European Review for Medical and Pharmacological Sciences 2010; 14: 269-271

# General principles of chemotherapy

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**Abstract. – *Background and Objective:*** **Over the last 50 years, medical treatment of solid cancers gained major advances in terms of effectiveness through breakthrough knowledge of cancer biology, technology development and identification of fundamental active drugs.**

***State of the Art:*** **We conventionally discriminate between medical treatment of the advanced or metastatic disease and of the early disease, namely adjuvant and neoadjuvant or primary treatment, if administered after or before surgery. New drugs or treatment associations can be sequentially introduced in medical treatment of cancer patients in phase I, II and III clinical trials. No drug or drug association can be proposed in the adjuvant or neoadjuvant setting of treatment without proven effectiveness in the advanced disease. Primary endpoints of medical treatment according to the phase of the disease are safety, activity and efficacy.**

**Different options of medical treatment may be selected for each tumor according to the specific phase of disease. In some metastatic cancers, such as colorectal cancer, the activity of medical treatment justified the development of strategies integrating also surgical resection of metastases, specifically liver, with the objective to increase efficacy.**

***Perspectives:*** **Open question in first and subsequent lines of treatment in advanced cancer patients, particularly in MCRC patients, is the proper individualization of medical treatment according to prognostic and predictive bio-markers.**

*Key Words:*

Chemotherapy, Metastatic colorectal cancer.

## Introduction

Over the last 50 years, medical treatment of solid cancers gained major advances in terms of effectiveness through breakthrough knowledge of cancer biology, technology development and identification of fundamental active drugs. It was consistently increased the number of chemotherapeutic drugs with known and new mechanisms of action as well as a panoplia of antitarget drugs.

The effectiveness of medical treatment of cancer can be evaluated through specific endpoints according to the phase of the disease in which treatment is administered (Table I).

Thus, we conventionally discriminate between medical treatment of the advanced or metastatic disease and of the early disease, namely adjuvant and neoadjuvant or primary treatment. The difference between adjuvant and neoadjuvant treatment depends upon the position of the medical treatment respective to other conventional treatment strategies (surgery or radiotherapy): *adjuvant medical treatment* if sequential to radical and potentially curative surgery (or radiotherapy) with the major objective of reducing the risk of developing metastatic disease; *neoadjuvant or primary* if the medical treatment is the primary treatment with the major objective of downsizing, (i.e. reducing the size of the primary tumor) and reducing the risk of metastasize and sequentially adding radical, curative and potentially conservative surgery (or radiotherapy).

New drugs or treatment associations are first introduced in medical treatment of advanced, pretreated patients in: phase I protocols aimed at evaluating safety; phase II and III clinical trials of untreated patients aimed at demonstrate primarily effectiveness balanced with safety. Then, new medical treatment may be proposed in phase II-III clinical trials as adjuvant or neoadjuvant treatment; thus, no drug or drug association can be proposed in these sets of treatment without proven effectiveness in the setting of advanced disease.

Primary endpoints of medical treatment according to the phase of the disease are: in metastatic patients, activity (i.e. clinical objective response) and efficacy, progression-free survival (PFS) and overall survival (OS); in early disease

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**Table I.** Medical treatment according to phase of disease.

| Phase | Type | Major objective | End-points |
|---|---|---|---|
| Metastatic | Metastatic | Efficacy | Activity (OR)<br>Efficacy (PFS, OS) |
| Early | Adjuvant | Risk reduction of metastases | DFS, OS |
| | Neoadjuvant (Primary) | Risk reduction of metastases | DFS, OS |
| | | Downsizing of the primary tumor | DFS,OS, Activity (pCR) |

treated with neoadjuvant or primary medical treatment, activity (clinical objective response, in particular pathologic complete responses) and efficacy, disease-free survival (DFS) and OS; in early disease treated with adjuvant medical treatment, efficacy through DFS and OS.

Today, different options of medical treatment are in indication (in-label) and may be selected for each tumor according to the specific phase of disease. In general, medical treatment should be proposed and properly chosen according to nutritional and functional patient condition and performance status (Table II); today, age and the comorbidity status may better drive the proper treatment selection; more, cost of treatment also raised up, as the activity increased, and it should be taken in to account among the criteria for the evaluation of clinical properness of treatment selection.

Metastatic colorectal cancer (MCRC) represents a model of cancer treatment evolution over the last 20 years. The incremental activity of medical treatment justified the development of strategies integrating also surgical resection of metastases, specifically liver ones, with the objective to increase efficacy up to the potential cure of some metastatic patients.

Multiple active drugs were used in substitution of 5-Fluorouracil (Capecitabine and other antimetabolites) or in addition to 5-Fluorouracil in doublet or triplet combinations of conventional drugs (Irinotecan and Oxaliplatin) and anti-targets (anti-vascular endothelial growth factor and anti-epidermal growth factor receptor), as first or subsequent lines of treatment of MCRC patients. Doublet combinations of 5-Fluorouracil or Capecitabine associated to Irinotecan or Oxaliplatin or Bevacizumab (anti-VEGF) obtain up to 40% overall response rate (ORR), progression free survival (PFS) 6-9 months and overall survival (OS) 15-22 months[1-2]. Triplet association of chemotherapy (5-Fluorouracil, Irinotecan and Oxaliplatin) demonstrated a statistically significant increase in ORR 60%, PFS 9.8 months, OS 22.6 months [3]; the addition of a third drug, either Bevacizumab or Oxaliplatin, equivalently increases the efficacy of doublet combination associating 5-Fluorouracil/Irinotecan. Recently, the association of Bevacizumab to the triplet chemotherapy ("poker" combination), in first line treatment of MCRC, increases activity up to 80% ORR, median PFS 11 months and median OS 21 months[4].

As the activity of MCRC treatment progressively increased using triplet combinations, liver-metastasectomies also raised up to 8-11% in triplet chemotherapy[3] and in 7.6% in Bevacizumab-containing associations[5]. In our recent experience using "poker" association, liver metastasectomies were performed in 26% of MCRC patients.

**Table II.** Factors determining clinical properness of medical treatment.

| Factors | Categories | Criteria |
|---|---|---|
| Therapy | Efficacy | ORR, PFS, DFS, OS |
| | Tolerability | Toxicity |
| | Costs | Economic |
| Patient | Individual features | Age |
| | | Comorbidity |
| Disease | Biological features | Genotype status |
| Medical oncologist | Choice of treatment | Free, in-label |

To date, open questions in integrated treatment strategies for MCRC patients are: the properness of different first-line treatment associations in view of integration with mestasectomies; evaluation of the treatment options of subsequent lines of treatment after disease progression; development of standard treatment for elderly patients and/or patients affected by comorbidities; development of individualized treatments according to prognostic and predictive bio-markers.

In EGFR-overexpressing patients[6,7], k-ras wild-type status was reported as statistically relevant predictive biomarker of higher activity and efficacy, using anti-EGFR (Cetuximab, Panitumumab). Instead, the effectiveness of bevacizumab (BEV)-containing treatments seems to be maintained either in k-ras wild-type as in k-ras mutated patients[8].

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