Intensive multidisciplinary treatment strategies and patient resilience to challenge long-term survival in metastatic colorectal cancer: a case report in real life and clinical practice

Gemma Bruera[1,2]^, Francesco Pepe[3], Umberto Malapelle[3], Mario Di Staso[4], Antonella Dal Mas[5], Daniela Di Giacomo[1,2], Gaia Scerbo[6], Michela Santilli[6], Eugenio Ciacco[6], Maurizio Simmaco[7], Giancarlo Troncone[3], Claudio Coco[8], Felice Giuliante[9], Enrico Ricevuto[1,2]^; on behalf of Oncology Network ASL1 Abruzzo

[1]Oncology Territorial Care, S. Salvatore Hospital, Oncology Network ASL1 Abruzzo, University of L'Aquila, L'Aquila, Italy; [2]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy; [3]Department of Public Health, University Federico II, Napoli, Italy; [4]Radiotherapy, S. Salvatore Hospital, Oncology Network ASL1 Abruzzo, L'Aquila, Italy; [5]Pathology, S. Salvatore Hospital, Oncology Network ASL1 Abruzzo, L'Aquila, Italy; [6]Pharmacy Unit, S. Salvatore Hospital, Oncology Network ASL1 Abruzzo, L'Aquila, Italy; [7]Advanced Molecular Diagnostics, S. Andrea Hospital, Rome, Italy; [8]Unit of General Surgery, Department of General Surgery, Catholic University of Sacred Heart, Rome, Italy; [9]Unit of Hepatobiliary Surgery, Department of General Surgery, Catholic University of Sacred Heart, Rome, Italy

Correspondence to: Prof. Enrico Ricevuto. U.O.S.D. Oncology Territorial Care, S. Salvatore Hospital, Oncology Network ASL1 Abruzzo, University of L'Aquila, L'Aquila, Italy; Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Via Vetoio, L'Aquila, 67100, Italy. Email: enrico.ricevuto@univaq.it.

Abstract: In fit metastatic colorectal cancer (MCRC), multidisciplinary treatment strategy integrating intensive FIr-B/FOx triplet chemotherapy associated to bevacizumab and secondary metastasectomies significantly improved clinical outcomes up to progression-free survival (PFS) 17 months and overall survival (OS) 44 months. A non-elderly woman affected by rectal cancer, lymph nodes involvement, synchronous unresectable liver metastases, was treated with first-line FIr-B/FOx integrated with two-stage liver resections, short course radiotherapy, anterior rectal resection, with a PFS 9 months and progression-free interval (PFI) 4 months off-treatment. After progression characterized by single liver and lymph node inferior mesenteric axis metastases, FIr-B/FOx was re-introduced, liver and lymph node resections were performed, with a PFS 8 months and PFI 3 months. FIr-B/FOx was further proposed due to bilateral lung, and liver metastases with stable disease, PFS 8 months. Patient experienced a limiting toxicity syndrome multiple sites (LTS-ms) with G3 diarrhea, G2 asthenia, nausea, requiring irinotecan reduction and 5-fluorouracil discontinuation, and subsequent oxaliplatin discontinuation, due to infusional hypersensitivity reaction. Overall, integrated first-line medical and surgical treatment strategies gained PFS 26 months. Further lines II–V of treatment obtained a combined PFS 28 months: modulated aflibercept/irinotecan, PFS 8 months; panitumumab, PFS 8 months, proposed due to *KRAS/NRAS/BRAF* wild-type and *EGFR* c.2156 G>C (p.G719A) mutation, achieving biomarkers reduction, lung, liver, lymph nodes partial responses; regorafenib, PFS 8 months; trifluridine-tipiracil, PFS 4 months and induced an LTS-ms, with febrile G4 leucopenia, G3 neutropenia, thrombocytopenia, asthenia, G2 anemia, diarrhea, hypotension. After 2 months of palliative care, patient died, at OS 58 months, gained by intensive medical/surgical treatments coupled with patient's resilience. To date, selection of tailored medical treatments, according to clinical (age, performance and comorbidity status) and molecular (*RAS/BRAF* and pharmacogenomic analyses) evaluations, careful monitoring of individual toxicity syndromes, potential integration of metastasectomies, and furthermore individual resilience as patient life priority need to challenge MCRC long-term survival.

^ ORCID: Gemma Bruera, 0000-0002-8407-2479; Enrico Ricevuto, 0000-0001-5641-3187.

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Introduction

Effectiveness of first-line medical and surgical treatment strategy of metastatic colorectal cancer (MCRC) is based on activity and efficacy of intensive treatments integrated with secondary resection of metastases, specifically liver metastases, increasing progression-free survival (PFS) up to 17 months (1-6). Decision-making including functional, nutritional, co-morbidity status (Comorbidity Index Rating Scale, CIRS stage) selects patients fit for integrated strategies, or unfit, requiring tailored treatments (7), properly weighing expected safety and efficacy, also according to patient's life priorities.

First-line FIr-B/FOx triplet chemotherapy/bevacizumab reached in fit patients objective response rate (ORR) 82%, PFS 12 months, overall survival (OS) 28 months, 26% secondary liver resections, 15% pathologic complete response (CR), significantly improving clinical outcome of liver-limited MCRC, PFS 17 and OS 44 months, compared with multiple metastatic sites (2,4), not significantly affected by *KRAS/NRAS/BRAF* genotype, even if trendy favourable in triple wild-type (6). In non-elderly *RAS* wild-type MCRC, first-line FIr-C/FOx-C triplet chemotherapy plus cetuximab was highly active and tolerable at recommended doses, with median PFS 12 months (3). Prognosis after progression to FIr-B/FOx was significantly increased in patients re-challenged with intensive regimens; ORR 80% correlated with 40% secondary resections, PFS 13 months, 2-year OS 80% (8). Patients unfit for FIr-B/FOx, due to age (≥75 years) and/or comorbidities, are prevalent, treated with tailored triplet or doublet chemotherapy, achieving worse clinical outcomes (7).

In patients progressing to oxaliplatin-based first line, aflibercept/FOLFIRI significantly improved clinical outcomes (9). Third-line panitumumab in *RAS* wild-type (10), regorafenib (11), trifluridine/tipiracil (12) in chemorefractory patients demonstrated significantly increased efficacy.

In clinical practice, careful, continuous monitoring of patient's safety is required to realize integrated multidisciplinary intensive strategies in fit patients. To this aim, we developed the evaluation of limiting toxicity syndromes (LTS) to monitor individual patient toxicity (2,13-15).

We reported a multidisciplinary management in clinical practice of fit, non-elderly, MCRC patient with synchronous, unresectable liver metastases treated with first-line FIr-B/FOx, converted to two-stage hepatectomy and rectal anterior resection, and further lines of treatment, driven by clinical, genetic and pharmacogenomic analyses, who approximately reached 5-year survival, to underline the relevance of multidisciplinary clinical management weighed with individual patient's resilience as life priority to challenge MCRC long-term survival.

We present the following article in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6636).

Case presentation

Due to right lumbar/abdominal pain, a 59-year-old woman, medical radiologist, with Lynch-like family history (a familial colon, two gastric, a bladder, a testicular cancer), made by herself an ultrasound showing multiple bilateral liver nodules, confirmed at computed tomography (CT) scan, the largest 10-cm diameter, and pathologic rectal enlargement with involved regional lymph nodes. Endoscopic examination confirmed rectal adenocarcinoma, 10 cm apart from anal verge, *NRAS* codon 61 c.183 A>T (Q61H) mutation; bone scan negative. CIRS stage was stable without comorbidities. Pharmacogenomic analyses revealed an alteration of irinotecan metabolism (3), consisting of *UGT1A1*28* 6R/7R heterozygote variable number of tandem repeats (VNTR). Due to bilateral liver involvement, locally advanced rectal cancer with nodal involvement, medical oncologist, hepato-biliary surgeon, radiotherapist shared indication to systemic therapy. Patient underwent first-line intensive FIr-B/FOx (2): irinotecan 160 mg/m^2 d1, 15, oxaliplatin 80 mg/m^2 d8, 22, bevacizumab 5 mg/kg d1, 15, timed-flat-

Table 1 Timeline of patients' cancer history

Timeline	Treatment	No. cycles	Objective response	PFS (months)	PFI (months)	OS (months)
I line	FIr-B/FOx	4	PR	9	4	–
Two-stage hepatectomy, short-course RT and anterior rectal resection	–	–	–	–	–	–
Re-introduction, liver and lymph-node resections	FIr-B/FOx	3	PR	8	3	–
Re-introduction	FIr-B/FOx	8	SD	9	–	–
II line	FIri/aflibercept	6	SD	8	–	–
III line	Panitumumab	8	PR	8	–	–
IV line	Regorafenib	7	SD	8	–	–
V line	Trifluridine/tipiracil	3	PD	4	–	–
Best supportive care	–	–	–	2	–	–
Exitus	–	–	–	–	–	58

PFS, progression-free survival; PFI, progression-free interval; OS, overall survival; RT, radiotherapy; PR, partial response; SD, stable disease; PD, progressive disease.

infusion fluorouracil 900 mg/m^2/d d1–2, 8–9, 15–16, 22–23, every 28 days, for 3 cycles. Received dose-intensity (rDI) was >90% for each drug. Safety profile was characterized by: G2 diarrhea, G1 constipation, nausea, mucositis, asthenia, rhinitis, epistaxis, neuropathy, fever, alopecia. Partial response (PR) of liver metastases was obtained, and of primary rectal cancer, at CT scan, magnetic resonance imaging (MRI), endoscopic evaluation. Multidisciplinary team shared indication to fourth cycle, followed by two-stage hepatectomy, short course radiotherapy (RT) and anterior rectal resection with protection ileum stoma. Five weeks after last chemotherapy administration, patient underwent multiple resections at left lobe, and 10 days after, right hepatectomy. Histological examination confirmed multiple metastatic lesions with consistent necrosis (35% to >60%), 2 out of 6 metastatic lymph nodes of hepatic artery. Six weeks after, patient underwent short-course RT 5 Gy for 5 days, and 9 weeks after hepatectomy, laparoscopic anterior rectal resection was performed. Histological examination confirmed rectal adenocarcinoma, TRG4 according to Mandard staging, ypT3 ypN2a; 5 out 19 metastatic lymph nodes with capsular invasion. *KRAS*/*NRAS*/*BRAF* wild-type genotype on rectal cancer cells was reported by next generation sequencing (NGS). Patient completed first-line medical treatment, two-stage liver metastasectomies, short-course RT, anterior rectal resection in 8 months; at PFS 9 months, progression-free interval (PFI) 4 months off-chemotherapy (*Table 1*), CT scan showed a new third segment liver metastasis (3 cm × 2.5 cm), and lymph node of inferior mesenteric axis involvement.

Treatment was re-introduced (8) with irinotecan 140 mg/m^2 and 5-fluorouracil 800 mg/m^2/d doses reduction, due to ileum stoma, 3 cycles. CT scan showed PR, positron emission tomography (PET) negative. At PFS 6 months, 6 weeks after last administration, patient underwent II/III liver segments, right obturator lymph node resections, and colon canalization restoring. Histological examination confirmed liver and lymph node metastases. At PFS 8 months, PFI 3 months, CT scan showed bilateral lung metastases, a suspected third segment liver nodule (10 mm). Chemotherapy was resumed with irinotecan 120 mg/m^2 and 5-fluorouracil 750 mg/m^2/d doses reduction, 3 cycles. Patient experienced LTS-ms (2,13-15): G3 diarrhea, G2 asthenia, G2 nausea, requiring irinotecan reduction 100 mg/m^2. Disease was stable, 3 more cycles were planned. From fifth cycle, 5-fluorouracil was discontinued due to LTS single site (LTS-ss) G3 diarrhea; then, oxaliplatin was discontinued, due to severe infusional hypersensitivity reaction. Stable disease was maintained after 8 cycles. At PFS 9 months, CT scan showed progression of third/fourth segments liver metastases; thermoablation 50 W was performed. Overall, integrated medical/surgical

first-line treatments obtained PFS 26 months.

Due to described LTS, modulated second-line treatment was proposed: aflibercept (4 mg/kg) d1, 15, irinotecan (110 mg/m^2), d1, 15, every 28 days. Irinotecan schedule was modified at first cycle, 60 mg/m^2/week. Safety profile was characterized by G2 diarrhea, asthenia, hypertension, G1 rhinitis, epistaxis, mucositis, dysphonia, constipation, nausea. CT scan showed PR of liver, and stable lung metastases, justifying 3 more cycles. Stereotactic liver radiation therapy 54 Gy/six fractions was added, determining 4 months later secondary ulcerative hepatic colon flexure lesion, resolved 7 months later. At PFS 8 months, progression of lung and thoracic-abdominal lymph nodes metastases was detected.

Due to *KRAS/NRAS/BRAF* wild-type genotype by NGS, associated with *EGFR* c.2156 G>C mutation (p.G719A), third line anti-EGFR panitumumab was proposed, 4 cycles. Consistent biomarkers reduction, >30% bilateral lung PR with excavation signs, liver metastases, thoracic-abdominal lymph nodes was obtained. Further 4 cycles were administered. At PFS 8 months, CT scan showed increase of thoracic lymph nodes, right shoulder blade metastasis with discontinuation of cortex. During panitumumab, moderately differentiated, ulcerative, infiltrating, cutaneous squamous cell carcinoma of wing of nose was radically resected. Patient underwent RT 800 cGy, cryoablation of bone lesion 13 weeks apart.

Then, fourth-line modulated regorafenib 120 mg/d, 3 weeks on/1 week off was administered, 4 cycles. Safety profile was characterized by: G2 hand-foot syndrome, constipation; G1 diarrhea, hypokalemia, asthenia, anorexia, dysgeusia, mucositis, rhinitis, erythema, fever, rash, paronychia, skin dry, neuropathy. CT scan showed slightly enlarged lung metastases with marked excavation signs, new hepatic and lymph nodes lesions determining right hydro-ureteral distension, requiring placement of ureter stent, stable liver, bone metastases. Three more cycles were administered. At PFS 8 months, CT scan showed increased lung, lymph nodes metastases. Fifth-line trifluridine-tipiracil 35 mg/m^2/bid, d1–5, 8–12 was administered, every 28 days. At first cycle, patient experienced LTS-ms: febrile G4 leucopenia, G3 neutropenia requiring granulocyte colony stimulating factors and antibiotics, G3 thrombocytopenia, G3 asthenia, G2 anemia, diarrhea, hypotension, associated with G1 nausea, mucositis. Dose was reduced at 25 mg/m^2/bid. After fourth cycle, PFS 4 months, CT scan showed progression of lung, lymph nodes, liver, bone, pelvic metastases. Overall, second–fifth treatment lines obtained PFS 28 months.

No druggable, nor actionable molecular target was detected; ERBB2 and MGMT on liver metastases, MLH1, MSH2, MSH6, PMS2 in primary rectal cancer by immunohistochemistry were normally expressed; microsatellite instability analysis showed stable (MSI-S) genotype.

Then, patient was on best supportive care (BSC); 6 weeks after progression, she was admitted in Palliative Care Unit due to rapidly decreasing clinical conditions and 2 weeks apart she died. *De novo* metastatic disease OS was 58 months, gained by intensive integration between first-line FIr-B/FOx and secondary resections of liver metastases, short-course RT, primary rectal cancer resection, further second–fifth lines of treatment (*Table 1*).

All procedures performed in this case report were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration (as revised in 2013). Step-by-step, patient was informed about diagnostic, clinical, biologic features, each proposed multidisciplinary treatment strategy. She shared each proposed treatment, signed written informed consent. Written informed consent was obtained for publication of any potentially identifiable images or data included in this article.

Discussion

The complexity of combined clinical and human features frequently and variably characterizing MCRC patients are summarized in the reported CRC patient who gained OS 58 months, due to the efficacy of subsequent multidisciplinary intensive medical and surgical treatment strategies and, more, due to her resilience to challenge the affecting metastatic disease, as a life priority. Patient was affected by bulky, bilateral liver-limited metastases from locally advanced rectal cancer with lymph nodes metastases. She was fit for multidisciplinary intensive first-line FIr-B/FOx (2), previously developed from doublet and triplet chemotherapy (16,17), and after a PR, liver metastases were converted to resectability (4), and also resection of primary cancer after short-course RT was performed. Eight months of intensive, integrated medical, surgical, radio-therapeutic approaches converted the bulky into oligometastatic disease, consisting of single liver and inferior mesenteric nodal metastasis, at PFS 9 months. Two further FIr-B/FOx cycles re-introduction were proposed due to PFI 4 and 3 months, respectively, obtained by integrated metastasectomies, gaining overall PFS 26 months and OS 58 months (8).

In fit patients, first-line FIr-B/FOx reported ORR 82%, secondary liver resections 26%, PFS 12 months, median OS 28 months (2); >50% liver metastasectomies, PFS 17 months, OS 44 months in liver-limited (4,6); *KRAS* exon 2 wild-type liver-limited patients reached significantly prolonged outcome due to secondary surgery, compared to mutant (5). Increased efficacy and liver resections were confirmed in non-elderly *RAS* wild-type patients treated with intensive FIr-C/FOx-C triplet chemotherapy associated with cetuximab, reaching PFS 12 months (3). FIr-B/FOx re-challenge, in patients with previous OR, PFS ≥10 months, PFI ≥3 months, no previous limiting toxicities, achieved ORR 80%, 40% secondary resections, PFS 13 months, 2-year OS 80% (median OS not reached at median follow-up 31.5 months) (8). Clinical outcome was significantly favourable in re-challenged patients, unfavourable in c.35 G>A *KRAS* mutant (8,18,19).

In the reported patient, further lines of treatment raised OS 31 months from second line treatment: second line modified schedule/dose aflibercept/irinotecan gaining PR of liver metastases, integrated with stereotactic radiation therapy, PFS 8 months; third line anti-EGFR panitumumab, driven by *KRAS/NRAS/BRAF* wild-type and *EGFR* c.2156 G>C mutation (p.G719A), PR of bilateral lung, liver, lymph nodes metastases, PFS 8 months; fourth line regorafenib achieved a stable disease, PFS 8 months; fifth line trifluridine-tipiracil, PFS 4 months before markedly disease progression. In patients resistant or progressing after oxaliplatin-based first-line treatment, aflibercept/FOLFIRI significantly improved OS 13.5 months, PFS 6.9 months, ORR 19.8%, and 22.3% of patients reached 30 months OS; in real life, PFS 5.3–6.8 months, OS 12 months, ORR 21.8% were reported; modified schedules/doses required in >50% of patients did not significantly affect clinical outcomes. Synchronous MCRC patients showed significantly worse PFS 5 months, OS 10 months, while left-sided longer PFS 7 months, OS 12 months. Prevalently reported limiting toxicities were diarrhea, asthenia, mucositis, neutropenia, hypertension (9).

In *KRAS/NRAS* wild-type, second-line panitumumab/FOLFIRI reached PFS 6.4 months. In early trial, panitumumab demonstrated efficacy after first and second lines failed (10). Concomitant *EGFR* mutation, reported in 1.6% colorectal cancer, even more justified third-line panitumumab treatment, achieving PFS 8 months; EGFR exon 18 c.2156 G>C (p.G719A) is a deleterious, gain-of-function mutation with predictive relevance. Other EGFR extracellular domain mutations detected after treatment justify acquired resistance to anti-EGFR.

In chemorefractory patients, regorafenib reported OS 6.4 months (11), PFS 1.9 months, disease control rate 41%. In Asian population (60% treated with VEGF- or EGFR-targeted drugs, or both) greater benefit was reached: OS 8.8 months, PFS 3.2 months, disease control rate 51%. In real-life, OS 5.6 months: patients received 78.9% planned dose, 76% dose modifications. Hand-foot skin reaction occurrence during first month was associated with significantly better OS 7.7 months, 6-month OS (61%). Trifluridine-tipiracil significantly increased OS 7.1 months, 1-year OS 27%, PFS 2.0 months, disease control rate 44%; patients received 89% planned dose, 4% withdrawal (12). Prevalent G3–4 adverse events were neutropenia 38%, febrile neutropenia 4%, thrombocytopenia 5%, vomiting 2%, diarrhea 3%.

Multidisciplinary strategies characterized by intensive medical treatments require careful toxicity monitoring, proper clinical management, treatment modulations due to moderate/severe toxicities (1). To better evaluate toxicity burden in individual patients, we recently proposed innovative concept of LTS: LTS-ss, characterized by the limiting toxicity (LT), LTS-ms, including LT associated to G2 or other LT (2,13-15). In FIr-B/FOx treated patients we reported LTS 44%, mainly represented by LTS-ss (2); in young-elderly 46%, mainly including diarrhea (69.2%), and significantly more LTS-ms compared to LTS-ss (13-15). Patient experienced LTS-ms at FIr-B/FOx re-introductions, G3 diarrhea, associated with G2 asthenia, nausea, requiring irinotecan reduction, 5-fluorouracil discontinuation. Reported LTS may be favored by mutations of genes affecting fluoropyrimidine and/or irinotecan metabolism, mainly including dihydropyrimidine dehydrogenase (*DPYD*) and *UGT1A1* genes, justifying inter-patient safety variability (20); in patients treated with triplet chemotherapy (COI regimen), plus bevacizumab or cetuximab, independent significant association with severe toxicity and treatment modifications was found for *DPYD* and a trend for *UGT1A1**28 mutations (P=0.054) (20). In patients treated with FIr-C/FOx-C (3), reduced FUDR, *UGT1A1**28, and *CYP3A4* single-nucleotide polymorphisms (SNPs) were prevalently detected in patients with LTS and may predict individual LTS occurrence, specifically gastrointestinal; most patients (65%), specifically developing gastrointestinal LTS (78%), showed >1 pharmacogenomic alteration (1-3). In reported patient, safety profile of further treatment lines was characterized by specific toxicity syndromes; fifth-line trifluridine-tipiracil by LTS-ms. Concomitant occurrence of

several, different toxicities in individual patient confirmed relevance of evaluating individual toxicity syndromes (15).

Overall, reported patient affected by *de novo*, bulky metastatic disease gained OS 58 months, PFS 26 months of integrated first line, OS 31 months from second line, by intensive, multidisciplinary treatment strategies, requiring careful, continuous toxicity monitoring, patient's resilience for such a long commitment to complex, continuous therapeutic pathway, including several treatments lines, surgical resections, topical treatments. Careful evaluation of toxicity syndromes represents a clinical parameter measuring how much patient suffers from oncological treatments, indicating individual resilience. Step-by-step, patient was informed about diagnostic, clinical, biologic features of disease and multidisciplinary strategy. Clinical management was shared with patient, weighing each proposed treatment with patient's priorities, regarding options, safety, implications on daily living, modulations/suspensions, surgery and integration of interventional approaches. In individual MCRC patient fit for intensive treatments, clinical outcome and care also depends upon resilience, careful monitored at each step of disease evolution.

Conclusions

In clinical practice, selection of MCRC patients eligible for intensive medical treatments to achieve optimal activity and long-term OS by close integration with surgical strategies should evaluate biological (*RAS/BRAF*), clinical (age, performance status, CIRS) parameters, integrated with careful monitoring of individual safety using LTS, and patient's resilience as life priority to challenge long-term survival.

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