Case Report

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Implication of Murphy's Law in Clinical Trials

Maxim Kosov*, Veronika Kolesnik, John Riefler and Maxim Belotserkovskiy

PSI Pharma Support America, Clinical Research Organization (CRO), King of Prussia, Pennsylvania, USA

***Corresponding author:** Maxim Kosov, PSI Pharma Support America, Clinical Research Organization (CRO), King of Prussia, Pennsylvania, USA, Tel: +1 267 464 2554; E-mail: Maxim.Kosov@psi-cro.com

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Abstract

Assessment of performance status (PS) is an essential part of inclusion criteria in oncology clinical trials. It correlates with the major study outcomes. Among limitations of PS assessment is lack of well-defined criteria which may lead to difference in interpretation. We present 3 cases of misinterpretation of patients' clinical condition that lead to different PS assessment. In 2 cases activity of patients was limited due to factors other than oncology disease, recent surgery and concomitant medical condition (obesity). Such situations as presence of concomitant factors that have a potential to limit patient's ability to perform working or daily living activities, should be carefully considered while assessing PS.

Keywords: Eastern Cooperative Oncology Group (ECOG); Performance status; Cancer; Activity level; Inter-rater reliability

Introduction

Murphy's Law states that "if something can go wrong, it will". We see many examples in everyday life, and also in medicine. Does this law apply to clinical trials? This question is of particular interest when we speak about eligibility criteria that are a kind of a watchdog for inclusion of only correct patients. Inclusion and exclusion criteria are complicated in oncology clinical trials and very frequently subjective, leaving room for different, sometimes opposing interpretations, depending on personal experience and opinion of the reviewer. Every oncology clinical trial has inclusion criteria of study subject's performance status, with Eastern Cooperative Oncology Group (ECOG) performance status (PS) scale the most widely used. Performance status correlates with response to treatment, duration of survival, and ability of a patient to tolerate chemotherapy. Most clinical trials have a cutoff of ECOG PS ≤ 2, as patients with a higher score have poor outcome [1]. Thus, an accurate assessment of PS is one of the key elements in patients' selection. Reliability of every method that requires a subjective judgment is determined by concordance rate between observers or reviewers. Opinions differ on PS scales' reliability, ranging from good concordance between observers to significant differences in opinion [2]. The nature of discordance is due to differences of interpretation, and lack of clear guidance. Herein, we present 3 cases of different interpretation of patients' condition.

Case Reports

Case 1

A 60-year-old female subject was approved for enrollment in the study of rapidly progressing multiple myeloma that has exhausted all available anti-cancer treatments with ECOG PS ≤ 2. Two weeks prior to obtaining Informed Consent (IC) the patient underwent a surgery for a pathologic fracture of the distal femur. The surgery included a local excision of tumor under spinal anesthesia with subsequent internal fixation. After discharge from the hospital, the patient started screening procedures and at that time was confined to a wheelchair but was able to carry on self-care activities. A sub-investigator managing the patient at that time assessed the patient's ECOG PS=2. Several days after randomization, the patient was allowed to stand on the operated leg and her condition gradually improved to ECOG of 1. The patient received 10 complete cycles of study treatment with partial response and was later discontinued from the study due to disease progression and stayed in long-term follow-up for overall survival. At the end of the study, all patient's data were re-evaluated and the ECOG PS was changed to 4. This lead to a retrospective re-assessment of the patient as not eligible. Both the Sponsor's and the CRO Medical Monitor disagreed with the investigator's assessment. Although the patient was confined to a wheelchair after surgery, this was a temporary measure due to the surgeon's recommendation to take weight off the operated leg, and was not a consequence of multiple myeloma. However, the investigator's assessment was left unchanged, the patient was considered not eligible for the study and this decision negatively influenced study data.

Case 2

A 55-year-old female subject was consented for the study of metastatic breast cancer in patients who received ≥ 2 prior HER2-directed treatment lines and had ECOG PS of 0-1. During screening, she developed grade 2 shortness of breath caused by metastatic pleural effusion that was a sign of disease progression, and as pulmonary embolism had been ruled out, the patient was discharged from the hospital. The patient still

had dyspnea on moderate exertion, so, she continued on supplemental oxygen at home. With further oxygen intake, the Investigator assessed ECOG PS as 1. He explained that the extent of the pleural effusion and, consequently, the severity of dyspnea will improve with the start of the study treatment, and insisted on patient's randomization. The sponsor agreed with the investigator's assessment and approved randomization. On the next day, after randomization, shortness of breath worsened to grade 3 and pleural effusion was drained urgently. The patient was discontinued from the study prior to start of the study treatment, but included into Intention-to-treat (ITT) population analysis.

Case 3

An 81-year old subject entered the study of refractory or relapsed diffuse large B-cell lymphoma. One inclusion criterion of the study was ECOG PS ≤ 2. Initially, the Investigator considered the ECOG PS>2 due to the fact that the patient was using a wheelchair, but reached out to the Contract Research Organization (CRO) Medical Monitor to discuss this matter. During discussion it turned out that the patient had significant obesity with a body mass index (BMI) of 42 kg/m^2 and this resulted in confinement to a wheelchair for more than 50% of time. The Investigator confirmed that without a wheelchair, the patient's cancer-related ECOG will be =2. The patient was considered eligible and randomized. The patient completed study treatment with the best radiologic response of partial response, and died 15 months after enrollment due to concomitant condition– abdominal infection.

Discussion

The key element of a successful clinical trial is enrollment of appropriate, eligible patients. Inclusion and exclusion protocol criteria are based either on objective parameters (laboratory and instrumental methods) or on investigator's clinical judgment. One of criteria intended to select those patients that are fit enough for anti-cancer therapy, is assessment of performance status (PS). Correlation of PS with survival has been well documented for different types of malignancies [3-5], and considering that overall survival is the most reliable and preferred cancer endpoint [6], accurate assessment of PS is a powerful tool for appropriate selection of study subjects. Besides not unanimous agreement on the general results of PS scales with variable inter-expert agreement in a wide range from kappa=0.19 to kappa=0.92 [2], the methodology of assessment does not suggest well-defined criteria and is based on the ability to perform working and self-service activities [7]. The rationale is to assess the influence of the main oncology disease on these parameters, but in the absence of a clear and widely-recognized guideline, there is the potential to perform such assessment irrespective of cancer pathology, mixing up consequences of cancer and other concomitant conditions. We can see from presented cases, once such possibility exists, it will be used. In cases 1 and 3 the ability of patients to move and perform self-service activities were limited either by a recent surgery or concomitant medical condition (obesity) and were not related to cancer. It is important to consider, that the original ECOG PS refers to limited capabilities to perform work activities or carry out self-care and to the percentage of time when a patient is confined to bed or chair [7], but not to a wheelchair. These are different situations, and chair and wheelchair are not equivalent. The reason of limited activity should be considered, as well as the reason of why the wheelchair is used and if it is because of a surgery, like in case 1, or for patient's convenience like in case 3, the assessment should be performed as if there is no wheelchair. Case 2 demonstrates that lack of a clear definition will lead to a possibility of either underestimating (like in this case), or overestimating patient's condition.

Conclusion

To complicate the matter of PS assessment in clinical trials, evaluation of PS is usually considered a self-evident, routine, and easy assessment, and is not paid enough attention at the Investigators' Meetings or trainings of clinical investigators. It would be worthwhile to either include a separate slide about PS assessment in the study protocol presentation at the Investigator's Meeting, or specifically address this question during site initiation visit, while describing the key eligibility criteria. Additionally, in cases of unstable clinical condition it may be reasonable to choose a higher score of PS. It will help to eliminate a possibility of Murphy's Law influencing study data.

Conflict of Interest

The authors declare no conflicts of interest.

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