

Systemic Treatment in Colorectal Cancer

a report by

Hans-Joachim Schmoll*Head, Department of Haematology and Oncology, Martin Luther Halle-Wittenberg University Hospital*

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Hans-Joachim Schmoll is Head of the Department of Haematology and Oncology and Associate Professor of Haematology and Oncology & Internal Medicine at Martin Luther Halle-Wittenberg University Hospital in Germany. Previously, Dr Schmoll was a Professor of Internal Medicine, and later Director of the Department of Haematology/Oncology of the Medical University of Hanover. He is on the Board of Directors of the European Society for Medical Oncology and serving on the Membership Programme Committee of the American Society of Clinical Oncology. Dr Schmoll is also Chair of the Gastrointestinal Tumours Section of the Association of Medical Oncology of Germany (AIO) within the German Cancer Society. He is a founder and the President of the Saxony-Anhalt Cancer Society and Chair of the Cancer Centre at the Martin Luther Halle-Wittenberg University Hospital. Dr Scholl is a member of many scientific societies, including the European Organisation for Research and Treatment of Cancer (EORTC) and the American Association of Cancer Research. He is Editor in Chief of *Onkologie*, Associate Editor of *Cancer Research*, and an editorial board member for the *European Journal of Cancer*, *Annals of Oncology*, *Critical Reviews in Hematology and Oncology* and *Cancer & Chemotherapy Reviews*. Dr Scholl has been awarded the 1981 Johann-Georg-Zimmermann award for Cancer Research and the 2001 German Cancer Award and he has been an Honorary Member of the Hungarian Cancer Society since 2006.

Epidemiology

Colorectal cancer is a frequent disease in Western countries and ranks as second after lung cancer in men and breast cancer in women with about 500,000 new cases in Europe and 150,000 in the US. The mortality of 40–50% is high; however, in recent years this has been steadily improving due to early detection and better treatment measures, in particular adjuvant chemotherapy. In advanced disease, the improved efficacy of systemic chemotherapy leads to a substantial long-term survival by means of neoadjuvant chemotherapy followed by radical resection of metastases in the liver and/or lung.

On-going pre-clinical and clinical research with drugs directed to multiple targets is using colorectal cancer as a paradigm for early investigation of new drugs in combination with classical chemotherapy and this will hopefully create further substantial improvement in cancer treatment in the near future.

This disease is diagnosed mostly in resectable stages; however, 35–40% of patients have clinically detectable metastatic disease at the time of first diagnosis. Owing to the relatively aggressive nature of colon cancer in a relevant fraction of patients, synchronous and metachronous metastases occur in 50% of cases, resulting in an overall mortality of 40–45%. In recent years the introduction of adjuvant chemotherapy with single agent 5 fluorouracil (5FU), and most recently 5FU/oxaliplatin, significantly improved the long-term survival and cure rate of patients with stage II and III disease (no lymph nodes involved and lymph node positive, respectively), leading to a substantially reduced mortality, at least in the US. However, a stage shift with increasingly early detection by effective screening programmes (e.g. Hemoccult blood testing and – more importantly – a screening-colonoscopy as part of a general early detection programme, will reduce the mortality of colorectal cancer in the future. Also, in advanced disease, the efficacy of combination chemotherapy including new targeted drugs has improved the median survival from 1–1.5 to 2–2.5 and even nearly three years in some recent

phase II studies. Some of these new developments will be described in the following.

Advances in Adjuvant Treatment of Resectable Disease**Peri-operative Treatment of Colon Cancer**

For patients with high risk stage II and III, adjuvant chemotherapy with 5FU/oxaliplatin has become standard. Treatment should start within 5–6 weeks after surgery and should be given for six months. Combination chemotherapy is preferred over single-agent 5FU since the relapse rate is significantly improved by the addition of oxaliplatin with acceptable short and long-term toxicity. Since a relapse in this disease mostly means an incurable situation, this event should be avoided as much as possible and combination chemotherapy should be preferred for most patients, as well as for older patients. Patients with stage II disease lacking risk factors (e.g. obstruction, perforation, less than 12 lymph nodes resected, poor grading) also might benefit from adjuvant chemotherapy, at least single agent 5FU as shown in the British QUASAR trial. Despite these data, the decision for adjuvant treatment in stage II disease without high risk features can be decided on an individual basis.

Several prognostic factors have been investigated; however, currently none of them form the basis for individual selection of patients for specific adjuvant treatment modalities. These factors include loss of heterozygosis, chromosome 18q, microsatellite stability or instability, insulin-like growth factor- β -receptor type II, excision repair cross-complementing rodent repair deficiency, complementation group 1 (ERCC1), etc. None of these markers should be currently used as argument for or against adjuvant chemotherapy outside clinical trials.

There is cumulative evidence that infusional 5FU, which has been the standard partner for oxaliplatin in adjuvant treatment, can be exchanged for oral 5FU, particularly capecitabine. The large Roche trials with

4,000 patients have shown that capecitabine is an excellent partner for oxaliplatin in early disease as well as for adjuvant treatment, with a treatment-related mortality of 0.6% for FOLFOX and for XELOX. Efficacy data from this adjuvant chemotherapy trial (XELOXA trial) in high-risk stage II/III will be available in 2007. However, a large clinical trial in advanced disease comparing FOLFOX with XELOX (Jim Cassidy et al., European Society for Medical Oncology Presidential Symposium 2006) demonstrated the excellent practicability and tolerability of this combination for a limited period of six months. Therefore, in adjuvant treatment the oral XELOX combination is favoured as standard. Currently, the role of bevacizumab (Avant trial) and cetuximab (Pan-European Trials in Alimentary Tract Cancer – PETACC-8 trial) is being investigated for adjuvant treatment of high risk stage II and III colon cancer; however, efficacy results are not available before 2009.

Peri-operative Treatment of Rectal Cancer

The standard treatment of locally advanced rectal cancer including low located tumours is neoadjuvant chemoradiation with 5FU infusion, followed by special rectal cancer surgery (total mesorectal excision). There is much evidence that post-operative adjuvant chemotherapy with 5FU in addition to pre-operative chemotherapy should also be a standard due to some effect on survival. For less extended or higher located tumours, five x 25Gy radiation (one week) without chemotherapy, followed by total mesorectal excision (TME), is an alternative option. Current prospective trials (the National Surgical Adjuvant Breast and Bowel Project – NSABP – in the US and the PETACC-6 trial in Europe) investigate the combination of capecitabine/oxaliplatin for chemoradiation as adjuvant chemo-therapy after surgery (PETACC) or the addition of bevacizumab to 5FU/oxaliplatin (NSABP). The NSABP control arm with FOLFOX indicates that, at least in the US, adjuvant treatment for rectal cancer does not differ from colorectal cancer. The role of targeted drugs, e.g. bevacizumab and/or cetuximab as inhibitor of epidermal growth factor (EGF) receptor pathway together with chemotherapy as well as radiation, are currently being evaluated in phase II trials, and preliminary data show highly interesting efficacy.

Advanced Disease

As in any other tumour type, survival of patients with advanced disease depends on the sensitivity to the chosen chemotherapeutic drugs reflecting the biology of the tumour, and the number of treatment

regimen or individual drugs given might influence the course of disease. In addition, individual cases with limited metastases to the liver and/or lung with good response to chemotherapy are candidates for secondary and even repeated metastatic resection, resulting in an excellent long-term outcome for 30% of these patients. Therefore, the treatment strategy for patients with advanced disease should be prospectively planned and sequential treatments with alternative drugs should be given as much as possible, depending on the individual registration characteristics in different countries.

Most importantly, before any treatment decision, the patient should be categorised with respect to the aim of the treatment, either 'curative', aiming for long-term survival or 'palliative'. For patients with limited metastases and major response resectable disease, optimal combination chemotherapy should be chosen as the first-line treatment, as well as for those patients with fast-growing metastases and a risk for rapid development of major tumour related symptoms. While for rapid and substantial reduction of tumour mass combination, chemotherapy including targeted drug use should be standard, for the other patients (e.g. 30%) with slow-growing metastases or severe co-morbidity, single agent 5FU, preferably capecitabine or uracil and ftorafur (UFT)/leucovorin, should be selected as initial treatment. This must be followed by combination chemo-therapy in cases of progression under first-line single agent 5FU.

The most active treatment combinations for standard treatment from clinical trials are FOLFOX/bevacizumab, XELOX/bevacizumab, FOLFIRI/bevacizumab or FOLFOX/irinotecan, with response rates in the range of 45–65%. It is of major importance that in cases of progression under the chosen first-line combination, second-line treatment is mandatory to maintain the possibility of long-term survival. All these protocols have more or less comparable efficacy, but different toxicity, e.g. oxaliplatin is associated with neuropathy and no alopecia, whereas irinotecan is associated with alopecia. Therefore, an irinotecan-containing combination can be given for a more prolonged time, whereas an oxaliplatin combination is limited due to the occurrence of neuropathy after median treatment duration of about six months in the majority of the patients, leading to discontinuation of oxaliplatin. The selection of an oral 5FU regimen (XELOX) has many advantages for the patients over infusional 5FU (FOLFOX or FOLFIRI) since the patient does not need a port with pumps for two days every two weeks. Therefore, the oral 5FU-based combination should be preferred. The combination of oral capecitabine plus irinotecan has

not been sufficiently investigated and is associated with toxicity and should therefore not be used outside clinical trials.

The role of cetuximab in first-line treatment is under investigation, and the results of large phase III studies for first and second-line treatment are expected in 2007. Phase II data have been promising with response rates from 50–80%, progression free survival (PFS) from 9–12 months and an overall survival of 30 months. At least for second- and third-line treatment, cetuximab is an excellent option. Beyond the single agent activity of cetuximab (10%), the combination of cetuximab plus irinotecan and probably also oxaliplatin shows synergistic activity with acceptable toxicity. Therefore, according to the current registration label, cetuximab is mandatory for patients failing irinotecan combination. Bevacizumab, if not given as part of the first-line treatment combination, is able to double the response rate, PFS and survival in second-line treatment, if combined with FOLFOX (and probably also XELOX), and has therefore proven activity even in second-line treatment. However, it

I trials, e.g. epothelone, histone deacetylase-inhibitors, insulin-like growth factor receptor type II-inhibitors, etc., and warrant further investigation in phase II trials and in combination with other drugs. In addition, the combination of drugs inhibiting different targets, and the inhibition of one tyrosine kinase pathway with different modalities including receptors as well as the intracellular tyrosine kinase domain, are highly promising. Recently, it has been shown in a phase I trial that, even for refractory colorectal cancer patients the combination of gefitinib plus cetuximab, without the addition of chemotherapy, yielded a response rate of between 15% and 16% indicating that double inhibition of a relevant pathway, at least in colon cancer, is a promising treatment strategy.

The combination of different targeted drugs, in particular those inhibiting the EGF and vascular endothelial growth factor (VEGF) 1/2/3 receptor pathway like cetuximab or panitumumab plus bevacizumab, alone or in combination with irinotecan, has shown significant activity in patients refractory to chemotherapy. The preliminary data

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is not known whether bevacizumab, as a part of second-line combination chemotherapy, is active in those patients who had bevacizumab-containing combination treatment as their first-line treatment. The treatment of bevacizumab beyond progression for second-line treatment is unproven and should not be undertaken on a regular basis outside of the on-going clinical trials investigating this procedure. Bevacizumab is, in contrast to cetuximab, not active as single agent, at least in colorectal cancer and therefore only used for combination with chemotherapeutic drugs.

For third, or first-line treatment mitomycin C in combination with capecitabine is a valid option for some patients. In particular, in cases with metastases confined to the liver and refractory to systemic treatment, locoregional chemotherapy or chemoembolisation, it is an appropriate measure with a good response rate even in advanced stages.

Current Development in Chemotherapy

Several new drugs have shown some activity in phase

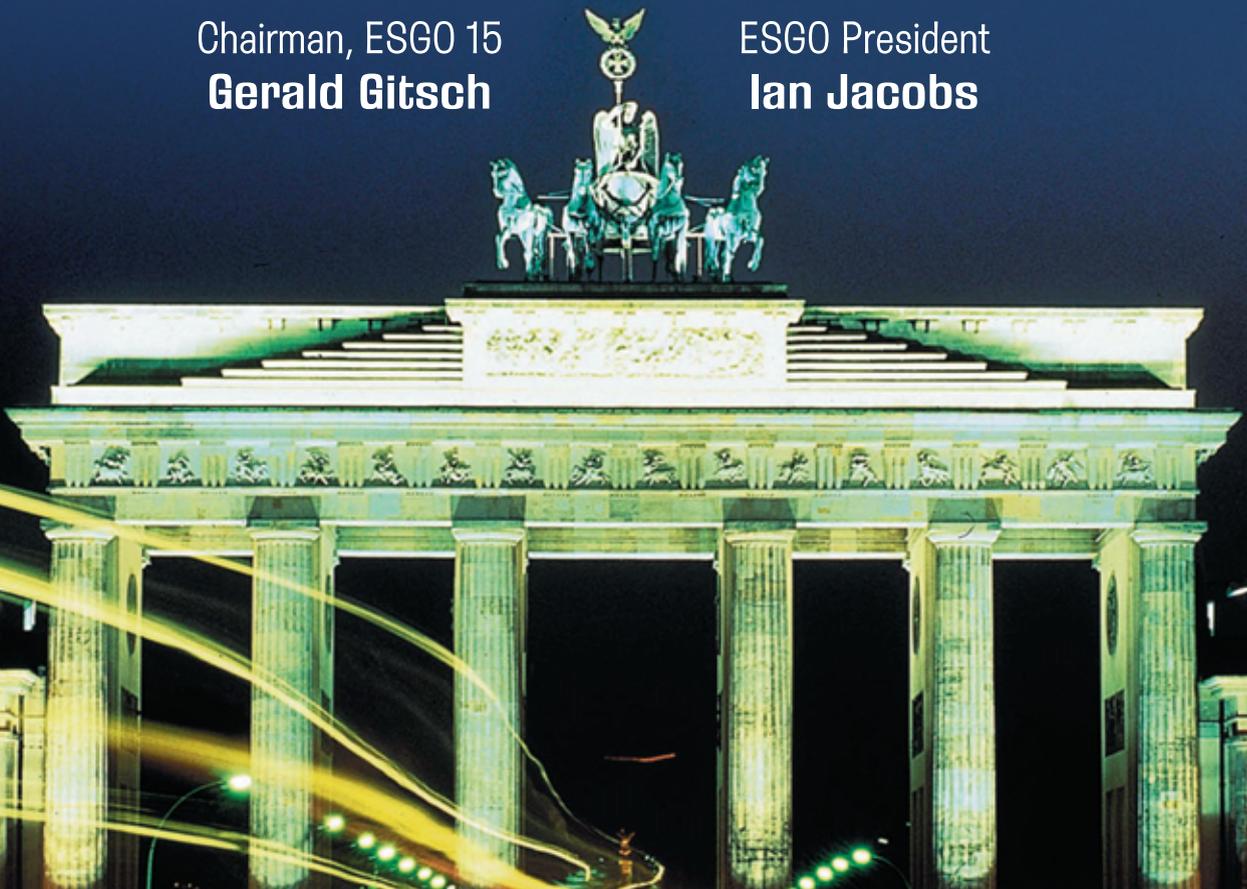
indicate a synergy if both pathways are inhibited, together with chemotherapeutic drugs. The on-going Intergroup study in US is therefore investigating FOLFOX or FOLFIRI plus either bevacizumab or cetuximab or both. Furthermore, phase I/II trials are investigating the addition of a third drug, irinotecan, to the FOLFOX/bevacizumab/cetuximab combination. The value of oral tyrosine kinase inhibitors targeting several pathways (e.g. EGF receptor, VEGF/EGF-receptor, platelet-derived growth factor, etc.), in combination with chemotherapy is currently being investigated. The potential role of further new targets including EGF-receptor or aurora kinase inhibitor drugs are the focus of current clinical research.

Colorectal cancer remains an excellent paradigm for the development of new drugs, in particular targeted drugs in combination with classical chemotherapy, and it serves as a model for other tumour types. Hopefully the survival of patients with advanced colorectal cancer will be significantly increased. There is clear hope that the number of long-term survivors will increase substantially in the near future. ■

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MEETING SECRETARIAT - ESGO 15

Kenes International - 17 rue du Cendrier,
P.O. Box 1726, CH-1211, Geneva 1, Switzerland
Tel: +41 22 908 0488, Fax: +41 22 732 2850
E-mail: esgo15@esgo.org

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