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ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Mehmet Ali Nahit ?endur, MD, Associate Professor, Department of Medical Oncology, Ankara Ataturk Training and Research Hospital, Faculty of Medicine, Ankara Yildirim Beyazit University, Ankara 06800, Turkey

AIM AND SCOPE

World Journal of Gastrointestinal Oncology (*World J Gastrointest Oncol*, *WJGO*, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGO covers topics concerning carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, molecular mechanisms, and therapy of benign and malignant tumors of the digestive tract. The current columns of *WJGO* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJGO*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

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EDITORIAL

Real practice studies in oncology: A positive perspective

Alessandro Ottaiano

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Abstract

In the majority of phase Ⅲ clinical trials, patients are generally excluded on the basis of specific comorbidities, performance status Eastern Cooperative Oncology Group ⩾ 2, age ⩾ 65 years, previous malignancies, brain metastases, active infections, psychiatric disorders, non-measurable disease, number and type of previous lines of chemotherapies or biologic therapies. A question is raised: Can results of phase Ⅲ studies be extended to the general population? There is increasing attention to and a resurgence of some terms as "real world" or "real practice" which are wrongly viewed as contrary to clinical trial protocols. In fact, the general perception is that a contraposition exists between "wrong" (retrospective and biased) and "right" (prospective, randomized, well statistically designed) clinical research. We have to change this perspective. Real practice studies, generally retrospective in their nature, deserve to be reevaluated; biases are physiologically present but their punctual and rigorous description and analysis can help the interpretation of and in some cases reinforce results and their hypothesis-generating power. The correct and balanced interaction between clinical trials and real practice reports can help the scientific community to improve the knowledge on anti-cancer drug efficacy.

Key words: Clinical trials; Real practice; Methodology; Gastrointestinal oncology

Core tip: Oncologic patients enrolled in phase Ⅲ pivotal trials are usually selected on the basis of specific characteristics and they are quite different from the real practice populations: this could account for low reproducibility of results in the clinics real world. In this Editorial, differences between prospective clinical trials and real practice studies are discussed giving a critical and positive perspective on the results of real practice studies also through specific examples. The correct and balanced interaction between clinical trials and real practice results can help the scientific community to improve the knowledge on anti-cancer drug therapies.

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Anti-cancer drugs are evaluated through a process involving different phases of clinical research. The methodological pathway is based on: (1) "early" clinical trials (phase Ⅰ) in unselected patients designed to find dosages and toxicities; (2) "intermediate" disease-oriented trials (phase Ⅱ) designed to define activity and toxicity; and (3) "late" randomized trials (phase Ⅲ) comparing the new versus standard treatment for efficacy (progression-free survival, overall survival, quality of life) in highly selected cohorts. In recent years the introduction of biologic therapies has partially changed some methodological issues further refining patient selection on the basis of specific molecular alterations and biomarkers. In the "post-marketing" period, phase Ⅳ studies can be pursued in order to evaluate predominantly the long-term safety in a greater number of patients; these are observational studies in their nature.

Usually, competent Authorities refer to phase Ⅲ trials to register a specific drug or combination of drugs for a particular clinical use[1]. Some exceptions to this process exist, but their descriptions are beyond the scope of the present Editorial. In phase Ⅲ studies, the patients gain the same chance to undergo different treatments through randomization. The power of prospective, randomized phase Ⅲ trials is to normalize any factor that could influence final results, so that treatment arms are quite equivalent with regard to known prognostic and predictive factors. However, one of the most important pitfalls of these trials resides in clinical criteria for patient selection[2-5]. In the majority of phase Ⅲ studies, patients are generally excluded if they present one or more of the following conditions: specific comorbidities (unstable diabetes, chronic liver or kidney diseases, cardio-vascular diseases, *etc.*), performance status Eastern Cooperative Oncology Group (ECOG) ⩾ 2, age ⩾ 65 years, previous malignancies, brain metastases, active infections, psychiatric disorders, non-measurable disease. In some cases, other selection criteria such as number and type of previous lines of chemotherapies or biologic therapies are added. A question is raised: Can results of phase Ⅲ studies be extended to the general population? This deserves some reflection because in clinical practice few patients present with the characteristics required by a phase Ⅲ clinical trial; one or more excluding conditions are frequently present.

We have recently presented at European Society of Medical Oncology (ESMO) Congress 2018 (abstract 1927, "Folfiri-Aflibercept *vs* Folfiri-Bevacizumab as second-line treatment of *RAS* mutated metastatic colorectal cancer in real practice") a study reporting an efficacy comparison (overall survival) between two different second-line therapies (Folfiri-Bevacizumab, arm A *vs* Folfiri-Aflibercept, arm B) in advanced *RAS* mutated oxaliplatin and bevacizumab-pretreated colorectal cancer patients in a "real world" population. There is actually need to clarify therapy of this clinical setting, and prospective randomized trials on these different sequences of therapy do not exist [Folfox-Bevacizumb first followed by Folfiri-Bevacizumab (arm A) or Folfox-Bevacizumb first followed by Folfiri-Aflibercept (arm B)]. In arm A, after an induction phase of 6 mo, maintenance with bevacizumab was permitted; by contrast no maintenance therapy in arm B was applied. Interestingly, in arm B we found a lower risk of cancer-related death *vs* arm A (HR: 0.42; 95%CI: 0.15 to 1.15; $P = 0.0425$) during the induction phase. Three important biases were present consisting of: (1) the predominance of more extended disease (> two metastatic sites) in arm B [26/43 (60.5%) *vs* 10/31 (32.2%) arm A; $P = 0.0414$]; (2) the duration of first-line chemotherapy which was significantly shorter in patients treated in arm B (12 patients < 6 mo arm B *vs* 1 patient in arm A; $P = 0.0278$); and (3) the lack of a maintenance treatment with aflibercept. These biases do not stultify even if they reinforce the positive impact of Folfiri-Aflibercept in *RAS* mutated advanced colorectal cancer.

Real practice studies may also have a hypothesis-generating role. Until now, after a long period of skepticism still resisting in some parts of the scientific community, many preclinical and clinical studies have demonstrated that the interactions between immune system and tumor cells can be exploit for therapeutic scopes. The issue is extremely complex, innovative and largely unknown and oncologists have just "started" to apply in clinics basic knowledges from the immunology. Very recently, we have collected information about a cohort of 47 multi-organ oligo-metastatic colorectal cancer patients refusing metastasectomies and treated with depotentiated courses of chemotherapy and stereotactic radiotherapy (SRT) finding high disease control, with median survival of 44 mo (95%CI: 39.9-52.1) and two patients still alive at 82 and 86 mo from diagnosis with stable disease. In that, a possible role is played by abscopal effect of SRT: First described in 1953 as an effect of radiotherapy, the abscopal effect was observed in the clinical practice when a localized treatment produced also the shrinking of untreated distant tumor masses. Evidences demonstrate that this phenomenon is mediated by the immune system leading to tumor cell recognition and destruction, a specific and regulated process involving lymphocytes, dendritic cells, T regulatory subset cells, and other suppressor cells[6-8]. Based on that, many prospective clinical and translational trials in advanced lung, melanoma and colorectal cancer are now recruiting patients through protocols based on SRT and immunotherapies with different mechanisms of action (pembrolizumab, durvalumab, tremelimumab, dabrafenib, trametinib, MK-3475, *etc.*) (Clinicaltrials.gov).

There is increasing attention to and a resurgence of some terms as "real world" or "real practice" which are wrongly viewed as contrary to clinical trial protocols.

In fact, the general perception is that a contraposition exists between "wrong" (retrospective and biased) and "right" (prospective, randomized, well statistically designed) clinical research. We have to change this perspective. Real practice studies, generally retrospective in their nature, deserve to be reevaluated; biases are physiologically present but their punctual and rigorous description and analysis can help the interpretation of and in some cases reinforce results.

This perspective should be adopted also by editors, reviewers, clinicians and researchers when evaluating results of studies. Sometimes real practice study results are not consistent with those of phase Ⅲ studies; this happens as much as the fraction of treated patients does not meet the eligibility criteria of the corresponding phase Ⅲ trial. One recent example in colorectal oncology is represented by the clinical benefit obtained with trifluridine/tipiracil in refractory metastatic colorectal cancer patients in real life[9] *vs* the phase Ⅲ study[10]. The correct and balanced interaction between clinical trials and real practice reports can help the scientific community to improve the knowledge on anti-cancer drug efficacy.

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