It's creative chaos in the colorectal cancer clinic

Report from the ESO colorectal cancer observatory

Marc Beishon

After years of relying on 5FU, colorectal cancer clinicians now have a wealth of targeted therapies and combination protocols to choose from. The question is, what to use in which patients and when?

All the experts are agreed – we are in a new era of treatment of colorectal cancer, thanks to the latest combinations of chemotherapy drugs and targeted therapies, routine use of imaging technologies such as MRI, and of course the uptake of screening and better public awareness of the disease. But the new era – for metastatic colorectal cancer especially – is characterised by 'creative chaos', according to Roberto Labianca, head of medical oncology at the Riuniti hospital, Bergamo, Italy.

Speaking at the ESO colorectal cancer observatory, held at the 9th World Congress on Gastrointestinal Cancer at Barcelona in June, Labianca said, "We used to have just one drug [fluorouracil, or '5FU'] for one disease. Now we know that colorectal cancer is not just one disease and we have several different chemotherapy and targeted drugs." It's a good situation of course, he added, but the choices for treatment strategies have rapidly become much more complex, especially for what he terms the 'continuum of care' – the outcome for individual patients across possibly several lines of treatment, where the balance between survival and quality of life is the crucial consideration.

Margaret Tempero, medical oncology chief at the University of California, San Francisco, and a past president of the American Society of Clinical Oncology, concurred with this view. She first presented data showing how deaths from colorectal cancer in men in the US had declined in recent years. "This is not a surprise given we now have prevention, early detection and far better treatment," she said. Turning to adjuvant chemotherapy, she remarked that relatively recently there has been marked improvement in outcomes for stage 3 disease. "It was back in 1990 that in the US we had a consensus on the use of 5FU and leucovorin, and we had not gone much further until the results of the MOSAIC trial, which showed an impressive improvement in survival." MOSAIC looked at the addition of the chemotherapy drug oxaliplatin to standard treatment in the so-called FOLFOX4 combination (oxaliplatin, 5FU and leucovorin).

However, updated results from MOSAIC, presented at this year's ASCO meeting, showed an increase in survival of only 4% at the six-year point for stage 3 disease, Tempero reported. "It's slow and incremental progress." Nevertheless, the probability of surviving stage 3 disease with FOLFOX4 at six years is 72.9%, according to the MOSAIC researchers.

Looking at metastatic disease, Tempero showed how median survival times have risen impressively with the addition

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of combination therapy, from six months with no treatment to more than 20 months. "That's not only with oxaliplatin, but with irinotecan, bevacizumab [Avastin] and cetuximab [Erbitux]." Presenting US National Comprehensive Cancer Network guidelines, she showed just how complex – and confusing – the current picture is for treatment choices. "There is little order in second-line treatment. It is difficult to know how to treat patients if they fail to progress after initial therapy.

"The dilemma is great. We have these new drugs and they do improve survival, but they add great cost and in some cases significant toxicity."

Stage 2 disease is also a complex picture. It is important to identify high-risk patients correctly, so as to know when to apply adjuvant chemotherapy, but current guidelines can't make that distinction. "At stage 2, 20–30% will relapse and we don't know who they are," said Mario Dicato, head of haematology-oncology at the Luxembourg Medical Centre and co-chair of the Congress.

Personalised therapies

The search for more tailored treatment for patients such as those with stage 2 cancers is the tantalising prospect now energising colorectal specialists, commented Labianca. He noted that chemotherapy has yet to reach a 'plateau' in the treatment of colorectal cancer: there are new oral therapies and more combinations to come with targeted agents.

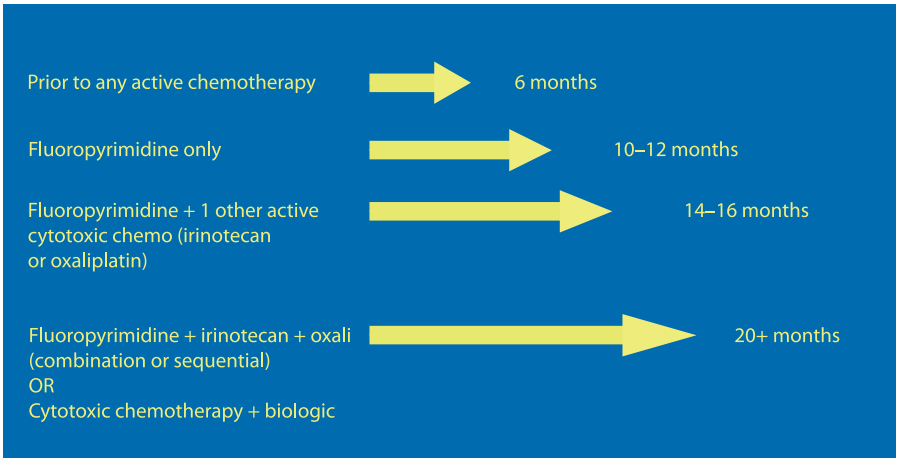
Dicato outlined what is known about the various prognostic and predictive factors. He talked of a wide range of non-molecular markers for colorectal cancer, relating to both the person and the tumour, and said genetic diversity, such as ethnicity, can also affect the way that drugs are metabolised.

Among the many molecular determinants for colorectal cancer outcomes, Dicato advised that the two 'markers to follow' are microsatellite instability and loss of heterozygosity at chromosome 18q, both of which are being used to divide stage 2 colon cancers into high- and low-risk groups in a key trial by the Eastern Cooperative Oncology Group in the US.

Turning to the 'fashionable' topic of gene expression profiling using microarrays, Dicato talked about a 'seminal' study of a 23-gene signature that gave a high accuracy in predicting recurrence in stage 2 colorectal cancer (Wang et al. 2004, JCO), and a study last year (Barrier et al. 2006, JCO), which gave an even better result on a 30-gene signature. He also drew attention to the abstract of a training study at the Congress involving Agendia, the Dutch company specialising in microarrays, which has shown much better prediction than existing ASCO good and bad prognostic markers.

He warned, however, of major limitations with current gene expression studies – not least lack of overlap of genes identified, and a lack of a 'common language'. Evidence is growing, says Dicato, that the picture is incomplete without proteomic (protein) analysis. "For now, molecular markers have to be considered as a complement to clinical and pathological data, and proteomics is likely to improve predictability," was his take-home message.

MEDIAN SURVIVAL FOR METASTATIC CRC



Source: University of California at San Francisco Comprehensive Cancer Center

Chris Verslype, of Gasthuisberg University Hospital, Belgium, saw the past year as one in which targeted therapy has "definitely acquired its place in the field of colorectal cancer. Both cetuximab and bevacizumab have been found of value in the entire treatment algorithm," (i.e. first, second and third line). Regarding biomarkers, he highlighted recent knowledge about KRAS mutations as predictive of cetuximab resistance in metastatic disease. He also emphasised the importance of offering 'drug holidays', maintenance therapy and early involvement of surgeons in operating on metastases in the 'continuum of care'.

Tempero pointed to the urgent need for building high-quality tissue banks. "We will have to develop large clinically annotated bio-repositories of tumour and germline DNA – the assays we could be running are on broad expression profiles, candidate genes and proteins, and metabolites, but we must be prepared to do it in a rigorous fashion. In terms of germline DNA, there is no reason why we can't sequence now many of the genes we normally carry that activate or detoxify certain agents.

"The real challenge is how to layer the information into a relational database so we have the power to determine what's truly important. The weakness is in bioinformatics – I hope it will be addressed by the National Cancer Institute and by institutions in Europe, but it really is a problem that we do not have the capability to handle all of this related data." In turn, she mentioned a gene expression 'training set' (hypothesised signature) for predicting response to the FOLFIRI regimen (chemotherapy for advanced colorectal cancer involving irinotecan – see Del Rio et al. 2007, JCO). "This is the direction we should all be going in," she said.

The importance of funding and infrastructure to create the independent, academic biobanks and large scale studies required to speed up the process was a theme running throughout these contributions.

The role of radiotherapy

The radiotherapist's view was put forward by Robert Glynne-Jones, a colorectal clinical oncologist at Mount Vernon hospital in the UK. He described how various technologies are combining in the treatment of rectal cancer, a disease where pre-operative radiotherapy has proved very important in helping stop local recurrence – although not without a cost in damage to healthy tissue. "Key questions are how to define who needs such radiotherapy, how to improve accuracy, the optimal chemo-radiation regimen and use of targeted agents, and if we can detect chemo-radio resistance at an early stage."

MRI, he says, can differentiate patients with various penetrations of tumour into the bowel wall, which predicts the risk of nodal metastases, helps define high-risk groups, and also indicates the margin for performing surgery. "MRI is becoming routine in the UK and we are integrating it into our planning process with CT," he said, adding, however, that MRI is much less used in other parts of Europe. This imaging technique is also being used to distinguish between different areas of the primary tumour, making it possible to increase the dose to, say, radioresistant hypoxic areas ('dose painting').

Virtual colonoscopy is adding to non-invasive ways to view tumours, says Glynne-Jones, and functional imaging using PET/CT will "revolutionise the way we look at things, because we can look at the whole tumour and also see ones that aren't apparent on CT alone. We will also be able to detect early radioresistance and plan alternative therapies." PET has the capacity to reduce interobserver variability in tumour delineation in trials, but Glynne-Jones commented that currently there are huge differences in the way that patients are planned among radiotherapy centres.

As for targeted therapies, he said integration with imaging seems to be getting 'further away'. One limitation he flagged up was that no current imaging technology will detect micro-metastases in lymph nodes.

Lynn Faulds Wood, president of the European Cancer Patients Coalition (ECPC), and a colon cancer survivor, made a series of salutary points. In order to help promote understanding and awareness about this disease, she reiterated a plea she's been making for some time: start using a common name for the disease – 'colon cancer' is preferred over the more UK-centric 'bowel cancer' – and ban the word 'embarrassment' when talking about it.

Faulds Wood talked about the screening programmes now starting to take off in the European Union. The ECPC is a partner in a consortium that is set to draw up best-practice guidelines for quality assurance of colorectal screening – something that just does not exist at present. "I

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also hear about barriers to screening, with some European gastroenterologists saying that colonoscopy is a painful procedure," she said. "In the UK, we now regard that as a training issue. I know too that some people find the bowel preparation very unpleasant – we'd like a much more delicious option." As she pointed out, if someone is not motivated by symptoms, these barriers could curtail screening uptake.

Faulds Wood also urged greater use of laparoscopic surgery, fewer colostomies and greater use of stenting – although with younger surgeons practising laparoscopy, there must be backup for complications that may arise. "In the UK now we also think you should not be operated on without being treated in a multidisciplinary team," she added.

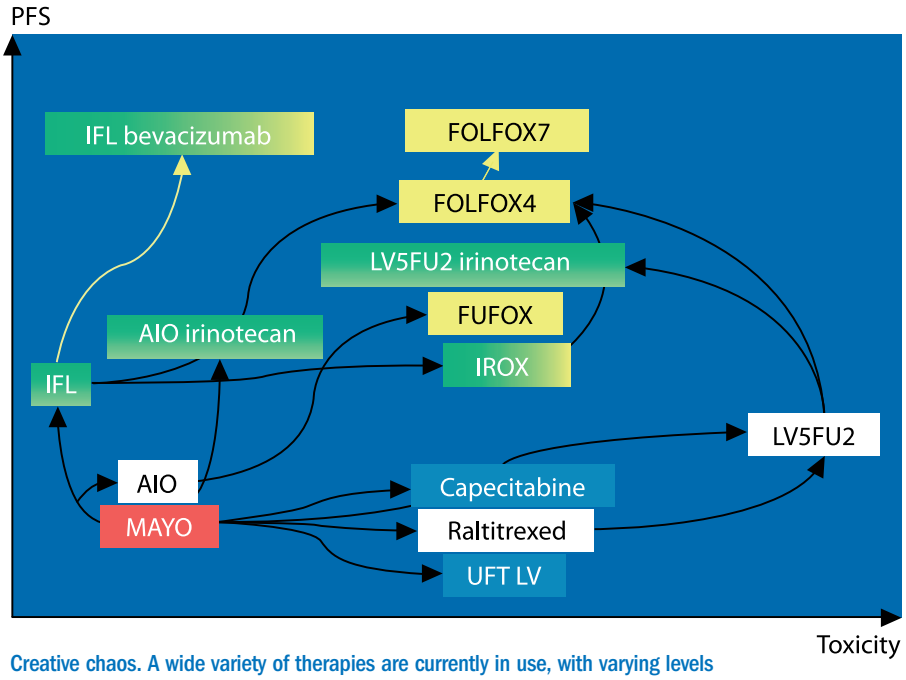
The role of nurses

The potential for nurses to play a more important role across the patient journey was addressed by Jan Foubert, executive director of the European Oncology Nursing Society. Progress in this direction is, however, limited by the dearth of research on colorectal cancer nursing.

He talked of common issues in gastrointestinal cancer care: managing wounds, stomas, incontinence, bowel function, fatigue and pain – mainly the side-effects of treatment. Some countries in Europe – notably the UK – have developed colorectal nurse specialists, and a Colorectal Nursing Research Unit has recently been launched at the Homerton University Hospital in London. Few hospitals, however, are in any position to resource such a specialism, said Foubert. "I feel that nurses should know much more about the advances and evidence in screening and clinical trials, as they often do with breast cancer," he said. "Nurses should have good access to education and resources to help raise awareness of prevention and early detection, and they can help focus on specific populations in our multicultural societies to break down barriers to screening. There is also a big need for much more patient information, especially for older people."

Nurses, he added, could also play a much larger role in caring for survivors after treatment has finished. "Nurses can be great coaches for groups of people with bowel problems." Such moves, he recognises, could mean major reorganisation of services and resources, and there is certainly a need for more research on nursing interventions and training to prevent and treat disease across the cancer journey.

EVOLUTION OF CURRENT TREATMENTS FOR METASTATIC CRC



Creative chaos. A wide variety of therapies are currently in use, with varying levels of toxicity and average progression-free survival (PFS)

IFL: irinotecan + 5FU + leucovorin; FOLFOX: 5FU + leucovorin + oxaliplatin; LV5FU2: leucovorin + 5FU; FUFOX: 5FU + leucovorin + oxaliplatin; IROX: irinotecan + oxaliplatin; AIO: folic acid + 5FU + irinotecan, MAYO: 5FU +leucovorin; UFT LV: tegafur + uracil + leucovorin

Source: Aimery de Gramont (2005)