EDITORIAL

“Continuum of care means that from start to finish, the treating physician must reconcile the two key medical principles—first, do no harm *(primum non nocere)* and second, help *(bonum facere).* Thus, the physician should start treatment with a regimen that is more or less aggressive depending on what the clinical condition demands and then adjust the intensity of the treatment, including chemotherapy-free periods, according to what is needed as the disease progresses, stabilizes, or shrinks.”

Improving outcomes in metastatic colorectal cancer: is there still room for improvement?

by A. Sobrero, *Italy*

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Advances

Advanced colorectal cancer treatment has improved substantially in the last 2 decades. Median survival is around 30 months in most recent clinical trials. In addition, a growing percentage of patients with one or few metastases in a single organ can be cured by the combined approach of systemic therapy and surgery, meaning that more than 50% of patients live longer than 30 months; it is not uncommon to see patients who live 5 years and beyond. These results are due to a combination of factors, including the use of a growing number of chemotherapeutic drugs and biologic agents, better surgical procedures for the eradication of metastases and the use of other locoregional procedures, and improved diagnostic imaging helping to earlier diagnose stage 4 disease. However, the crucial advancement lies in the contribution of the new agents.[1] With extension of survival from 10 months to the current 30 months and over, the new drugs have encouraged a wider use of local approaches, which have a synergistic effect.

Globally, therapeutic options for treating this disease can be divided into five groups: (i) fluorouracil or capecitabine; (ii) oxaliplatin and irinotecan—the basis of the most widely used chemotherapeutic doublets; (iii) the antiangiogenic compounds bevacizumab, aflibercept, and ramucirumab; (iv) the anti–epidermal-growth-factor-receptor (EGFR) agents cetuximab and panitumumab; and (v) the two agents for third- and fourth-line treatments—regorafenib (a multikinase small-molecule inhibitor) and trifluridine tipiracil (a novel fluoropyrimidine).

Continuum-of-care concept

The rational use of as many of these families of agents as possible without forgetting the possibility of surgery and/or locoregional treatment constitutes what is called the “continuum of care.” Continuum of care does not mean continued chemotherapy nor does it imply that a patient must receive the same drug or drug combinations until the disease progresses. Continuum of care means that from start to finish, the treating physician must reconcile the two key medical principles—first, do no harm *(primum non nocere)* and second, help *(bonum facere).* Thus, the physician should start treatment with a regimen that is more or less aggressive depending on what the clinical condition demands and then adjust the intensity of the treatment, including chemotherapy-free periods, according to what is needed as the disease progresses, stabilizes, or shrinks. These principles extend to second-, third-, and fourth-line treatments and beyond, with more or less aggressive therapies as needed, as well as rechallenge with treatments that may have initially produced good results but were then stopped because of toxicity or mild disease progression.

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Initialization of first-line treatment: four approaches

Currently, there are four classical ways to initialize the systemic treatment of stage 4 unresectable colorectal cancer: (i) a chemotherapeutic doublet plus bevacizumab; (ii) a chemotherapeutic doublet plus an anti-EGFR; (iii) a chemotherapeutic triplet plus or minus bevacizumab; and (iv) single-agent fluoropyrimidine plus bevacizumab.[2] The last treatment option is reserved for very elderly patients or patients who cannot tolerate aggressive regimens because of comorbidities. FOLFOXIRI—a triple chemotherapeutic regimen consisting of fluorouracil leucovorin, oxaliplatin, irinotecan—is reserved for exceptional cases where patients have never received adjuvant oxaliplatin-based adjuvant therapy, have a very good performance status, and need the tumor to shrink because of severe tumor-related symptoms or because there is potential for conversion of unresectable liver metastases into resectable conditions. However, the two most used first-line therapies are the chemotherapeutic doublets plus one of the two classes of biologic agents. The debate is about how to choose between a chemotherapeutic doublet plus bevacizumab or a doublet plus one of the two anti-EGFR agents.

Contribution of molecular factors and sidedness to the choice of biologics

The debate around choice of biologics is simplified by the fact that anti-EGFR agents are beneficial only if the tumor is *RAS* wild-type (RAS being a family of small GTPases involved in cellular signal transduction); otherwise, these antibodies are detrimental. Thus, *RAS* mutational status must be determined before deciding on a first-line treatment. In general, there is a preference for the anti-EGFR agents if the primary tumor is located on the left side of the colon, whereas bevacizumab is preferred for tumors located on the right or transverse colon.[3] Tumor location as a major driver of treatment choice has only recently been established.[4] The remarkable consistency of the data, at least among the most important recent randomized trials, makes sidedness very important in the decision-making process (sidedness probably represents a surrogate of different molecular assets on the two sides of the colon). The four most recent trials on this topic show that the anti-EGFR agents, when given as first-line treatment in combination with chemotherapy for left-sided tumors, produced an approximate 5-to-10–month gain in overall survival compared with bevacizumab. In contrast, the opposite is true for right-sided tumors, where bevacizumab is more beneficial than anti-EGFR by approximately the same extent.[3]

In general, these findings have simplified our approach. Of course, exceptions exist: for example, if the patient has a left-sided tumor with metastases of minimal size and an indolent clinical course, it is certainly not a mistake to use bevacizumab in first-line therapy. On the contrary, if a right-sided tumor has a very large liver metastasis that could be resected if reduced in size, it is certainly not a mistake to first use an anti-EGFR agent. Two additional concepts that simplify our treatment choices regard the widely accepted principles that (i) anti-EGFR agents are useful for shrinking tumors, whereas bevacizumab is useful for delaying disease progression and that (ii) bevacizumab is better for maintenance treatment than anti-EGFR because it has lower toxicity.

Second-line treatments

Once the patient's disease progresses, physicians are confronted with the problem of choosing an appropriate second-line treatment. A simple principle should guide the physician's decision: tumor-shrinking combinations should be used where the clinical course is worrisome or if surgical eradication of the metastases is still considered possible; for *RAS* wild-type patients, the alternative chemotherapeutic doublet plus anti-EGFR should be used; for *RAS*-mutated patients, the FOLFIRI chemotherapeutic regimen (fluorouracil leucovorin, irinotecan) plus aflibercept has the strongest indication. If, on the contrary, disease progression is slow and not so worrisome, the most logical choices are to continue bevacizumab beyond progression or to use ramucirumab.

Third- and fourth-line treatments

If conditions call for third-line treatment, there are two main challenges: (i) how tired patients are of side effects; and (ii) the extent to which their bone marrow reserves are compromised. These two challenges are recognized as the most relevant decisional factors for the treating physician because the two possibilities that we have are based on two completely different agents: regorafenib[5] and trifluridine tipiracil.[6] Regorafenib poses a particular challenge in terms of toxicity (asthenia and painful callous-like lesions on the hands and feet), whereas trifluridine tipiracil is very light in terms of symptomatic toxicity, but strongly affects leukopenia and thrombocytopenia. Therefore, patients who have received extensive amounts of chemotherapy resulting in a reduced bone marrow reserve should preferably receive regorafenib first and then trifluridine tipiracil. However, patients that had debilitating side effects from previous treatments should receive the drugs in reverse sequence, ie, trifluridine tipiracil first and then regorafenib. It is curious that if the toxicities described develop after treatment with one or the other of these two agents, the efficacy is more pronounced.[7,8] Trifluridine tipiracil was developed after regorafenib; therefore, whereas we have data showing that trifluridine tipiracil may still work on regorafenib-resistant patients, we have no data regarding regorafenib efficacy in trifluridine-tripiracil–resistant patients.

Future developments

Finally, three avenues seem particularly promising as future developments: (i) checkpoint inhibitors; (ii) the anti–stem-cell compound napabucasin; and (iii) the anti-carcinoembryonic-antigen (CEA) bispecific antibodies. Of these, the checkpoint inhibitors pembrolizumab and nivolumab are the most advanced.[9] Results of initial trials are impressive in that through treatment with these immunological agents, tumor regression

occurred even with extremely advanced tumors. However, there was a complete absence of effect in patients with microsatellite-stable (MSS) colon tumors. The clinical data are strengthened by the plausibility of these effects. In fact, checkpoint inhibitors would probably be more efficacious against tumors with a high mutational load, eg, tumors with microsatellite instability (MSI) have a very high mutational load compared with MSS tumors. Unfortunately, only a low percentage of stage 4 tumors are MSI (3%); therefore, the challenge facing the new immunotherapeutic agents is that a way must be found to change the average colon tumor, which is "cold," ie, poorly responsive to immunotherapy because of a poor lymphocytic infiltrate, to "hot." Several approaches are under study, including the use of combinations of checkpoint inhibitors with other immunologic compounds, targeted agents, chemotherapy, and radiotherapy.

Considering the growing success that immunotherapy is achieving in almost all types of cancers, with few exceptions, it is likely that this avenue of research will substantially improve treatment outcomes for colorectal cancer, with longer and longer plateaus in survival and potential cures. ■

References

1. Sargent D. Improved outcomes in metastatic colon cancer: giving credit where credit is due. *JAMA Oncol.* 2015;1(6):795-796.
2. Van Cutsem E, Cervantes A, Adam R, et al. ESMO Consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol.* 2016;27 (8):1386-1422.
3. Arnold D, Lueza B, Douillard JY, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Ann Oncol.* 2017;28(8):1713-1729.
4. Schrag D, Weng S, Brooks G, Meyerhardt JA, Venook AP. The relationship between primary tumor sidedness and prognosis in colorectal cancer. *J Clin Oncol.* 2016;34(15 suppl):3505-3505. doi:10.1200/JCO.2016.34.15_suppl.3505.
5. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381(9863): 303-312.
6. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372(20):1909-1919.
7. Grothey A, Huang L, Wagner A, Van Cutsem E. Hand-foot skin reaction (HFSR) and outcomes in the phase 3 CORRECT trial of regorafenib for metastatic colorectal cancer (mCRC). *J Clin Oncol.* 2017;35(15 suppl):3551-3551. doi:10.1200/JCO.2017.35.15_suppl.3551.
8. Ohtsu A, Yoshino T, Falcone A, Garcia-Carbonero R, Argiles G, Sobrero AF. Onset of neutropenia as an indicator of treatment response in the phase III RECOURSE trial of TAS-102 vs placebo in patients with metastatic colorectal cancer. *J Clin Oncol.* 2017;35(4 suppl):775-775. doi:10.1200/JCO.2017.35.4_suppl.775.
9. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med.* 2015;372(26):2509-2520.

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