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Review

Progression-free survival as an end-point in solid tumours – Perspectives from clinical trials and clinical practice

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Abstract Progression-free survival (PFS) is an end-point in an increasing number of cancer clinical trials, informing both regulatory bodies and clinical practice. PFS is utilised both as a surrogate end-point for overall survival and as a primary trial end-point in itself. Understanding the history of clinical trial definitions of progression provides some context for how PFS may be applied to clinical practice as well as some of its limitations that need to be considered in patient care decisions. This commentary reviews recent drug approval for anti-cancer agents in solid tumours, reviews various concepts of progression in clinical trials and outlines some future directions for patient care and clinical trial research using progression free survival.

Quantity and quality of life (overall survival [OS] and QOL) are the outcomes of interest in the treatment of patients with cancer, and the end-points of ultimate interest in phase III clinical trials. In recent years there has been an increase in the number of new cancer agents approved and trials reported utilising a progression free survival (PFS) end-point in solid tumours [1]. Understanding the history evolution of PFS is important to understand the current challenges in using PFS to inform clinical practice decisions. This paper will review the history of the definitions of progression used in clinical trials from Zubrod to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 and the implications of some of the assumptions inherent in the definition that may impact clinical practice.

1. Progression/response – a regulatory perspective

From a regulatory perspective, guidance documents from both the European Medicines Agency (EMEA) [2] and the United States Food and Drug Administration

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(FDA) [3] include PFS as an end-point that may be used to demonstrate clinical benefit [4].

The EMEA states that 'Acceptable primary end-points include cure rate, OS (overall survival) and PFS/DFS (progression free survival/disease free survival). Convincingly demonstrated favourable effects on (overall) survival are ... the most persuasive outcome of a clinical trial. Prolonged PFS/DFS as such, however, is considered to be of benefit to the patient.' [4].

The FDA considers PFS as a surrogate end-point for regular approval. The FDA statement on PFS advises that whether PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and risk–benefit of the new treatment compared to available therapies [3].

A review of FDA new drug approvals reported by Sridhara et al. [5], showed that 21 new cancer drug indications were approved in the advanced/metastatic setting in solid tumours from 2005 to 2007. Ten were approved on the basis of OS, six PFS or time to progression (TTP) and two demonstrated both TTP/PFS and OS improvement. No new drugs/indications were approved in this time frame based solely on symptom benefit.

We have updated these results for the period from January 2008 until October 2013 as shown in Table 1. During this time the FDA approved 44 new indications for cancer drugs in solid tumours. PFS is now the most common basis for granting approval of an indication, ($n = 19$). For small molecules (kinase or mTOR inhibitors), 14 of 20 indications were based on PFS, while for conventional cytotoxic agents, only one of seven new indications was based on PFS.

It is clear that PFS gains are considered by regulatory agencies to be relevant to decisions about new drug approval, and clinical trials will continue to use PFS as a primary end-point in some settings. In translating clinical trial results to clinical practice, evidence informed practitioners will use evidence generated in clinical trials (and leading to regulatory approval) to inform bedside decisions. In order to examine the clinical implications of this translation from trial to practice, it is important to consider – what does progression really mean? What are the values attached to PFS by practitioners and patients, and what are the assumptions embedded in it as a measure of benefit?

2. Progression/response – a historical perspective

Progression as a measurable objective outcome has a history of over 50 years of use as a clinical trial end-point.

In 1960, Zubrod published a clinical trial in solid tumours comparing nitrogen mustard with thiotepa [6]. In the introduction, one of the goals of the study was to

> '*apply known principles of the therapeutic trial to clinical cancer chemotherapy. Most of the drugs now available are so toxic that one is usually balancing minor therapeutic gain against the possibility of serious therapeutic mischief*'.

Treatment was considered to give a positive response if the total measured tumour mass decreased, with no lesions increasing in size and no new lesions appearing, or the group of voting physicians considered that the treatment had been of benefit to the patient as a whole, considering subjective responses and untoward effects in addition to tumour measurements. Follow-up studies consisted of physical examinations as well as X-rays of chest and bone. This was a very advanced cancer population – 50% of the breast metastatic patients had cutaneous metastases, as did 15% of the lung patients. Median survival for breast patients was 4–6 months, and was 3 months in lung and melanoma patients. These were toxic therapies, sick patients, and it is reasonable to assume that stopping treatment on the basis of new lesions, or worsening disease was certainly in the patient's best interests. These definitions of 'response' and 'progression' were developed in an era when life with metastatic cancer was very short, disease was very obvious and therapies relatively toxic.

In 1975, the Union for International Cancer Control (UICC) began the process of formalising response criteria further, beginning with breast cancer [7]. The introduction stated

> '*Guidelines are intended for use in designing clinical trials to assess the objective response of locally advanced or metastatic breast cancer to treatment, subjective response to treatment is not considered*'.

Progressive disease was defined as occurring when either new lesions appeared, or there was an increase by 25% in the sum of the products of the diameters of each lesion measured. In the UICC criteria, progressive disease could be of two types: mixed – some lesions regress while others grow or appear, or failure – no lesions regress, and there is progression of other lesions or new lesions.

In 1979/81 the World Health Organisation (WHO) criteria were developed and were largely derived from the breast cancer guidelines – including the report from the Breast Cancer Treatment Task Force committee 1977 and the UICC breast cancer project on response mentioned above [8]. In the WHO criteria, overall disease progression was deemed to occur if it was documented at any site of disease. Absent in this adaptation was the division of progression into 'mixed' and 'failure'. A caveat about the use of the 25% increase in bidimensional sum was expressed in this paper: '*This percentage should not necessarily be regarded as influencing the management of the patient*'.

The next major modification of the WHO criteria was that of the Southwestern Oncology Group in 1992. Acknowledged in this paper was that progression had