Current stages of adjuvant treatment of colon cancer

C. H. Köhne1,2,3*

1Clinic for Oncology/Hematology, Klinikum Oldenburg gGmbH, Oldenburg; 2Carl von Ossietzky University Oldenburg, Oldenburg; 3Clinic for Oncology/Hematology, European Medical School Oldenburg, Groningen, Germany

Key words: adjuvant therapy, chemotherapy, colon cancer, elderly

adjuvant treatment in stage II colon cancer

In 1990, Moertel et al. [1] established the use of adjuvant therapy with fluoropyrimidine in stage III colon cancer. While the initial treatment had a duration of 1 year, subsequent studies demonstrated equivalent efficacy for a 6-month treatment duration with 5-fluorouracil (5-FU) in combination with folinic acid (FA) [2]. The absolute increase in survival gain is ∼15%.

Investigators from the X-act study [3] reported that the oral fluoropyrimidine capecitabine was non-inferior to the classical bolus 5-FU/FA regimen. A total of 1987 patients entered this study. Of note is that the initially applied capecitabine dose of 2500 mg/m² given on days 1–14, repeated on day 21 had to be reduced in ∼60% of patients due to gastrointestinal toxic effect and hand–foot syndrome. This creates some uncertainty for those patients, in which capecitabine rather than i.v. 5-FU is considered. Patients treated with capecitabine had a 5-year overall survival of 71.4% when compared with 68.4% for patients with bolus 5-FU folinic acid. The hazard ratio of 0.86 even indicated a slight albeit non-statistically significant superiority of capecitabine over bolus 5-FU/folinic acid (P-value of 0.06). Nevertheless, this study demonstrated that capecitabine is an alternative to i.v. bolus 5-FU/folinic acid.

André et al. [4] reported that infusional 5-FU in combination with oxaliplatin (FOLFOX 4 regimen) was superior over infusional 5-FU–folinic acid alone with a hazard ratio of 0.80 [95% confidence intervals (CIs) 0.65–0.97] and an absolute survival gain of 4.2% (P-value 0.023) in stage III colon cancer patients at 6 years. Such results were subsequently confirmed by the National Surgical Adjuvant Breast and Bowel Project (NSABP) study C-07 [5] using bolus 5-FU–oxaliplatin (FLOX) instead of infusional FOLFOX. The indirect toxic effect comparison of the United States and the European region favours FOLFOX over FLOX. Based on these results, we would expect an additional 4% gain in survival accounting for a total of ∼20% for patients treated with FOLFOX when compared with those who received surgery only (Figure 1).

Haller et al. [6] randomised a total of 1886 patients to receive the classical bolus 5-FU/folinic acid regimen or capecitabine in combination with oxaliplatin, at 7-year follow-up. A hazard ratio of 0.83 (95% CI 0.70–0.99, P-value = 0.0367) indicated that also capecitabine–oxaliplatin was able to improve the overall survival with a reduction of death due to colon cancer by 6%. There is no direct comparison of FOLFOX versus capecitabine–oxaliplatin in the adjuvant setting. To gain an understanding of the relative benefits of capecitabine, capecitabine–oxaliplatin, bolus 5-FU–oxaliplatin and infusional 5-FU–oxaliplatin (FOLFOX) against standard bolus 5-FU/folinic acid the results regarding hazard ratios, absolute differences and P-values are displayed in Table 1. According to this cross-trial comparison, FOLFOX appears to be the most efficacious one based on the hazard ratio of 0.80 (95% CI 0.66–0.98). The hazard ratio of capecitabine alone (0.86, 95% CI 0.69–1.01) is very close to the combination of capecitabine–oxaliplatin (0.83, 95% CI 0.70–0.99) reinforcing capecitabine as an alternative to oxaliplatin-containing regimens in those patients in which oxaliplatin is not desirable or acceptable due to side-effects or other reasons. Nevertheless, the 95% CIs of those hazard ratios are overlapping and physicians are encouraged to consider either of these regimens for their individual patients. Oxaliplatin is associated with long-lasting neuropathy. Fortunately, higher grades are mostly reversible after 1 year. Lower grades of toxic effect may last for several years and may be a burden to individual patients. As the survival gain is only estimated to be ∼4% in addition to what has already been achieved with 5-FU/FA alone, a careful estimate of the benefit and toxic effects shall be discussed with the patient.

adjuvant treatment in elderly patients

While in stage III colon cancer patients, adjuvant chemotherapy with FOLFOX is considered to be the standard of care, its efficacy in elderly patients is under debate. According to population-based registries (Surveillance Epidemiology and End Results (SEER)), nearly 40% of patients diagnosed with colorectal cancer are above the age of 75 of which about 12% are >85 years old [7]. Along with these data, the median life expectancy of a 80-year-old man is estimated to be 7 years and of women 9 years [7]. Thus, also elderly patients will potentially benefit from a reduction of colorectal cancer death by adjuvant chemotherapy. Pooled data with 5-FU/folinic acid as adjuvant treatment confirm that also patients >70 years of age benefit from adjuvant chemotherapy.
when compared with their younger counterparts [8]. According to registry data collected by Schrag et al. [9], patients >80 years or age will receive adjuvant chemotherapy in only ~30% when compared with younger patients who may receive adjuvant chemotherapy in ~80% of cases. Several reasons may account for this disparity which may already be based on concerns about the fitness to receive treatment due to underlying co-morbidities, could be related to patients preference, physician judgements and the social support and other reasons.

Nevertheless, retrospective data of patients who had entered clinical trials indicate a similar benefit for the use of 5-FU/ folinic acid containing regimens in younger and elderly patients [10].

While the adjuvant use of 5-FU/FA can be regarded as certain in elderly patients, oxaliplatin combinations result in a higher toxic effect over 5-FU/FA and create further uncertainty for its use in elderly patients. In contrast to the administration of 5-FU/FA, retrospective analyses of the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) [4] and CO7 study [5] revealed that the benefits of adjuvant oxaliplatin-containing regimens were only seen in patients <70 years of age. In the most recent study using capecitabine and oxaliplatin versus bolus 5-FU/leucovorin, data in elderly patients >70 years of age were also less favourable when compared with patients of younger age [11] (HR 0.86 95% CI 0.69–1.08 versus 0.94 95% CI 0.66–1.34). In a recent publication [12], pooling together data from NSABP C08, Avant, Xeloxa and the X-Act trial, Haller et al. claim a disease-free and overall survival benefit of oxaliplatin-containing regimens regardless of co-morbidities score and age. Other data from large databases as presented by Sanoff et al. [13] demonstrated little to no benefit of oxaliplatin when added to the adjuvant chemotheraphy of 5-FU. Interestingly, there was a benefit demonstrated for the general administration of 5-FU; however, this could not be seen for the subgroup of patients that received oxaliplatin-based chemotherapy. Cen et al. [14] looked at the SEER database from 2003 to 2005 and identified over 46 000 patients above the year of 65. Only 12% of those patients had received 5-FU as adjuvant chemotherapy and only 5% in combination with oxaliplatin. There was an increase in the adverse events and particularly associated with the use of oxaliplatin.

These data may be summarised as such: (i) there is a low rate of adjuvant chemotherapy administered to elderly patients. (ii) There is a survival benefit observed with the use of fluoropyrimidines but no survival benefit in general for oxaliplatin. (iii) The administration of oxaliplatin is associated with higher rates of toxic effect; however, it is highly utilised in academic centres (>70%) [13]. (iv) Physicians will have to take a careful individual decision whether to use or not to use oxaliplatin-containing regimens taking into account the co-morbidities of the patients.

![Figure 1. Estimation of the absolute gain of adjuvant chemotherapy on survival for stage III colon cancer.](image)

### bevacizumab included in adjuvant chemotherapy regimens

Several attempts were undertaken to include the new biologicals into the adjuvant setting. Allegra et al. [15] presented at ASCO 2011 the data of the NSABP-C08 study. Within the NASBO-C08 study over 2000 patients were randomized to either receive FOLFOX alone or in combination with bevacizumab. The overall survival of both patient groups did not differ. There was a transient progression free survival advantage for patients in the bevacizumab arm. This difference was however not statistically significant.

The second study presented by Andre et al. [16] at ASCO 2011, in which patients either received FOLFOX, FOLFOX–bevacizumab or capecitabine–oxaliplatin–bevacizumab also demonstrated no advantage for the use of bevacizumab combinations when compared with FOLFOX4. In fact, the hazard ratio of 1.17 (95% CI 0.98–1.39) for FOLFOX–bevacizumab and the hazard ratio of 1.07 (95% CI 0.90–2.28) for capecitabine, oxaliplatin–bevacizumab both indicated a slightly lower overall survival when compared with standard care.

### Table 1. Estimation of the absolute gain of adjuvant chemotherapy on survival for stage III colon cancer

<table>
<thead>
<tr>
<th>Comparison with bolus 5-FU/folinic acid</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>Absolute difference (%)</th>
<th>Follow-up (years)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX</td>
<td>0.80 (0.65–0.97)</td>
<td>4.2</td>
<td>6</td>
<td>0.023</td>
</tr>
<tr>
<td>Capcitabine</td>
<td>0.86 (0.74–1.01)</td>
<td>3.0</td>
<td>6.9</td>
<td>0.06</td>
</tr>
<tr>
<td>Capcitabine/G–oxaliplatin</td>
<td>0.83 (0.70–0.99)</td>
<td>4</td>
<td>7</td>
<td>0.037</td>
</tr>
<tr>
<td>FLOX</td>
<td>0.85 (0.72–1.00)</td>
<td>2.7</td>
<td>5</td>
<td>0.052</td>
</tr>
</tbody>
</table>
Thus, there is now evidence from two randomised trials that bevacizumab is not adding efficacy to adjuvant FOLFOX over the use of FOLFOX alone. One may speculate about the reason for these consistent albeit disappointing findings. First of all, the use of in first-line metastatic disease bevacizumab is currently under revision in metastatic colorectal cancer [17]. Newer randomised trials conducted in metastatic disease did not result in an increased objective response rate when bevacizumab was added to FOLFOX, nor was there a prolongation in the progression-free survival or overall survival seen while there is consistent efficacy when bevacizumab used in second line. Another reason why bevacizumab did not work in the adjuvant setting might be due to the fact that microscopic disease does not depend on neovascularisation. Thus, inhibition of angiogenesis might not be an important aspect in the treatment of microscopic disease.

**cetuximab included in adjuvant chemotherapy regimens**

At ASCO 2010, Alberts and co-workers [18] reported on their randomised trial of FOLFOX alone or in combination with cetuximab for stage III colon cancer. When the trial started, the importance of the Kras mutation status was unknown. Therefore, patients with Kras wild-type and Kras mutant tumours entered the study (1847 patients). At 3 years, 87.8% of patients with FOLFOX were alive compared with 83.9% with FOLFOX plus cetuximab. This resulted in a hazard ratio of 1.3 with a 95% CI of 0.96–1.8. The P-value demonstrated non-significance (0.13). Thus, in Kras wild-type patients, cetuximab decreased the chances of survival by ~30%. This was even more pronounced in those patients with Kras wild-type tumour. A total of 711 patients belonged to this cohort. At 3 years, the survival for patients treated with FOLFOX was 80.0% when compared with 84.4% for patients who received cetuximab in addition. Here, the hazard ratio of 1.5 (95% CI 0.9–2.3) with a P-value of 0.12 indicated an over 50% reduction in the chances of survival when cetuximab was added to FOLFOX. Thus, surprisingly cetuximab reduced rather than improved on the survival of patient’s period. The results of the PETACC8 study comparing FOLFOX versus FOLFOX–cetuximab are pending, but are expected to have a similar outcome.

In patients with metastatic CRC and Kras wild-type tumours, there is a consistent improvement of response rate, prolongation of PFS and OS reported [17]. The reason why the results were negative is currently not explained. Randomised data from patients with metastatic disease indicate an inferior outcome in the case of Kras mutant tumours in the presence of epidermal growth factor receptor (EGFR) inhibitors. Thus, the negative outcome in the cohort of patients with Kras mutant tumours may well be explained. However, it is surprising that the same was observed in Kras wild-type tumours. Whether there is a negative interaction with platinum compounds and EGFR inhibitors is speculative.

It is currently not advisable to use either EGFR inhibitors or vascular endothelial growth factor inhibitors for the adjuvant setting outside of clinical trials.

**irinotecan as part of adjuvant chemotherapy regimens**

Irinotecan combinations are superior over 5-FU/FA combinations in metastatic disease and held great promise to replace oxaliplatin in the adjuvant treatment due to the lack of long-term toxic effect.

Saltz et al. [19] randomised patients either to bolus 5-FU/folinic acid or bolus 5-FU/irinotecan and leucovorin regimen (IFL regimen). There was no survival benefit observed in this study. Van Cutsem et al. [20] compared the FOLFIRI regimen with the infusional 5-FU/folinic acid regimen in the PETACC3 study. There was a small benefit in favour of the use of irinotecan with a hazard ratio of 0.89 with a 95% CI crossing the border of 1 (0.772–1.11; P-value 0.091). Thus, this study was not completely negative but failed to be positive. In the third study, Ychou et al. [21] randomised patients with high-risk stage III colon cancer (>4 positive lymph nodes) to FOLFIRI against infusional 5-FU/folinic acid. There was also no benefit seen for the irinotecan combination with a 3-year disease-free survival in favour of 5-FU/leucovorin done (60% versus 59%, hazard ratio 1.19, 95% CI 0.90–1.59). Thus, based on these three studies, irinotecan has not been further investigated in the adjuvant setting. However, in the N0147 study [22], patients with Kras wild-type or Kras mutant tumours were randomly assigned to receive either a modified FOLFOX6 regimen or FOLFIRI alone both with or without the addition of cetuximab. Due to the negative outcome of the PETACC3 study, the FOLFIRI arm was closed after randomisation of 106 patients into the FOLFIRI arm and 40 patients into the FOLFIRI–cetuximab arm. Huang et al. analysed these patients and observed a 3-year survival rate of 69.8% versus 92.3% for FOLFIRI and for FOLFIRI–cetuximab, respectively, the hazard ratio of 0.31 for progression-free survival was statistically significant (P-value of 0.04). There was also a trend in favour for survival of FOLFIRI–cetuximab (92.0% versus 85.2%). Whether in the future, we will see a randomised trial with the inclusion of FOLFIRI–cetuximab however remains questionable, not due to a lack of scientific background but rather lack of financial support.

**stage II**

The use of adjuvant chemotherapy in stage II colon cancer patients remains questionable. Patients with stage II colon cancer have a highly variable outcome [23]. For stage IIa (T3 N0), an 87.5% five-year overall survival is expected. For stage IIb patients (T4a N0), the 5-year survival is estimated to be 79.6%. For stage IIc patients (T4b N0), the 5-year survival of 58.4% is worse when compared with most patients with stage III tumours (Figure 2). The current situation for the adjuvant treatment of stage II colon cancer may be summarised as follows:

- A small benefit of ~3% may be achieved with of 5-FU/folinic acid according to the QUASAR1 study. This is the largest trial ever been reported on stage II cancer patients with over 3200 patients randomised. In this study, 92% of patients had
stage II disease and 71% had colon cancer. Those patients with rectal cancer had received radiotherapy as well [24].

- There appears to be no further improvement with FOLFOX over the use of 5-FU/folinic acid according to the experience of the MOSAIC study in stage II patients. Although the 5-year survival was improved by 3.8% (hazard ratio 0.84, \( P = 0.26 \)), this difference did not translate into an overall survival benefit which was nearly identical with a hazard ratio of 1.0 (\( P = 0.0986 \)) [4].

- For high-risk stage II colon cancer defined by at least one of the following criteria: T4 tumour, tumour perforation, bowel obstruction, poorly differentiated tumour, venous invasion, below 10 lymph nodes examined, a 5-year progression-free survival benefit of 7.2% was observed for FOLFOX (HR 0.74, 95% CI 0.52–1.06) over infusional 5-FU/FA alone [4].

- The NSABP looked at the observed 5-year adjusted survival for patients entering their consecutive trials. A total of 1542 patients were identified to belong to the high-risk group of stage II cancer patients, while a total of 1458 patients belonged to the low-risk group. There was a marginal improvement in the overall survival for high-risk and low-risk patients in the range of 2.5%–3.5% [25].

- The majority of patients does not benefit from the use of adjuvant FOLFOX in stage II cancer either because they are already cured by survival or with relapse instead the use of adjuvant oxaliplatin-containing chemotherapy (Figure 3).

### possible future ways to identify the subgroups of patients who might benefit from adjuvant chemotherapy in stage II of colon cancer

The small benefit observed with fluoropyridine in stage II colon cancer has encouraged to search for a biological marker that may enrich those patients most likely to benefit from adjuvant chemotherapy.

Microsatellites stability is such a potential marker [26, 27]. Tumours can be classified into microsatellite deficient and microsatellite proficient. Untreated patients with stage II colon cancer which carry deficient tumours have a better prognosis when compared with patients who have proficient microsatellite mismatch repair. This difference could not be observed if patients had received a fluoropyridine as adjuvant.
chemotherapy [26]. It turned out that this was due to the fact that patients with proficient mismatch repair genes gained a survival benefit after chemotherapy, while patients with deficient mismatch repair capacity had a lower survival with chemotherapy when compared with be untreated. Therefore, adjuvant chemotherapy in stage II colon cancers may be considered in those who have a proficient mismatch repair capacity, only.

Gene expression signatures is another tool to define prognostic groups in stage II colon cancer [28, 29, 30]. All of these tests were able to distinguish between a high- or low-risk and a high-, intermediate- or low-risk group. It is, however, currently unknown whether patients with a high risk of a relapse defined by gene expression assays are those who actually benefit most from adjuvant chemotherapy or whether patients harbouring low-risk tumours can be left without adjuvant chemotherapy. The gene expression analysis [30] identifies 13% patients with T4, mismatch repair proficient tumours (~13% of patients). In this group of patients we would consider adjuvant therapy based on the T-stage already, thus there is no addition gain to determine the MSI status. In contrast patients with T3 and mismatch refer deficient tumours (11%) are those with a very low risk of relapse (~5%). The best discriminant appears to be in those patients with T3 and mismatch repair proficient tumours (74%) with a high recurrent score (over 40 points) in which the risk of relapse is >20%. Based on these data this subgroup might serve as a potential cohort to be studied within a clinical trial testing this recurrence score as a treatment decision tool.

Currently, retrospective data [30] does not predict for the efficacy of adjuvant chemotherapy although patients with high-risk tumours may benefit the most from adjuvant chemotherapy. It is for this reason that none of the gene expression assays can be advocated as definite answers to select high-risk patients with stage II cancers who may benefit the most from adjuvant chemotherapy.

As outlined in Figure 4, cancer mortality and non-cancer-related 5-year mortality are a function of tumour stage and age. In patients with pT3 N0 disease and of around 60 years of age, the risk of dying of cancer is estimated to be ~10%, while the non-cancer-related death is just <10%. If patients are older than 60 years the non-cancer mortality is higher than the cancer related mortality most likely due to co-morbidities. The image is different in T4 and N0 patients; here, patients with 60 years of age have a ~20% 5-year mortality clearly higher than the non-cancer-related death.

Thus, a reduction of cancer-related mortality ~3% (as in Quasar) [24] may be worthwhile to consider particularly if the individual patient is young and/or has no major co-morbidities.

At current, the decision to treat or not to treat an individual patient with stage II disease is an individual decision.

disclosure

The author has received honoraria for lectures for Merck, BMS, Pfizer, Sanofi, Roche.

references

16. Andre T, Van Cutsem E, Schmoll H et al. A multinational, randomized phase III study of bevacizumab (Benv) with FOLFOX4 or XELOX versus FOLFOX4 alone as adjuvant treatment for colon cancer (CC); a subgroup analysis of individual patient data from four randomized controlled trials. In ASCO 2012 General Poster Session (Abstract 3522).


