOT) study was designed to compare 3-month and 6-month oxaliplatin-based adjuvant chemotherapy in patients with colorectal cancer in terms of efficacy, toxicity, health-related quality of life and economic aspects.

Objectives

The objectives of the study were to assess the efficacy of 3-month versus 6-month adjuvant chemotherapy for colorectal cancer and to compare the associated toxicity and health-related quality of life. The primary end point of the study was disease-free survival, with the null hypothesis being that 3-month chemotherapy is inferior to 6-month chemotherapy with a hazard ratio of > 1.13. Secondary end points were overall survival, safety, health-related quality of life and cost-effectiveness parameters.

The economic evaluation explored the cost-effectiveness of 3-month versus 6-month adjuvant chemotherapy (in terms of incremental cost, quality-adjusted life-year gains and net monetary benefit with a willingness-to-pay threshold of £30,000/quality-adjusted life-year), using trial data on treatment and hospitalisation costs, health-related quality of life, and survival outcomes within the timeframe of the SCOT clinical trial.

Methods

The SCOT trial was an international, randomised (1 : 1), open-label (non-blinded), non-inferiority, Phase III, parallel-group trial comparing 3 months with 6 months of oxaliplatin plus fluoropyrimidine adjuvant chemotherapy in patients with high-risk stage II or stage III colorectal cancer. The study was conducted in 244 oncology clinics in six countries (the UK, Denmark, Spain, Sweden, Australia and New Zealand). Eligible patients were adults aged ≥ 18 years who had undergone curative resection for high-risk stage II (having one or more of the following risk features: T4 disease, tumour obstruction and/or perforation of the primary tumour, < 10 lymph nodes harvested, poorly differentiated histology, perineural invasion or extramural venous/lymphatic vascular invasion) or stage III adenocarcinoma of the colon or the rectum.

Patients were randomised (one to one) to receive either 3 months or 6 months of treatment using a minimisation algorithm incorporating a random component. Minimisation factors were study centre, treatment regimen, sex, disease site (colon or rectum), N stage (X, 0, 1 or 2), T stage (X, 0, 1, 2, 3 or 4), and capecitabine starting dose (for those receiving oxaliplatin and capecitabine). The adjuvant treatment regimen used could be oxaliplatin with 5-fluorouracil or oxaliplatin with capecitabine, with the treatment selected on an individual-patient basis to reflect the choice of the patient and/or physician.

Disease-free survival was defined as the time from randomisation (or trial registration for those randomised after 3 months of therapy) to relapse, development of a new colorectal cancer, or death from any cause. Overall survival was defined as the time from randomisation (or registration for those randomised at 3 months) to death from any cause. Comparison of disease-free survival between treatment groups was based on a Cox regression model incorporating minimisation factors as covariates; the population selection was intention to treat.

Toxicity was assessed by the investigators after each cycle of chemotherapy, with adverse events graded using the National Cancer Institute common terminology criteria for adverse events (version 3). Patients were followed up for a minimum of 3 years to a maximum of 8 years. Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer questionnaires QLQ-C30 and QLQ-CR29, and using EuroQol-5 Dimensions, three-level version. Neuropathy was assessed with the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx4) questionnaire.

The economic analysis was undertaken from the perspective of the UK NHS and Personal Social Services for 2016. The effectiveness measure for the economic analysis was the discounted quality-adjusted life-year gain per patient. Overall survival data were partitioned into three health states, (1) time on treatment, (2) disease free and (3) recurrence, with Kaplan–Meier sample averages used to compute the quality-adjusted survival time in each health state over the 8-year within-trial period; a separate model estimated health-related quality of life for each health state. Costs associated with patient treatment were calculated by measuring and valuing resources used by patients during the treatment and follow-up periods. The total cost of treatment per patient was estimated as the Kaplan–Meier survival analysis, considering the main cost categories of chemotherapy treatment and hospitalisation. Bootstrapping was used to account for uncertainty of the results and probabilistic sensitivity analysis was reported through confidence intervals and cost-effectiveness acceptability curves.

Results

A total of 6088 patients from 244 centres were randomised into the trial between 27 March 2008 and 29 November 2013: 5244 patients were randomised at 164 study centres in the UK, 311 patients were randomised at 10 centres in Denmark, 237 patients were randomised at 19 centres in Spain, 197 patients were randomised at 32 centres in Australia, 83 patients were randomised at 14 centres in Sweden and 16 patients were randomised at five centres in New Zealand. Of these, 6065 patients were included in the intention-to-treat analysis population and 6022 patients started study treatment. Data cut-off point for the analyses was 1 December 2016, at which time patients in both treatment groups had reached a median follow-up of 37 months.

Baseline data identified approximately 60% of patients as male and 40% as female, with the median age being 65 years. Most patients (> 80%) had a diagnosis of colon cancer and approximately 80% had stage III disease. For about 67% of patients, the planned treatment comprised oxaliplatin and capecitabine, with the remaining 33% of patients planned to receive oxaliplatin and 5-fluorouracil. Baseline characteristics were comparable for the 3-month and 6-month treatment groups.

Overall, 83.3% of patients randomised to the 3-month treatment group received 3 months of treatment and 58.8% of those randomised to the 6-month treatment group received 6 months of treatment; 6.9% of patients randomised to the 6-month treatment group stopped treatment at 3 months. The most common reason for not completing 6 months of treatment was an inability to tolerate the associated toxicity. The median percentage of the full fluoropyrimidine dose delivered was 95.3% for the 3-month and 83.2% for the 6-month treatment group; the median percentage of the full oxaliplatin dose delivered was 96.6% for the 3-month and 70.2% for the 6-month treatment group.

By the time of analysis, there were 1482 disease-free survival events (740 in the 3-month treatment group and 742 in the 6-month treatment group). The 3-year disease-free survival rate was 76.7% (standard error 0.8%) for the 3-month treatment group and was 77.1% (standard error 0.8%) for the 6-month treatment group; this equated to a hazard ratio of 1.006 (95% confidence interval 0.909 to 1.114; *p*-value for non-inferiority = 0.012). The study, therefore, confirmed non-inferiority for 3-month versus 6-month oxaliplatin-based adjuvant chemotherapy. By the time of analysis, there were 787 deaths, with the 3-year overall survival rate for the 3-month treatment group being 90.0% (standard error 0.6%) and for the 6-month treatment group 89.6% (standard error 0.6%), equating to a hazard ratio of 0.994 (95% confidence interval 0.964 to 1.143; *p*-value for non-inferiority = 0.035).

Treatment safety/toxicity was assessed for 868 patients. The most common adverse events seen during the study were alopecia, anaemia, anorexia, diarrhoea, fatigue, hand–foot syndrome, mucositis, sensory neuropathy, neutropenia, pain, rash, altered taste, thrombocytopenia and watery eye; these adverse events showed a statistically significant increase in severity for the 6-month treatment group compared with the 3-month treatment group. Sensory neuropathy, diarrhoea, neutropenia, fatigue, pain, nausea and hand–foot syndrome were the most common grade ≥ 3 adverse events reported, with statistically significant differences observed between treatment groups for diarrhoea ($p = 0.033$), neutropenia ($p = 0.023$), pain ($p = 0.014$), hand–foot syndrome ($p = 0.031$) and sensory neuropathy ($p < 0.001$). The most marked increase in the proportion of patients with grade ≥ 3 with 6-month adjuvant chemotherapy was for sensory neuropathy (16.4% vs. 4.3% with 3-month treatment). Serious adverse reactions were reported for 421 patients in the 3-month treatment group and for 511 patients in the 6-month treatment group. Thirty-two patients died as a result of events attributed to treatment toxicity, with the events distributed equally between the randomised groups (16 patient deaths for both the 3-month and the 6-month treatment groups).

Peripheral neuropathy was also assessed using the FACT/GOG-Ntx4 questionnaire, with data available for 2871 patients who were assessed for up to 7 years. The neurotoxicity standardised adjusted area under the curves for questionnaire scores differed markedly between treatment groups ($p < 0.001$), with a higher rate of neuropathy for the 6-month treatment group being apparent from 4 months and persisting to ≥ 5 years ($p < 0.001$).

Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer QLQ-C30 and CR29 ($n = 1829$) and EuroQol-5 Dimensions, three-level version ($n = 1828$) and the area under the curves was compared. European Organisation for Research and Treatment of Cancer QLQ-C30 global health status and functional and symptom scales demonstrated a statistically significant difference between treatment groups. Scores for the two groups mirrored each other for the first 3 months of treatment but subsequently showed functional improvement and decreased side effects in those who stopped treatment at 3 months. The largest difference between the treatment groups was seen at 6 months and, thereafter, mean values became more comparable as patients completed 6 months of treatment. For the European Organisation for Research and Treatment of Cancer QLQ-CR30, a subset of symptoms showed statistically significant differences, indicating fewer side effects in patients who received 3-month adjuvant chemotherapy (body image, $p = 0.037$; dry mouth, $p < 0.001$; hair loss, $p = 0.035$; taste alteration, $p < 0.0001$). The magnitude of the mean differences in functional and global health status scales between treatment groups was indicative of 'moderate' differences in global health status, role functioning and social function and 'a little' difference in physical, emotional and cognitive functions. Statistically significant

differences in area under the curves between the treatment groups were also seen for both the EuroQol-5 Dimensions self-rated visual analogue scale ($p = 0.00081$) and the EuroQol-5 Dimensions, three-level version health index ($p = 0.00081$), with differences apparent from months 4 to 6.

Adjuvant chemotherapy costs were higher for the 6-month treatment group ($p < 0.001$) and hospitalisation costs differed between treatment groups from 4 to 6 months after the start of treatment ($p < 0.001$). However, 6-month adjuvant chemotherapy was also associated with higher hospitalisation costs over the 7- to 12-month period ($p = 0.030$), possibly reflecting the persistence of treatment-related complications. No difference in cost was seen between the treatment groups after 12 months. Overall, the cost was significantly higher for the 6-month treatment group ($p < 0.001$), driven primarily by hospitalisation (–£2835) rather than the by cost of the adjuvant chemotherapy agents (–£1829). The 3-month treatment strategy was dominant, as it was cost saving and showed an improvement in quality-adjusted life-years, with an incremental net monetary benefit of £7246 per patient. Three-month adjuvant chemotherapy for colorectal cancer showed 99% probability of being cost-effective across the UK decision threshold range of £20,000–30,000 per quality-adjusted life-year.

Conclusions

The SCOT study showed that the efficacy of 3 months of oxaliplatin-containing adjuvant chemotherapy is non-inferior to 6 months of the same regimen; 6-month treatment was also associated with considerably higher levels of toxicity, particularly neurotoxicity, which can be chronic. Compared with traditional 6-month adjuvant chemotherapy, the 3-month treatment strategy costs significantly less and has no significant detrimental impact on patient outcomes (health-related quality of life and survival). Three-month oxaliplatin-based chemotherapy should, therefore, be considered as an option as adjuvant therapy for patients with high-risk stage II or stage III colorectal cancer, particularly when using oxaliplatin and capecitabine combination therapy.

Recommendations for research

The SCOT trial raised questions regarding whether 3-month treatment is applicable when using oxaliplatin and 5-fluorouracil as the adjuvant regimen or when treating patients with high-risk disease (T4 or N2 pathology). Further research should be conducted to identify any specific patient groups (e.g. patients with specific high-risk pathological features) for whom 6 months of adjuvant chemotherapy might be appropriate and if this is dependent on the regimen selected. The translational tissue samples from the SCOT study (3383 tumour samples and 3100 blood samples) and other similar studies should be used to build molecular predictors of which patients may benefit from a longer treatment duration. Some of this work is currently underway for the SCOT study.

Trial registration

This trial is registered as ISRCTN23516549 and EudraCT 2007-003957-10.

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