Chemotherapy for liver metastases

Rob Jansen

Medical oncologist MUMC+

June 3, 2016

Maastricht UMC+

academisch ziekenhuis Maastricht azM | Maastricht University

Disclosures

Advisory boards of Amgen, Roche

No conflicts of interest

Chemotherapy for liver metastases

- Synchronous metastases
- Metachronous metastases
- Resectable metastases
- Primarily irresectable metastases
- Definitively irresectable metastases

(Neo)(adjuvant) Chemotherapy

- 5-FU or capecitabin
- Oxaliplatin
- Irinotecan
- Bevacizumab
- Cetuximab/panitumumab
- Aflibercept
- Regorafenib
- Tas-102
- Ramicurumab

Chemotherapy- general consideratios

1. In adjuvant setting only fluoropyrimidines alone or in combination with oxaliplatin have proven benefit
2. In general: concomitant or sequential systemic therapy: not much difference for OS (however side-effects!!)
3. However: for respons combination is better than monotherapy
4. So: what is the goal of your therapy??

Adjuvant chemotherapy? (Initially resectable disease)

- In the 1990's: 2 randomized trials--→ combined analysis--→ better PFS (28 vs. 19 mnths.) and OS (62 vs. 47 mnths.), being probably clinical meaningful, however not statistically significant
- Japanese trial: significant better PFS, but not OS
- These trials were with "inferior" chemotherapy

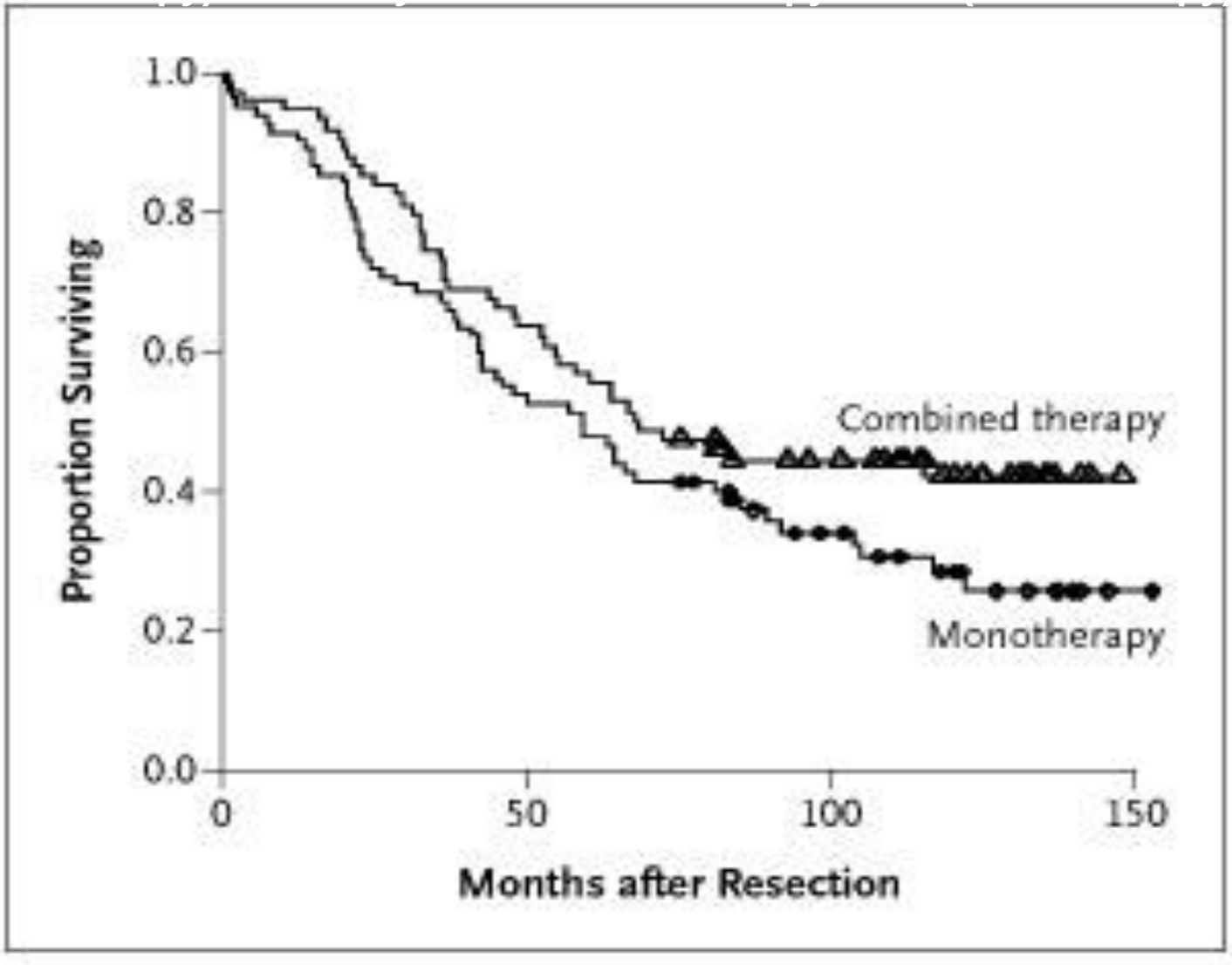
Modern chemotherapy

- EPOC-study (EORTC 40983): after 5 years 52 vs. 48 % OS, HR 0.88 for perioperative FOLFOX (however trial not powered for OS)
- Irinotecan added to fluoropyrimidine in adjuvant setting has no benefit in stage II-III disease
- Cetuximab added: perioperatively significantly worse PFS ?(“new EPOC”)
- However NCCN guidelines recommend 6 months of perioperative chemotherapy!?

So which way to go??

- Hepatic intraarterial chemotherapy:
  - Trials did not succeed
  - Often failure outside the liver
- HIA plus systemic therapy:
  - Intergroup study “failed”
  - MSKCC-study: better outcome after patient selection

Overall Survival among Patients with Metastatic Colorectal Cancer Who



Kemeny NE, G

Patient selection!

- Mostly now based on Fong-criteria
    - Node-positive primary
    - DFI < 12 months primary – CRLM
    - Number of CRLM > 1
    - CEA > 200 ng/ml
    - Size biggest CRLM > 5 cm

- Worse prognosis if at least 3 criteria

Selection in liver metastases

- NASBP C-09 (HAI!)
- Charisma (adjuvant chemotherapy!)
- EORTC BOS-2
- …….

Primarily irresectable livermetastases

- Primary goal: the most effctive therapy to get a respons= “conversion therapy” (if patient is expected to tolerate therapy)
- What is the definition of “irresectable”??
- At least doublet chemotherapy!
- Is triplet chemotherapy better?
- What is the role of biologicals?

(Ir)resectable livermetastases

- In general response (RECIST) on systemic therapy = 40-70 %
- Respons = not the same as resectable
- If resectable (15%?)-→ prognosis is as good as for primarily resectable livermetastases

What systemic therapy?

- Doublet vs. Triplet: FOLFOX/CAPOX or FOLFIRI vs. FOLFOXIRI-→ 3 trials with contradictory results
- Italian trial: 244 pts. with 6 months of FOLFOXIRI or FOLFIRI (both with bevacizumab):
    - longer PFS (9.8 vs. 6.8 months)
    - longer OS (23.4 vs. 16.7 months)
    - better 5-year survival (15 vs. 8 %)
- Secondary surgical resection higher: 36 vs. 12 %

TRIBE-trial

- With 48 months follow-up:
    - Better OS (29.8 vs. 25.8 months)
    - Estimated 5-year survival 24.9 vs. 12.5%
    - However not a better result for secondary resections (15 vs. 12%)!
- More grade 3-4 toxicity

HORG-trial

- Conclusion: “The present study failed to demonstrate any superiority of the FOLFOXIRI combination compared with the FOLFIRI regimen, although the observed median OS is one of the best ever reported in the literature”
- OS = 20-22 months
- Secondary metastectomy: 10 vs. 4 %
- Dose of chemotherapy less!

Role of biologicals: bevacizumab

- Better PFS and OS, however modest effect
- In first trial improved response rates (45 vs. 35 %)
- Potentially serious side-effects (not common), including disturbed wound healing
- Stop generally (4-) 5 weeks before surgery

Cetuximab/panitumumab

- Only in RAS-wild-type!
- CRYSTAL- study: better PFS, OS and response rate including higher amount “curative” resections
- OPUS-trial: slightly better PFS and response rate (61 vs. 37 %)
- MRC-COIN and NORDIC-trial: no PFS-benefit
- Combination with a oxaliplatin-regimen: not in NCCN!!
- Effect in liver metastases??
- No combination with bevacizmab!

What biological? Triplet?

- In the Netherlands CAIRO 5 study:
- Randomisation based on RAS-status
    1. RAS-wild type: FOLFOX/FOLFIRI with bevacizumab or panitumumab
    2. RAS mutated: FOLFOX/FOLFIRI vs. FOLFOXIRI both with bevacizumab
- In primar irresectable “liver only” metastases

How long (neoadjuvant) systemic therapy?

- With longer treatment more toxicity
- With longer treatment (maybe) better result
- Toxicity: S(inusoidal)O(obstruction)S(yndrome) with oxaliplatin and steatosis/steatohepatitis with irinotecan
- Conflicting data considering the risk of surgery
- In general it is recommended to treat no longer than 12-16 weeks before surgery

Conclusions

- 1. (Neo)adjuvant chemotherapy in liver metastases probably must be based on selection criteria
- 2. Most likely for primary irresectable liver metastases

  triplet chemotherapy is best, however more toxic
- 3. Biological and which one: questionable!?

MULTIDISCIPLINARY TREATMENT/DISCUSSION!!!!