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LETTER TO THE EDITOR

Perioperative and adjuvant chemotherapy in colon cancer: results of SAKK trial 40/93

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Dear Editor:

The liver is a common site for the development of metastases in colorectal cancer. Since spread from the primary cancer site is believed to happen via the portal vein, attempts have been made to apply chemotherapy via this route in the immediate postoperative period in order to eliminate micrometastases in the liver. Following encouraging reports by others, the Swiss Group for Clinical Cancer Research (SAKK) has performed a large trial (SAKK 40/81) comparing perioperative intraportal adjuvant chemotherapy with 5-fluorouracil (5-FU) and mitomycin C with surgery alone (Swiss Group for Clinical Cancer Research, Lancet 1995).

In this randomized multicenter trial, there was a significant survival advantage following perioperative intraportal chemotherapy. In 1987, prior to the analysis of SAKK 40/81, the SAKK initiated a subsequent randomized three-arm trial (SAKK 40/87) which compared among perioperative intraportal chemotherapy, the same intravenous chemotherapy and surgery alone. In 1993, after a significant survival benefit had been shown by the use of adjuvant 5-FU in combination with levamisol (Moertel et al., N Engl J Med 1990), the SAKK initiated a new three-arm trial (SAKK 40/93), where all patients received perioperative intraportal or intravenous chemotherapy and were then randomised to additionally receive no further treatment (arm A) or 5-FU 450 mg/m^2 iv bolus weekly for 12 months in combination with levamisol (arm B) or 5-FU 600 mg/m^2 iv bolus for 12 months (arm C). Due to the fact that the previously reported adjuvant treatments with 5-FU and levamisol had been restricted to colon cancer and adjuvant radiochemotherapy by then had been established in rectal cancer, in SAKK 40/93, only colon cancer patients have been included. After 3.5 years and the inclusion of 284 patients, the trial had to be closed because the first results of SAKK 40/87 became available that failed to confirm an advantage of perioperative intraportal chemotherapy over surgery only (Laffer et al., Int J Colorectal Dis epub August 8, 2008). In this letter, we would like to report the results of this prematurely terminated trial, SAKK 40/93.

Between September 1993 and May 1997, 284 [one withdrew consent for his data, so only 283 patients were evaluable] out of 1,500 planed patients have been randomized from 24 institutions in Switzerland, Germany, and Luxembourg. Patient eligibility criteria included stages II (pT 3/4, N0, M0) and III (any pT, pN+, M0), potentially curative resection, no previous radio- or chemotherapy, normal organ function, and absence of severe concomitant disease.

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Matthias Lorenz deceased.

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All analyses have been performed on an intention-to-treat basis. In addition, for German-speaking patients, a quality-of-life subtrial has been performed, the results of which have been published elsewhere (Bernhard et al. Ann Oncol 1999.).

Patient characteristics

Fifty-eight percent were male, 56% were <65 years of age, median age was 63 years, 54% stage II, 83% received intravenous perioperative chemotherapy.

Mostly, minor complications due to perioperative chemotherapy have been observed in 13% (intraportal) and 9% (intravenous), respectively.

Of 188 patients randomized to adjuvant chemotherapy, 21 never received any, mostly due to patient refusal. In a further ten patients, documentation of chemotherapy was not available. This left 80 patients in arm B and 77 patients in arm C evaluable for chemotherapy. In arm B (5-FU 450 mg/m^2), 94% of those who started chemotherapy completed 6 months and 65% completed 12 months. In arm C (5-FU 600 mg/m^2), 75% completed 6 months and 51% completed 12 months. In arm B >80% of the planed overall dose of 5-FU could be administered to 67% of treatment periods (12 weeks each), in contrast to only 50% in arm C.

Grade 3 or 4 non-hematologic toxicities have been observed in 9% of patients on arm B and in 12% on arm C, mostly diarrhea, during the first 12 weeks of the study. Hematologic toxicity was rare and there were no differences between these two arms.

The primary endpoint of this trial was disease-free survival. At 5 years, the event-free survival rates were 64%, 68%, and 68% for treatment arm A, B, and C with no statistical difference. Also, overall survival was not different between treatment arms.

Exploratory multivariate Cox regression analyses confirmed male sex, N+ stage, T4, and age >65 years as unfavorable prognostic indicators both for DFS and OS. While treatment on arm C as compared to arm A was associated with a significant DFS advantage (HR 0.279, p=0.032).

In conclusion, this initially slowly accruing trial had to be closed early for ethical reasons after new evidence had emerged from the earlier trial. The patient numbers available for analysis are far too small to draw any reliable conclusion. However, one of the research questions, namely, whether dose intensity is important in the adjuvant treatment of colon cancer remains still open. This trial demonstrates that higher bolus doses of 5-FU can be given in the adjuvant setting without major toxicities, although many patients had to have their doses reduced as time went by. The finding that patients in arm C appeared to fare better and the fact that women who are known to have a lower tolerance to 5-FU do better overall, would support more research of this issue.