Metastatic colorectal cancer

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Introduction

The presence of metastases classes patients in M1 of the TNM and stage IV of the UICC/AJCC classification. Involvement of the external or common iliac lymph nodes is considered M1. Metastases are observed in 40%–60% of cases (synchronous in 25% of cases). Of 100 patients with colon cancers, 15–20 have synchronous liver metastases and 20 will have metachronous liver metastases within 5 years.

Progress in chemotherapy and the arrival of targeted biotherapies should not make us forget that only surgical resection offers the possibility of cure. The main chemotherapy protocols and advice on the management of the undesirable effects of biotherapies (inhibitors of EGFr and angiogenesis) are presented, respectively, in annexes 1, 2 and 3.

Most of the recommendations in this second version of the National Digestive Cancer Guidelines stem from the updating of the recommendations for clinical practice of various learned societies (FFCD [1], SOR of the FNCLCC [2, 3], and GERCOR [4]), as well as documents from the 1998 consensus meetings [5] or the January 2003 good clinical practice meetings [6].

Pretherapy explorations [1, 2, 5, 6, 9]

References

- Complete clinical examination including digital rectal exam, palpation of lymph node areas, and evaluation of performance status (expert agreement)
- Biological tests: blood count, platelets, TP, TCK, creatinemia, protidemia, alkaline phosphatases
- ECG or cardiology consultation if necessary
- Thoracoabdominal-pelvic CT with injection, if possible multi-barrettes (level of evidence B)
- If metastasis excision is planned:
- Anesthesiology consultation
- Colonoscopy if the last one is more than 3 years old or was incomplete (expert agreement)

Alternatives

- Biological tests: ACE especially if disease is not measurable (level of evidence C), total LDH (expert agreement)
- Liver MRI with injection of gadolinium if the CT with injection is contraindicated (iodine allergy, renal failure) or is insufficient to characterize lesions (level of evidence B)
- Percutaneous liver biopsy if surgery is not planned and there is doubt concerning diagnosis (level of evidence C)

If excision of metastasis is planned:
- MorphoPET when this examination is available (level of evidence B)
- Clearance of indocyanine green if underlying liver disease (expert agreement)
- CT liver and tumor volume measurements if there is doubt on the percentage of normal liver after hepatectomy (level of evidence C)
- Biopsy puncture of nontumorous liver if doubt on associated liver disease (expert agreement)

Resectability and operability criteria

Surgical resection, which remains the only curative treatment, should always be discussed in a multidisciplinary consultation meeting including at least one surgeon and one radiologist experienced in liver disease. The discussion relies on the risk-benefit ratio of the surgery. For liver and lung metastases, the criteria are [1, 2, 6, 10]:

- Patient’s condition: compatible with anesthesia and metastasis resection
- Oncological: no extrahepatic or extrapulmonary tumors that cannot be totally resected
- Anatomical: vascular invasion (portal pedicle, suprahepatic), location parenchyma can be left with its own vascularization and biliary drainage
- Techniques: possibility of leaving residual volume >25%–40% of healthy liver. Based on the workup, two levels of difficulty and poor oncological prognostic criteria can be defined (Table I) [10].

Treatment

Resectable hepatic metastases [1, 2, 10-13]

References

The intervention begins by complete exploration of the abdominal cavity then visual and manual exploration of the liver
Alternatives to surgery include metastasectomy or lobectomy after thoracotomy or sternotomy. The hepatectomy techniques depend on the size, number, and topography of the metastases.

Excision should be done if possible:
- with a safety margin of healthy liver of at least 1 cm and at least 5 mm (level of evidence C)
- limiting blood loss using vascular clamps
- preserving a maximum of healthy tissue.

In case of synchronous metastases of the primary tumor: liver resection 2–3 months after colon excision except if:
- metastasis known preoperatively,
- easy access with minor excision (class I)
- uncomplicated primary tumor

=> resection in a single operation with digestive anastomosis before hepatectomy [14].

In case of associated resectable pulmonary metastases: begin by liver excision then lung resection 2–3 months later. (level of evidence C)

In case of class II resectability: management in an experienced center (expert agreement)

In case of pedicular or celiac adenopathy:
- if class I resectability, surgery with lymph node removal;
- if class II resectability, surgery is not recommended (level of evidence C).

Alternatives
- Laparoscopy with echolaparoscopy if there is a strong suspicion of nonresectability or carcinomatosis (level of evidence D)
- Preoperative right portal embolization [13, 15]
  — if right lobe hepatectomy with remaining left liver volume <25% (if between 25% and 40%, discuss on a case by case basis)

A30- to 45-day delay between embolization and hepatectomy

— given the risk of tumor growth in nonembolized liver, two operations [16] or radiofrequency treatment of the lesions of future liver remnant is advised [17] (level of evidence C)

- Hepatectomy in two operations [16]
- Preoperative chemotherapy should be discussed if class II resectability and/or poor oncological criteria and/or synchronous metastases with 5FU, folinic acid, and irinotecan or oxaliplatin for 2–3 months then re-evaluation in multidisciplinary consultation meeting [6, 18] (expert agreement)

- Radiofrequency destruction [19, 20] during operation or percutaneous in addition to surgery for lesions <3 cm and more than 1 cm of the bile duct (level of evidence D)
- Postoperative chemotherapy should be discussed, with LV5FU2 or FOLFOX4 for 6 months (expert agreement) or by induction CT that has made resection possible depending on the intensity of the response, cumulative toxicity, and postoperative events [18] (expert agreement)
- Postoperative hepatic intra-arterial chemotherapy in experienced centers [18] (level of evidence C)

Clinical trials
- GERCOR C01-2 MIROX: pre- and postoperative FOLFOX4 vs pre- and postoperative FOLFOLX7 x 6 and FOLFIRI x 6 (also if pulmonary metastases) (M Hebbat)
- FNCLCC-METHEP phase II–III (metastases of class II resectability): FOLFIRI vs FOLFOX4 vs FOLFIRI HD vs FOLFOX7 vs FOLFIRINOX (M Ychou)

Resectable extrahepatic metastases

References (level of evidence B2)

For lung metastases, the indications are the same as for liver metastases: surgery alone if complete excision is possible (wedge metastasectomy or lobectomy after thoracotomy or sternotomy).

Alternatives
- Complete resection is exceptionally possible in lymph nodes, peritoneum, brain, adrenal glands, and ovaries.
- Intraperitoneal chemotherapy (IPC) +/- hyperthermia (CHIP) [21-23] is indicated in cases of isolated peritoneal carcinomatosis or ovarian metastases in a patient with good performance status, who is under 65 years of age, with no visceral failure, in experienced centers after surgical resection (requires removal of all lesions and no residues remaining >2 mm in diameter if possible) (level of evidence C)
- Postoperative radiotherapy is recommended after resection of cerebral metastases (level of evidence B).

Nonresectable metastases

INDICATIONS AND CHOICE OF CHEMOTHERAPY [1, 3, 18]

References

Palliative chemotherapy aiming at maintaining quality of life and lengthening survival (level of evidence B) is recommended in the following conditions:
- without waiting for symptoms to appear
- at doses adapted to tolerance

French Guidelines for Digestive cancers. Metastatic colorectal cancer

Table I. – Level of resectability difficulty and poor oncological prognostic criteria [10]

<table>
<thead>
<tr>
<th>Class resectability</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I resectability</td>
<td>Obvious for classical hepatectomy (4 segments or fewer, leaving more than 40% residual parenchyma)</td>
</tr>
<tr>
<td>Class II resectability</td>
<td>Possible by complex or very wide hepatectomy (more than 4 segments) requiring a difficult and/or risky procedure (e.g., central hepatectomy with vascular exclusion, right-side wide hepatectomy, vascular reconstruction)</td>
</tr>
<tr>
<td>Resectability impossible</td>
<td>Involvement of 2 portal pedicles, involvement of one portal pedicle and the contralateral suprahepatic vein, involvement of 3 suprahepatic veins</td>
</tr>
</tbody>
</table>

Poor prognostic oncological criteria:
- size >5 cm, number >3, two-lobed, pedicular lymph node invaded, high ACE

completed by intraoperative ultrasound. Any suspect lymph node should be sampled. Excision surgery of liver metastases should radically remove any metastases individualized on the intraoperative morphological workup, completed by intraoperative ultrasound.

**Resection is indicated only when complete excision (R0) is possible (in 1 or 2 operations).**

**The hepatectomy techniques** depend on the size, number, and topography of the metastases.

References (level of evidence B)

- References (level of evidence B2)

- References (level of evidence B3)

- References (level of evidence C)

- References (level of evidence D)

- References (level of evidence E)

- References (level of evidence F)

- References (level of evidence G)

- References (level of evidence H)

- References (level of evidence I)

- References (level of evidence J)

- References (level of evidence K)

- References (level of evidence L)

- References (level of evidence M)

- References (level of evidence N)

- References (level of evidence O)

- References (level of evidence P)

- References (level of evidence Q)

- References (level of evidence R)

- References (level of evidence S)

- References (level of evidence T)

- References (level of evidence U)

- References (level of evidence V)

- References (level of evidence W)

- References (level of evidence X)

- References (level of evidence Y)

- References (level of evidence Z)

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• formal pathological proof of cancer at least on the primary tumor
• patient bedridden for at least 50% of the daytime (WHO performance status 0, 1, or 2)
• patient informed of treatment with benefits, restrictions, and potential side effects
• nonresectable metastases
• no serious visceral deficiency

The items in the prognostic classification of Köhne and al. (Table II) [24] can be used as stratification factors for clinical trials; their utility in the choice of therapeutic indications has not been validated.

For patients over the age of 75 years, chemotherapy is recommended after geriatric evaluation. Indication depends on the level of dependency and co-morbidities [3]. (expert agreement)

Effectiveness should be evaluated after 2–3 months of treatment:

• in case of response, surgery should be discussed again
• in case of response or stability, if metastases remain unresectable: pursue chemotherapy or discuss with the patient the possibility of pausing therapy until progression with re-evaluation every 2 months
• in case of progression: stop or change chemotherapy protocol (see above).

Which chemotherapy?

Seven regimens can be discussed depending on the patient’s wishes, toxicity, contraindications, and the disease characteristics:

• LV5FU2 [25] (level of evidence A)
• IRIFU2 (irinotecan 180 mg/m² (Campto®)-LV5FU2) [26]: contraindication if hyperbilirubinemia (>25 micromol/l or 15 mg/l) (level of evidence A)
• FOLFIRI (irinotecan 180 mg/m²-simplified LV5FU2)[27, 28] less restrictive (level of evidence A)
• FOLFOX4 (oxaliplatin 85 mg/m² (Eloxatine®)-LV5FU2) [29, 30] (level of evidence A)
• bevacizumab 5 mg/kg (Avastin®)-LV5FU2 according to Kabbinava and al. [31, 32] with modified 5FU protocol; contraindications including untreated brain metastases, proteinuria >1 g/24 h, recent and/or symptomatic arterial thromboembolic antecedent (<6 months), surgery <28 days, ulcer or unhealed wound, aspirin >325 mg/day, uncontrolled high blood pressure; caution if there is intra-abdominal inflammation (diverticulitis, colitis, ulcer) because of increased risk of perforation (level of evidence B)
• bevacizumab 5 mg/kg-FOLFIRI according to Hurwitz and al. [33] with modified 5FU and irinotecan protocol if good general health (WHO 0 or 1); contraindications, see bevacizumab and LV5FU2 (level of evidence A)
• OPTIMOX 1 (FOLFOX7 (simplified oxaliplatin 130 mg/m²-LV5FU2 with no FU bolus) 6 courses then simplified LV5FU2)[34], less neurotoxicity (level of evidence B) (this opinion has not been retained by all experts)

In case metastases could become resectable if there is response, a protocol giving a high response rate is preferable in view of secondary resectability [3, 18]. Several protocols of combinations that have been validated by phase III trials respond to this criterion: polychemotherapy combining 5FU, folinic acid, and irinotecan plus or minus bevacizumab or 5FU, folinic acid, and oxaliplatin if there is no contraindication (expert agreement). Bevacizumab has not yet been evaluated before liver surgery; a free interval of at least 6 weeks (2 half-lives) is necessary between the last administration of bevacizumab and surgery.

Alternatives

• A pause in therapy until there is new progression should be discussed with the patient if the chemotherapy has been effective and/or toxicity with re-evaluation every 2 months [35] (level of evidence C)
• Simplified LV5FU2 [36] is less restrictive but not validated by phase III trial (level of evidence D)
• LVfbolus5FU2 [37], shorter protocol than LV5FU2 (level of evidence B)
• Chemotherapy per os (capcitabine (Xeloda®) [38, 39] or uracil/tegafur (UFT®)+ folinic acid [40, 41]) in patients refusing hospitalizations or perfusions, but potential toxicities should not be forgotten (level of evidence B1); adopt doses to creatinine clearance for capcitabine
• Simplified FOLFOX4 (oxaliplatin 85 mg/m²-simplified LV5FU2) less restrictive (expert agreement)
• FOLFOX6 (oxaliplatin 100 mg/m²-simplified LV5FU2) [27] less restrictive but no comparison available with FOLFOX4 (level of evidence B)
• OPTIMOX 1 (FOLFOX7 (oxaliplatin 130 mg/m²-simplified LV5FU2 without FU bolus) 6 courses then simplified LV5FU2)[34] less neurotoxicity (level of evidence B)
• XELOX [42] less restrictive than FOLFOX but not validated by a phase III trial (level of evidence B)
• XELIRI [43, 44] less restrictive than FOLFOX but not validated by a phase III trial (level of evidence B)
• Intraarterial hepatic chemotherapy [45-47] if metastases only in liver; in experienced centers (level of evidence C)
• Chemotherapy with pharmacokinetic 5FU adaptation [48, 49] (level of evidence C)
• Radiotherapy if brain metastases; should be discussed if metastases incompletely resected and minimal tumor remainder, or if local, nonresectable or symptomatic recurrence.

Alternatives if contraindication to fluoropyrimidines (5FU, capcitabine, UFT):

• Raltitrexed (Tomudex®) [37, 50-52, 55] adaptation of doses to creatinine clearance; antidote = folinic acid (level of evidence C)
• Raltitrexed-oxaliplatin (TOMOX) [53, 54] (level of evidence D)
• Irinotecan-oxaliplatin (IRINOX) [30, 55] (level of evidence D)
• Irinotecan [56] (level of evidence D)
• Oxaliplatin 130 mg/m² every 21 days [58] (level of evidence D)

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Clinical trials

a) FFCD 2000-05 (strategic): simplified LV5FU2 then FOLFOX 6, then FOLFI R or FOLFOX 6, then FOLFI R, then third-line treatment (M Ducreux)
b) FFCD 2001-02 in patients >75 years: LV5FU2 vs simplified LV5FU2 +/- irinotecan (E Mitry)
c) GERCOR OPTIMOX2: modified FOLFOX7 x 3 months then maintenance with simplified LV5FU2 and reintroduction of FOLFOX at progression vs modified FOLFOX7 x 3 months followed by pause and reintroduction of FOLFOX at progression. (A de Gramont)
d) GERCOR DREAM: OPTIMOX3/FOLFOX7 + bevacizumab vs XELOX2 + bevacizumab +/- erlotinib (Tarceva®). (C Tournigand)
e) GERCOR CO4-1 (nonresectable lymph node with no visceral metastases) FOLFOX + radiotherapy (L Mineur)
f) FNCLCC Accord 13 MEXICO: FOLFI R-bevacizumab vs XEURI-bevacizumab (M Ducreux)
g) EORTC 40004 (CLOC C): FOLFOX 4 vs FOLFOX 4 + radio-frequency destruction
h) FFCD (a few centers, Nord region, France): alternate high-level FOLFI R and radiofrequency destruction (M Hebbar)
i) AERO-BGDO MC04: maintenance CT with capecitabine vs monitoring after stability or objective response after first-line chemotherapy (E Fabre-Guillemin)

What should be done if progression with CT?

Progression is defined as an increase >25% of one of the lesions or the sum of the products of the diameters of the measurable targets (WHO criteria) or >20% increase in the sum of the largest diameters (RECIST criteria) compared to the smallest sum, or the appearance of a new lesion whatever the response of the other targets.

References

Cessation of chemotherapy or initiating a new chemotherapy protocol should be discussed depending on the performance status and wishes of the patient. Symptomatic treatment without chemotherapy is necessary in a patient whose general health has deteriorated or who has jaundice or occlusion. The occlusion and the jaundice are not absolute contraindications if they can be treated by surgical derivation or endoscopic stent.

The different options should be discussed according to the patient’s wishes, toxicities, and contraindications:

a) if progression with LV5FU2, capecitabine, UFT, or raltitrexed:
   • Irinotecan 180 mg/m² + LV5FU2 (IRIFU2) [58] or simplified LV5FU2 (FOLFI R) [27, 59] (level of evidence B)
   • Oxaliplatin 85 or 100 mg/m² + LV5FU2 or simplified LV5FU2 (FOLFOX 4 or 6) [27, 60-62] (level of evidence C)
   • Bevacizumab (Avastin®) 5 mg/kg plus FOLFOX4 after Giat ronio and al. [64] in absence of first-line and taking contraindications into account (level of evidence B)

b) if the primary tumor is asymptomatic: given the contradictions to discuss on a case by case basis in multidisciplinary consultation meeting with either primary surgery [73, 74] or chemotherapy for 2 months, then discussion depending on effectiveness of chemotherapy, the patient’s performance status, and metastasis site [75-78] (level of evidence D)

• Cetuximab (Erbitux®) 400 mg/m² then 250 mg/m² weekly plus irinotecan every 14 days [63] if positive EGFr (one cell marked in immunohistochemistry) (level of evidence B)

Alternatives

References

a) If the primary tumor is symptomatic (anemia, stenosis): discuss surgery or endoscopic stent (if stenosis but no anemia).

b) If the primary tumor is asymptomatic: given the contradicto-ry data in the literature, the best strategy is to discuss on a case by case basis in multidisciplinary consultation meeting with either primary surgery [73, 74] or chemotherapy for 2 months, then discussion depending on effectiveness of chemotherapy, the patient’s performance status, and metastasis site [75-78] (level of evidence D)

• Oxaliplatin 85 or 100 mg/m² + LV5FU2 or simplified LV5FU2 (FOLFOX 4 or 6) [27, 60-62] (level of evidence C)
• Bevacizumab (Avastin®) 5 mg/kg plus FOLFOX4 after Giantonio and al. [64] in absence of first-line and taking contraindications into account (level of evidence B)

d) if progression with irinotecan and oxaliplatin:
   • Cetuximab (Erbitux®) 400 mg/m² then 250 mg/m² weekly plus irinotecan every 14 days [63] if EGFr positive (one cell marked in immunohistochemistry) (level of evidence B) or if EGFr negative [65, 66] in a patient in good general health and informed of the risks (level of evidence D)

e) if progression with fluoropyrimidines, irinotecan, oxaliplatin, and cetuximab:
   • Palliative care or therapeutic trial

Which treatment for primary colon tumor in case of nonresectable synchronous metastases?

References

a) FFCD 03-05 (subject >75 years): irinotecan vs CA PIRI (T Aparicio)
b) GERCOR: Pemetrexed + irinotecan
c) GERCOR: Velcade + FOLFIRI (C Louvet)
Clinical trials

**FFCD-FRENCH 03-06 trial:** FOLFIRI vs primary surgery followed by FOLFIRI (B Dousset)

Which treatment for rectal primary tumor when there are nonresectable synchronous metastases?

For these tumors with poor prognosis, the treatment goal is maintaining patient’s quality of life and avoiding, if possible, both painful pelvic progression and mutilating surgery of the abdominal-pelvic resection type.

**SYMPTOMATIC TUMOR:**

References

- either radiotherapy or coagulation (laser or argon plasma), endoscopic stent (if lower pole is more than 6 cm from the anal margin) or colostomy, then radiotherapy +/- chemotherapy
- or excision followed by chemotherapy

Alternatives

- short preoperative radiotherapy (25 Gy in 5 fractions), then surgery 1 week later.
- induction chemotherapy then radiochemotherapy

**NONSYMPTOMATIC TUMOR:**

Discuss in multidisciplinary consultation meeting radiotherapy or chemotherapy alone, and evaluation after 2 months.

**SYMPTOMATIC LIVER METASTASES:**

Discuss in multidisciplinary consultation meeting, if general condition allows, primary chemotherapy (bi-therapy).

**Post-therapy monitoring [5, 79]**

After curative treatment

References (level of evidence D)

In patients capable of sustaining a second intervention or chemotherapy:

- **Clinical examination** every 3 months for 3 years then every 6 months for 2 years
- **Abdominal ultrasound** every 3 months for 3 years then every 6 months for 2 years
- **Lung x-ray** every year for 5 years (thoracic CT every 6 months for 3 years if lung metastases resected)
- **Coloscopy** at 3 years then every 5 years if normal
  - except if three adenomas or more, one of which is >1 cm or villous component => at 1 year
  - except HNPCC syndrome => every 2 years.

Alternatives

- **Abdominal-pelvic CT** if patient is obese or only slightly echogenic or if several radiologists are requested to monitor patient
- **CEA** every 3 months if it was high before treatment.

After radiofrequency [19, 20]

References (level of evidence D)

- **CT or MRI** at 2 months then every 3 months
  - The CT efficacy criteria are:
    - Hypodensity present on all vascular constriction times
    - Size greater than the size of the treated lesion
    - No contrast
    - No new lesion

Alternatives

- **PET CT:** if doubt on CT scan or MRI, but the examination is infrequently available.
- **Doppler ultrasound with injection of contrast product** if doubt at CT scan or MRI
- **CEA** every 3 months if it was high before treatment

During palliative treatment

References (level of evidence D)

Before each course:

- **Clinical examination** (weight, performance status, tolerance to chemotherapy with neurological examination if oxaliplatin, blood pressure measurement if bevacizumab, and skin examination if cetuximab) (see annexes 2 and 3 for cetuximab and bevacizumab)
- **Hemogram + platelets** (plus bilirubinemia if irinotecan; plus creatinine clearance if raltitrexed or capcitabine; plus transaminases if raltitrexed or capcitabine; plus **urinary sling** if bevacizumab)

Every 2–3 months (= 4–6 courses if chemotherapy /14 days or 3–4 courses if chemotherapy /21 days):

- **CT with injection** with mass measurement.

Alternatives

- **Ultrasound** if outside of therapeutic trial and by the same operator
- **Chest x-ray F+P** if lung metastases
- **ACE** in particular if disease not measurable
- **CA19.9** if high initially and ACE normal

Treatment of recurrences

- In case of recurrence of metastases, discuss resectability and operability (see sections II and III)
- **If resectable and operable:** repeated resections can provide results that are comparable to first resections; a new hepatectomy is warranted based on the same criteria as the first resection [10] (level of evidence C) (see section 4.1 and 4.2).
- **If not resectable,** see section Non Resectable metastases.

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Annex I. Main chemotherapy protocols

LV5FU2 = folinic acid 200 mg/m² (or L-folinic acid 100 mg/m²) in 2 h in 250 ml 5% isotonic glucose solution, rinse then 5FU 400 mg/m² in 10 min in 100 ml of 5% isotonic glucose solution then 5FU 1200 mg/m² in continuous perfusion 44 h in 5% isotonic glucose solution in portable infuser (isotonic solution 220 ml, 5 ml/h (ref. LV5)), pump or portable syringe pusher. every 14 days with evaluation after 4 courses (2 months) [25]

IRIFU2 = irinotecan (Campto®) + LV5FU2 irinotecan 180 mg/m² in 90-min perfusion in 250 ml of 5% isotonic glucose solution on D1 of LV5FU2 = every 2 weeks with evaluation after 4 courses (2 months), subcutaneous atropine when cholinergic syndrome during one of the injections, precise instructions given to patient (with prescription for loperamide) and to family physician in case of diarrhea. every 2 weeks with evaluation after 4–6 courses (2–3 months) [26]

FOLFOX 4 = oxaliplatin (Eloxatine®) + LV5FU2 oxaliplatin 85 mg/m² in 2 h in 250 ml of 5% isotonic glucose solution in Y IV of folinic acid on D1 of LV5FU2, every 2 weeks with evaluation after 4–6 courses (2–3 months) [29, 30]

bevacizumab (Avastin®) = bevacizumab 5 mg/kg in 90 min at course 1 then 60 min at course 2 then 30 min at following courses in 100 ml of isotonic fluid after chemotherapy on D1 of LV5FU2 plus or minus irinotecan; contraindications, including untreated brain metastases, proteinuria >1 g/24 h, recent arterial thromboembolic antecedent (<6 months), and/or symptomatic surgery <28 days, ulcer or unhealed wound, aspirin >325 mg/day, uncontrolled high blood pressure. Caution if intra-abdominal inflammation (diverticulitis, colitis, ulcer) because of increased risk of perforation every 2 weeks with evaluation after 4–6 courses (2–3 months) (after [31–33, 64])

cetuximab (Erbitux®) = cetuximab 400 mg/m² in 2 h IV in course 1 then weekly maintenance dose 250 mg /m² in 1 h IV associated every 14 days after 1 h of rest with irinotecan 180 mg/m² in 90-min perfusion in 250 ml of 5% isotonic glucose solution. Premedication with anti-H1 and monitoring because of risk of allergy. every week with evaluation after 8–12 courses (2–3 months) [63]

raltitrexed (Tomudex®) = raltitrexed 3 mg/m² in 15 min in 250 ml of 5% isotonic glucose solution (peripheral route and home administration possible) every 3 weeks with evaluation after 3 courses [37, 50-52, 55]

capcitabine (Xeloda®) = 2500 mg/m²/day (1250 mg/m² morning and evening), 2 weeks out of 3 with evaluation after 3 courses (9 weeks). [38, 39]

tegafur-uracil (UFT®) = 300 mg/m²/day tegafur and 672 mg/m²/day uracil + 90 mg/day folinic acid in 3 parts (every 8 h); 4 weeks out of 5 with evaluation after 2–3 courses (2–3 months). [40, 41]

Simplified LV5FU2 = folinic acid 400 mg/m² (or L-folinic acid 200 mg/m²) in 2 h in 250 ml 5% isotonic glucose solution, rinse then 5FU 400 mg/m² in 10 min in 100 ml 5% isotonic glucose solution, then 5FU 2400 mg/m² in continuous perfusion 46 h in 5% isotonic glucose solution in portable infuser (QSP 230 ml, 5 ml/h (ref. LV5)), pump or portable syringe pusher. every 14 days with evaluation after 4 courses (2 months) [36]

Simplified LVFBbolus5FU2 = folinic acid 40 mg/m² (or L-folinic acid 20 mg/m²) in bolus IV in 250 ml 5% isotonic solution rinse then 5FU 400 mg/m² in 10 min in 100 ml of 5% isotonic glucose solution then 5FU 2400 mg/m² in continuous perfusion, 46 h in 5% isotonic glucose solution in portable infuser (QSP 230 ml, 5 ml/h (ref. LV5)), pump or portable syringe pusher. every 14 days with evaluation after 4 courses (2 months) [after [37]]

XEOOX = oxaliplatin 130 mg/m² in 2 h in 250 ml 5% isotonic glucose solution then capecitabine (Xeloda®) 2000 mg/m²/day (1000 mg/m² morning and evening), 2 weeks out of 3 (D2–D15). every 3 weeks with evaluation after 3 courses (2 months) [42]

XELIIRI = irinotecan 240 mg/m² in 90-min perfusion in 250 ml 5% isotonic glucose solution on D1 then capecitabine (Xeloda®) 2000 mg/m²/day (1000 mg/m² morning and evening), 2 weeks out of 3 (D2–D15). every 3 weeks with evaluation after 3 courses (2 months) [43, 44]

FOLFIRI = irinotecan (Campto®) + simplified LV5FU2 = irinotecan 180 mg/m² in 90-min perfusion in 250 ml 5% isotonic glucose solution in Y IV of folinic acid on D1 of simplified LV5FU2 every 14 courses with evaluation after 4 courses (2 months) [27, 28, 59]

FOLFOX 6 = oxaliplatin (Eloxatine®) + simplified LV5FU2 = oxaliplatin 100 mg/m² in 2 h in 250 ml 5% isotonic glucose solution in Y IV of folinic acid D1 of simplified LV5FU2 every 2 weeks with evaluation after 4 courses (2 months) [27, 62]

FOLFOX 7 = oxaliplatin (Eloxatine®) + simplified LV5FU2 without 5FU bolus = oxaliplatin 130 mg/m² in 2 h in 250 ml 5% isotonic glucose solution in Y IV of folinic acid 400 mg/m² (or L-folinic acid 200 mg/m²) in 2 h in 250 ml 5% isotonic glucose solution rinse then 5FU 2400 mg/m² in continuous perfusion 46 h in 5% isotonic glucose solution in portable infuser (QSP 230 ml, 5 ml/h (ref. LV5)), pump or portable syringe pusher. every 2 weeks with evaluation after 4 courses (2 months) [34]

LV5FU2+ mitomycin C = mitomycin C 7 mg/m² in 15 min on D1 every 4 weeks of simplified LV5FU2. every 14 courses (28 days for mitomycin) with evaluation after 4 courses (2 months) [70]

Continuous FU + mitomycin C = mitomycin C 8 mg/m² in 15 minutes on D1 every 8 weeks and 5FU 250 mg/m²/day in continuous IV in infuser, pump or portable syringe pusher a long course for 7 weeks out of 8 until toxicity or progression (maximum for mitomycin C: 50 mg/m²) [68, 69]
Capecitabine (Xeloda®) + mitomycin C = mitomycin C 7mg/m² in 15 min on D1 every 6 weeks then capecitabine 2000 mg/m²/day (1000 mg/m² morning and evening), 2 weeks out of 3 (D2–D15 then D23–D36). every 42 days with evaluation after 2 courses (3 months) [71, 72]

TOMOX=raltitrexed (Tomudex®) + oxaliplatin (Eloxatine®) = raltitrexed 3 mg/m² in 15 min in 250 ml 5% isotonic glucose solution then 45 min after oxaliplatin 130 mg/m² in 2 h in 250 ml 5% isotonic glucose solution every 3 weeks with evaluation after 3 courses [53, 54]

Annex II. Advice on management of undesirable effects of EGFr inhibitor (cetuximab)

According to the Digestive Oncology Network of Champagne-Ardenne Recommendations (RESCOD)

Acknowledgments of reader: Géraldine Perceau (Dermatology, CHU Robert Debré, Reims)

Xerosis

- maintain good skin hydration (e.g., Dexeryl® creme 2 applications per day after washing)
- antihistamines if pruritic (e.g., Clarityne® 1 capsule per day in the morning)

Acneiform eruption

AGGRAVATING FACTORS:

- excessive exposure to the sun
- concurrent radiotherapy
- insufficient skin hydration

PREVENTIVE TREATMENTS:

- emollients, no sun at all, total sun screen, washing with dermatologic soap
- no contraindication concerning tinted cover cream such as Dermablend®

CURATIVE TREATMENTS: (PRESCRIPTION EXAMPLES)

Minimal forms: emollient + local metronidazole

- Dexeryl® creme, 1–2 applications per day after washing
- Rosex® creme, 2 applications morning and evening

Inflammatory forms of the trunk: benzoyl peroxide locally

- Cutacnyl® gel 10%, 1 application in the evening

Intermediate forms: metronidazole locally, cyclins per os, + class III corticoid locally

- Dexeryl® creme, 1 application in the evening
- Rosex® creme 2, applications morning and evening
- Tolexine® 100 mg capsule, 1 capsule per day in the middle of meal for 1 month then one 50 mg capsule per day renewable for several months.
- Diprosone® creme 1 application in the evening

Serious forms (secondary infection) or atypical => dermatological consultation

- cessation of the anti-EGFr discussed between dermatologist, oncologist, and the patient.

Hypertrichosis

- cut eyelashes if eye irritation
- epilation if esthetic and psychological effect
Perionyx

PREVENTIVE TREATMENTS

- pedicure before beginning treatment
- do not cut nails too close in corners
- good hygiene, avoid microtraumas

CURATIVE TREATMENTS

- antiseptic (e.g., Betadine® scrub 4% bath once a day)
- if painful: antiseptic + local class IV corticoid (e.g., prescription below)
  - Biseptine® spray 1 application per day then
  - Dermoval® creme one thick layer then occluding bandage
  - Compresses 10 x 10 1 box of 100 Omnifix 1 box
- if secondary infection: dermatologist’s opinion

ASTHENIA AND/OR PARESTHESIAS

dosage of the magnesemia and calcemia then supplementation if deficiency

Annex III. Advice for management of undesirable effects of anti-angiogeneses (bevacizumab)

According to the Digestive Oncology Network of Champagne-Ardennes Recommendations (RESCOD)

Acknowledgements of reader: Jean-Pierre Chabert (Cardiology, CHU Robert Debré, Reims)

Arterial hypertension

— blood pressure measurement after at least 5 min of rest
— if systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg take after 5 more min of rest

MONITORING OF ANTI-ANGIOGENESIS THERAPY

| Grade 1 hypertension: asymptomatic, transitory (<24 h) up to 150/100 mmHg |
| => no treatment and continuation of anti-angiogenic |
| Grade 2 hypertension: recurring or persistent (>24 h) or symptomatic with diastolic BP increased by 20 mmHg or SBP/DBP >150/100 mmHg |
| => antihypertensive monotherapy without suspending antiangiogenic |
| Grade 3 hypertension: not controlled by monotherapy (or by bi-therapy for patients already treated for high blood pressure before antiangiogenic treatment) |
| => suspend antiangiogenic until BP balanced (SBP/DBP < 150/100 mmHg) |
| Grade 4 hypertension: High blood pressure affecting vital prognosis (e.g., hypertensive crisis) |
| => definitive cessation of antiangiogenic |

ANTIHYPTENSIVE TREATMENT (EXAMPLES TO FACILITATE PRESCRIPTION)

First intention = monotherapy

| diuretics: | Esidrex® 1 tablet/day |
| Lasilix® delay 60 mg 1 tablet/day |
| or enzyme conversion inhibitors (ECI): | Zestril® 20 mg 1 tablet/day |
| Triatec® 5 mg 1 tablet/day |
| if renal failure | Zestril® 5 mg 1 tablet/day |
| Triatec® 1.25 mg 1 tablet/day |
| or angiotensin 2 antagonist | Cozaar® 50 mg 2 tablets/day |
SECOND INTENTION = BI-THERAPY BY FIXED-DOSE ASSOCIATION

If after 4 weeks of monotherapy systolic BP >140 mmHg and diastolic BP >90 mmHg

<table>
<thead>
<tr>
<th>ECI + diuretic:</th>
<th>Co-renitec®1 tablet/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>or angiotensin 2 antagonist + diuretic:</td>
<td>Hyzaar® then Fortzaar® 1 tablet/day</td>
</tr>
</tbody>
</table>

THIRD INTENTION, IF RESISTANCE TO BI-THERAPY => SEEK CARDIOLOGIST’S OPINION

Antihypertensives and associated pathologies

<table>
<thead>
<tr>
<th>Associated pathologies</th>
<th>Preferred class</th>
<th>Class to avoid or use with caution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary failure</td>
<td>β-blockers, calcium channel blockers</td>
<td>Direct vasodilators</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>ECI, diuretics</td>
<td>β-blocker Calcium channel blockers (Verapamil, Diltiazem)</td>
</tr>
<tr>
<td>Conductive problems</td>
<td>ECI, diuretics</td>
<td>Calcium channel blockers (Verapamil, Diltiazem) β-blockers</td>
</tr>
<tr>
<td>Obstructive cardiopathy</td>
<td>β-blockers, verapamil, diltiazem</td>
<td>ECI, β-blocker, central antihypertensives, diuretics</td>
</tr>
<tr>
<td>Arteriopathy</td>
<td>ECI, calcium channel blockers</td>
<td>β-blockers</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Low-dose ECI, loop diuretics</td>
<td>Thiazides, K-sparing diuretics</td>
</tr>
<tr>
<td>Diabetes</td>
<td>ECI, calcium channel blockers</td>
<td>β-blocker</td>
</tr>
<tr>
<td>Asthma COPD</td>
<td></td>
<td>β-blockers</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>β-blockers, diuretics</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>Central antihypertensives</td>
</tr>
</tbody>
</table>

Monitoring if anticoagulants and/or thrombosis

IF TREATMENT AT PREVENTIVE DOSE

= association possible with Avastin®

• aspirin <325mg/day
• if anti-vitamin K or low-molecular-weight heparin = caution with monitoring by coagulation tests before each course

IF ARTERIAL THROMBOEMBOLIC EVENT

= definitive cessation of Avastin®

IF VENOUS THROMBOEMBOLIC EVENT

= suspension 2 weeks then start again if coagulation stable

monitor coagulation/ 2 days first week, then twice a week, then if stable at least before each course

When urinary sling proteinuria 2+ or 3+

Traitement 100%
Protéinurie ≤2g/24h avant la cure suivante

Protéinurie ≤2g/24h Traitement 100%
Protéinurie <2g/24h avant la cure suivante

>2g/24h ne pas administrer Avastin®

Protéinurie >2g/24h Traitement 100%
Protéinurie/24h après ≤1g/24h

>3g/24h ne pas administrer Avastin®

Protéinurie >3g/24h Traitement 100%
Protéinurie/24h après ≤1g/24h

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Contraindications

- untreated metastases of CNS
- pregnancy
- allergy to active substance

Precautions to take

- beginning of treatment at least 28 days after surgery and after complete healing of the surgical wound
- cessation of treatment at least 6 weeks before a planned surgical intervention
- increased risk of gastrointestinal perforation if diverticulitis or gastrointestinal ulcer
- increased risk of arterial thromboembolic event if patient over 65 years and/or has arterial thromboembolic event antecedent.
REFERENCES


4. GERCOR. Les Recommandations thérapeutiques (côlon) [on line]. 2005


14. GERCOR. Les Recommandations thérapeutiques (côlon) [on line]. 2005


