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EDITORIAL

Acta Oncologica and a new generation of scientists in oncology

BENGT GLIMELIUS[1], CHRISTOFFER JOHANSEN[2,3], LUDVIG PAUL MUREN[4] & MEF NILBERT[5]

[1]*Department of Radiology, Oncology and Radiation Science, Uppsala University, Uppsala, Sweden,* [2]*Department of Oncology, Finsen Centeret, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark,* [3]*Survivorship Unit, Danish Cancer Society Research Center, Copenhagen, Denmark,* [4]*Department of Medical Physics, Aarhus University, Aarhus University Hospital, Aarhus, Denmark and* [5]*Regional Cancer Centre South, Medicon Village, Lund, Sweden*

As part of several activities during Acta Oncologica's 50-year celebration in 2013 [1–3], we organised a "young scientist's workshop" during two days in September in Copenhagen, Denmark with the intention to create a forum for interactions between young Nordic scientists within the broad field of oncology. In preparation of the workshop, several challenging, edge cutting and clinically relevant topics with new emerging scientific knowledge were identified by members of the Editorial Board. These topics were circulated as potential review subjects and subsequently narrowed down to a short list where at least three to four young scientists from at least two Nordic countries signed up for contributing to a review. During the workshop, 26 young scientists representing many different oncological sub-disciplines initially learned about "how to write a systematic review", "good scientific conduct – in a hypercompetitive environment" and were presented different views on "good scientific writing" from the editors of the journal. Most of the time was, however, devoted to discussions in small groups around the selected topics under supervision of one or more senior scientists. The discussions ultimately shaped the themes into eight clean-cut topics ready for review. The outlines of a protocol for a systematic overview/meta-analysis were defined during the group discussions together with a suggestion of a time schedule. These outlines were presented by one of the group members for the entire group of young and senior researchers with further suggestions of modifications. The different groups had to present a final protocol for their systematic overview within three weeks, a task that was fulfilled by all eight groups.

The format of the workshop was much appreciated by all participants. The success of a new initiative like the present one is, however, not judged by a favourable appreciation from the participants, but what ultimately comes out of it. In this case, the immediate outcome will be systematic overviews of clinically relevant, hot topics to be published in Acta Oncologica after an independent external review process. On a longer term perspective, increased scientific activities and interactions between young Nordic scientists representing slightly different sub-disciplines are even more relevant. The relevance of the published overviews can be rapidly evaluated by all readers of the journal and quantified in terms of downloads, and within the coming years as citations. The latter can be beneficial for the authors of the publications, particularly in an early phase of a scientific career. The authors have already done all the hard work reading many thousands of titles, many hundreds of abstracts and many tens of articles and synthesised all the information. The articles can also be beneficial for Acta Oncologica, increasing its reputation and potentially citation index.

The first review paper resulting from the workshop is published in this issue of Acta Oncologica [4]. It was accepted for publication and available early online within five months from the workshop.

EGFR-inhibition and predictive mutations

In the treatment of patients with metastatic colorectal cancer, inhibition of the epithelial growth factor receptor (EGFR) has emerged as one way to improve the results with longer survival, better quality of life,

Correspondence: B. Glimelius, Uppsala University, Department of Oncology, Radiology and Clinical Immunology, Akademiska Sjukhuset, Uppsala, 751 85 Sweden. E-mail: bengt.glimelius@onkologi.uu.se

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and potentially more resections of distant metastases in the conversion situation. Conversion is the commonly used term when treating unresectable/not-readily resectable chiefly liver metastases with chemotherapy prior to attempts to radically resect the metastases. It differs from neo-adjuvant therapy when the aim is to kill micro-metastatic disease, not requiring any tumour down-sizing [5–7]. In the conversion situation it appears to be important to get as many objective tumour responses as possible [8,9]. Two recent updates of the Folprecht et al. initial retrospective analysis [8] of the relation between tumour response and liver resection rate has been confirmed in one study [10], but questioned in another [11]. The addition of an EGFR-inhibitor to the armamentarium of drugs in metastatic colorectal cancer, together with the recognition that surgery is important in responding patients with limited metastatic disease, have resulted in median survival times of above two years [5,12–14]. Since patient selection is behind some of the excellent results, the improvements in unselected patient populations have been much less impressive [15,16]. Major reasons for this are the inability of elderly patients to tolerate the intensive treatments, or possibly the unwillingness of doctors to treat elderly patients. Elderly patients have had their survival prospects prolonged but to a much lesser extent [16–18]. However, fit elderly patients included in clinical trials do not appear to do worse than younger patients [19,20].

In the first publication of clinical results from a randomised trial appearing 10 years ago [21], a statistically significant benefit was seen when the EGFR-inhibitor cetuximab was combined with a conventional cytostatic drug, irinotecan, versus cetuximab alone. In spite of the absence of an appropriate control group, it was possible to conclude that EGFR-inhibition had at least some effects in delaying progression in some patients. Cetuximab was approved for use in metastatic colorectal cancer in the second/third line situation after failure on at least an irinotecan combination. The effects in an unselected population (expression of EGFR using immunohistochemistry did not turn out to be relevant) were too limited and/or limited to too few individuals to be used in many countries, considering quite substantial toxicity and very high costs for the drug [22]. This also relates to the other EGFR-inhibiting antibody, panitumumab, approved a few years later [23].

Exploration of molecular changes in the RAS/RAF/MAPK and PIK3-AKT-mTOR signalling pathways downstream of EGFR-inhibition could soon report that certain mutations in the *KRAS* gene meant lack of clinical efficacy for EGFR-inhibition. Exclusion of the almost 40% of the patients with mutations in codons 12 and 13 in exon 2 of *KRAS* in the tumours resulted in a change from a meaningless and potentially only toxic treatment to a potentially more valuable treatment of the remaining 60% of the patients [23,24]. The indications to treat thus increased, although treatment was not universally recommended [25]. Since then, there has been controversy about the relevance of other, less common mutations in the *RAS* gene. After the publication and reporting of results from several studies during the autumn 2013, and the systematic collection of the data by Therkildsen et al. [4] it is now clear that *KRAS* and *NRAS* mutations in exons 2, 3 and 4 infer resistance to EGFR-inhibition. Thus, about 60% of the patients with metastatic colorectal cancer can be excluded from therapy, and the remaining 40% have a higher likelihood for treatment response. According to Swedish guidelines to be released in April 2014 (www.socialstyrelsen.se/riktlinjer), treatment is clearly motivated in the first-line conversion situation in RAS wild-type tumours and in the third-line palliative situation alone or with irinotecan. Treatment in Sweden is not recommended in the first and second-line situation if the intent is strictly palliative (group 2 according to ESMO guidelines [12]), and definitely not in group 3 where the need for palliative more efficient therapy is then not apparent.

The treatment-predictive role of *BRAF* mutations in relation to EGFR-inhibition is controversial. *BRAF* mutations have convincingly been linked to an adverse prognosis with short times to progression and death irrespective of treatment [26,27]. The relative rarity of *BRAF* mutations, about 10% (range 4–21%) in the clinical trial populations and the poor prognosis tell that it is methodologically difficult to discriminate between a prognostic and a predictive effect. Experimental studies indicate that resistance to EGFR-inhibition should be present. Therkildsen et al. [4] are careful in their conclusions but do not recommend EGFR-inhibitory treatment if *BRAF* is mutated. Thus, additional patients with *RAS* wild-type tumours can be excluded from treatment.

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References

[1] Glimelius B. 50 years with Acta Oncologica. Acta Oncol 2013;52:1–2.
[2] Glimelius B. The 50-year anniversary of Acta Oncologica. Acta Oncol 2014;53:1–2.
[3] Grau C, Hoyer M, Alber M, Overgaard J, Lindegaard JC, Muren LP. Biology-guided adaptive radiotherapy (BiGART) – more than a vision? Acta Oncol 2013;52:1243–7.
[4] Therkildsen C, Bergmann TK, Henrichsen-Schnack T, Ladelund S, Nilbert M. The predictive value of KRAS,

NRAS, BRAF, PIK3CA and PTEN for anti-EGFR treatment in metastatic colorectal cancer: A systematic review and meta-analysis. Acta Oncol Epub 2014 Mar 25.

[5] Glimelius B, Cavalli Björkman N. Metastatic colorectal cancer: Current treatment and future options for improved survival. Medical approach – present status. Scand J Gastroenterol 2012;47:296–314.

[6] Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): A randomised controlled trial. Lancet 2008; 371:1007–16.

[7] Saltz LB. Curative-intent treatment for colorectal liver metastases: A medical oncologist's perspective. Am Soc Clin Oncol Educ Book 2012;32:205–8.

[8] Folprecht G, Cunningham D, Ross P, Glimelius B, Di Costanzo F, Wils J, et al. Efficacy of 5-fluorouracil-based chemotherapy in elderly patients with metastatic colorectal cancer: A pooled analysis of clinical trials. Ann Oncol 2004; 15:1330–8.

[9] Padman S, Padbury R, Beeke C, Karapetis CS, Bishnoi S, Townsend AR, et al. Liver only metastatic disease in patients with metastatic colorectal cancer: Impact of surgery and chemotherapy. Acta Oncol 2013;52:1699–706.

[10] Jones RP, Hamann S, Malik HZ, Fenwick SW, Poston GJ, Folprecht G. Defined criteria for resectability improves rates of secondary resection after systemic therapy for liver limited metastatic colorectal cancer. Eur J Cancer Epub 2014 Mar 21.

[11] Sunakawa Y, Ichikawa W, Takahashi T, Shimada K, Sasaki Y. Does a higher response rate to systemic chemotherapy result in a higher resection rate in patients with initially unresectable colorectal liver metastases? Acta Oncol 2013; 52:1039–40.

[12] Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, et al. ESMO consensus guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Ann Oncol 2012;23:2479–516.

[13] Folprecht G, Gruenberger T, Bechstein W, Raab HR, Weitz J, Lordick F, et al. Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM-study). Ann Oncol Epub 2014 Feb 27.

[14] Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, et al. PEAK: A randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol Epub 2014 Mar 31.

[15] Sorbye H, Pfeiffer P, Cavalli-Bjorkman N, Qvortrup C, Holsen MH, Wentzel-Larsen T, et al. Clinical trial enrollment, patient characteristics, and survival differences in prospectively registered metastatic colorectal cancer patients. Cancer 2009;115:4679–87.

[16] Mol L, Koopman M, van Gils CW, Ottevanger PB, Punt CJ. Comparison of treatment outcome in metastatic colorectal cancer patients included in a clinical trial versus daily practice in The Netherlands. Acta Oncol 2013;52:950–5.

[17] Sorbye H, Cvancarova M, Qvortrup C, Pfeiffer P, Glimelius B. Age-dependent improvement in median and long-term survival in unselected population-based Nordic registries of patients with synchronous metastatic colorectal cancer. Ann Oncol 2013;24:2354–60.

[18] Sorbye H. Palliative chemotherapy in elderly patients with metastatic colorectal cancer: Do we know how it should be used? Acta Oncol 2012;51:819–21.

[19] Venderbosch S, Doornebal J, Teerenstra S, Lemmens W, Punt CJ, Koopman M. Outcome of first line systemic treatment in elderly compared to younger patients with metastatic colorectal cancer: A retrospective analysis of the CAIRO and CAIRO2 studies of the Dutch Colorectal Cancer Group (DCCG). Acta Oncol 2012;51:831–9.

[20] Papamichael D, Audisio R, Horiot JC, Glimelius B, Sastre J, Mitry E, et al. Treatment of the elderly colorectal cancer patient: SIOG expert recommendations. Ann Oncol 2009; 20:5–16.

[21] Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337–45.

[22] NICE. Technology appraisal guidance TA118. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. Available from: http://guidance.nice.org.uk/TA118. 2007.

[23] Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626–34.

[24] Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008;359:1757–65.

[25] NICE. Technology appraisal guidance TA242. Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy). Available from: http://guidance. nice.org.uk/TA242. 2012.

[26] Van Cutsem E, Kohne CH, Lang I, Folprecht G, Nowacki MP, Cascinu S, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: Updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011;29:2011–9.

[27] Tveit KM, Guren T, Glimelius B, Pfeiffer P, Sorbye H, Pyrhonen S, et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: The NORDIC-VII study. J Clin Oncol 2012;30:1755–62.