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Research Article

Progression-free survival as a primary end-point: Counting the cost

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Ogochukwu Izuegbuna[1]

1. Department of Haematology, Ladoke Akintola University of Technology Teaching Hospital, Osogbo, Nigeria

For some time in cancer clinical trials, overall survival (OS) has been the gold standard in determining the endpoint of the drug's efficacy. However, in recent times, there has been a gradual shift in the endpoint of drug efficacy towards progression-free survival (PFS). PFS has its merits, especially being cost-effective, but not without associated shortcomings. PFS is not an ideal surrogate for OS, and in some cases, the correlation is low to medium in strength with heterogeneity in the methodologies used. There have also been cases where PFS is used as an endpoint in place of OS, which was achieved, but with increased reports of significant adverse events/reduced quality of life (QoL) index. Current realities make using OS as an endpoint in some cancer drug trials a difficult task to demonstrate. However, even if PFS is used, data must be thoroughly assessed for quality of life indices and drug safety. It is therefore important that stakeholders in the business of cancer drug evaluation and trials note the risks and benefits of such drugs for the target population. In so doing, patient's QoL would be paramount in therapeutic decision-making.

Corresponding author: Ogochukwu Izuegbuna, Ogoizu@gmail.com

Introduction

On April 19, 2023, the American Food and Drug Administration (FDA) approved polatuzumab vedotin (Polivy) with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) as the first line treatment for DLBCL in newly diagnosed patients who have an International Prognostic Index (IPI) score of 2 or greater as against rituximab, cyclophosphamide, doxorubicin, oncovin, and prednisone (R-CHOP), the former standard of care (SOC) [1]. (Polivy has been approved in 2021 for DLBCL in previously treated patients.) Unlike the excitement and optimism that greeted the approval of ibrutinib (2014)[2] and zanubrutinib (2023)[3] from haematologists and oncologists, this time around many may not be willing to stake a bet on Polivy + R-CHP vs. R-CHOP. This is not surprising when you observe that approval was based on the efficacy of statistically significant progression-free survival (PFS) in the Polivy + R-CHP arm against the SOC (HR, 0.73; 95% CI, 0.57-0.95; p =.02) and the modified event-free survival (HR, 0.75; 95% CI: 0.58-0.96; p = 0.0244), with the PFS rate in the Polivy + R-CHP arm being 76.7% (95% CI, 72.7%–80.8%) vs 70.2% in the R-CHOP arm (95% CI, 65.8%–74.6%). Unfortunately, there's no significant difference in complete response rate or overall survival (OS) (HR 0.94; 95% CI: 0.67, 1.33)[1][4].

The approval raises the old question: is PFS a proper surrogate for OS as the primary endpoint for the efficacy of cancer drugs? For quite some time, the gold standard in cancer drug trials has been to show benefit in OS, while PFS has been seen as a secondary endpoint. Currently, there seems to be a shift in favour of PFS over OS as the gold standard in cancer

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drug trials. Is it justified (especially in this case of Polivy + R-CHP vs. R-CHOP)? Pasalic et al. observed in their study that PFS has a suboptimal positive predictive value for OS in metastatic solid cancer clinical trials[5]. A ten-year-old report by the NICE decision support unit also concluded that the level of evidence supporting a relationship between PFS and OS is inconsistent, even within specific cancer types[6]. However, in their meta-analysis, Shameer et al. showed some low- to moderate-level correlation in non-small cell lung cancer between hazard ratio PFS and hazard ratio OS, but with some caution in interpretation[7]. This debate has its highs and lows.

PFS in perspective: the good and the not so good

As this controversy rages on, Bergmann et al. argued seriously against PFS in cancer drug development, citing it as an unreliable surrogate for OS; that for PFS to be a surrogate marker for OS it must be strongly correlated to the latter, and the drug in question should have the same effect as the new surrogate[8]. In the same manner, Tannock et al. published last year in JAMA about the unbalanced evaluation in cancer drug trials as a result of the use of PFS over OS. Tannock et al. argued that when no OS benefit is seen, these drugs are rarely withdrawn from the market[9]. These arguments may not be entirely true; the recent initiation of the withdrawal of belantamab mafodotin-blmf (Blenrep®) from the US market is a case point[10]. The request was made by the FDA based on the DREAMM-3 trial. Belantamab mafodotin, an antibody-drug conjugate comprising a humanized BCMA monoclonal antibody conjugated to the cytotoxic agent auristatin F via a non-cleavable linker, was approved for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. The withdrawal was based on the outcome of the DREAMM-3 phase III confirmatory trial of belantamab mafodotin monotherapy vs. pomalidomide in combination with low-dose dexamethasone (PomDex) in patients with relapsed or refractory multiple myeloma (RRMM). Blenrep did not meet its primary endpoint, PFS, despite showing a deeper response rate compared to PomDex (25% vs. 8%). The median duration of response (DOR) was not reached for belantamab mafodotin (95% CI: 17.9, -) vs. 8.5 months (95% CI: 7.6, -) for PomDex. The median OS was 21.2 and 21.1 months for belantamab mafodotin and PomDex, respectively, with an HR of 1.14 (95% CI: 0.77, 1.68). Bevacizumab (Avastin), which got FDA-accelerated approval in 2008 for metastatic breast cancer based on PFS improvement (E2100; NCT00028990), had the approval withdrawn in 2011 when data from confirmatory studies showed that the PFS was significantly smaller than expected with no improvement in OS or QoL[11].

In a different scenario, the DETERMINATION clinical trial in MM (NCT01208662) showed that the use of autologous stem cell transplantation (ASCT) with VRD (Velcade, Revlimid, and Dexamethasone) with Revlimid maintenance vs. VRD alone had a superior PFS of 11 months but without any improvement in OS. There was also a modest increase in adverse events in the ASCT + RVD arm vs. the RVD-alone arm, although both arms showed very similar scores for QOL[12].

In another setting, the TROPiCS-02 phase 3 clinical trial (NCT03901339) compared the use of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients with hormone receptor-positive/HER2-negative (HR+/HER2-) advanced breast cancer. The TPC was capecitabine, eribulin, vinorelbine, or gemcitabine. There was an improved median PFS (5.5 vs. 4.0 mo; HR, 0.66; 95% CI, 0.53-0.83; P = 0.0003) in the SG vs. TPC. There was no significant difference in OS (13.9 vs. 12.3 mo; HR, 0.84; P = 0.143) between SG and TPC, and treatment-emergent adverse events were higher in the SG group than the TPC group (74% vs. 60%), with adverse events leading to drug discontinuation higher in the SG group than the TPC group (6% vs. 4%). There was also one treatment-related death in the SG arm and none in the TPC arm[13].

The treatments in the DREAMM-3 and the E2100 clinical trials did not meet the primary endpoint PFS, nor did they achieve higher OS or show improved QoL, so they were not approved by the FDA. However, the treatment protocols in the DETERMINATION and the TROPiCS-02 clinical trials showed an improvement in PFS without an OS benefit and are FDA-approved treatments, considered standard of care despite the lack of an OS benefit, increased adverse events and even treatment-related deaths in some cases.

So is PFS valid enough to serve as a surrogate for OS? Surrogacy validation is a meandering slope that has evolved in clinical trials. Prentice, in 1989, introduced the four criteria to be met to support surrogacy: (1) treatment has a significant impact on the surrogate

endpoint; (2) treatment has a significant impact on the true endpoint; (3) the surrogate and true endpoints are correlated; and (4) the full effect of treatment on the final endpoint is captured by the surrogate[14]. In a systematic review by Belin et al., they reported on about four studies investigating the surrogacy of PFS for chemotherapy in non-small cell lung cancer, of which three reported that PFS was not a relevant surrogate, and the only study that concluded that PFS was a valid surrogate was a meta-analysis of individual patient data[15]. Their study also observed the heterogeneity in methods and reporting of surrogacy.

PFS as an endpoint in clinical trials have been muted to have some advantages over OS including shorter study duration and lower number of patients needed (Table 1)[16]. Thus, PFS can be said to be more "cost-effective". Despite some of these advantages, PFS has been shown to have some shortcomings. A key one is bias and errors in measurements; unlike the measurement of OS where the exact time of mortality can be determined (Table 1). Miltenberger et al reported that progressions can only be diagnosed at assessments and this leads to an assessment time bias in the estimation of treatment benefits[17]. This variability in time and response differences can be problematic and may lead to different estimates between studies as noted by Casey et al[18], therefore requiring greater standardization for the use of PFS as an endpoint.

Pros	Cons
Enables quicker completion of trial	Less easy to measure than OS
Fewer patients required so cheaper to conduct	Establishing time to progression is subject to error and ascertainment biases
Measures effect of investigational drug directly	Difficult to establish if ‘clinical benefit’ is meaningful
Sensitive to cytostatic and cytotoxic mechanisms of therapy	Tumor shrinkage or stabilization may not be accompanied by tangible symptom relief
Not confounded by subsequent therapy given at disease progression	Few data about value patients may place on PFS
May be surrogate for OS	Does not always translate into OS

Table 1. The pros and cons of PFS as an endpoint in cancer clinical trials

Whatever standards are used in the cancer drug trials, the goal of cancer treatment remains the improvement in duration and/or quality of patient survival. Are these needs met before drugs are approved? A cacophony of responses will surely be the answer. However, in my opinion, an increase in PFS without an accompanying QoL benefits would not be enough approval for a cancer drug.

Counting the cost: Factoring in Cost Effectiveness and Quality of life

In the conundrum of PFS vs. OS, Kambhampati et al. recently did a cost-effectiveness study of Polivy-CHP vs. R-CHOP by looking at its incremental cost-effectiveness ratio (ICER), a relative benefit of a particular therapeutic strategy compared with the next best strategy per dollar spent, measured in quality-adjusted life years (QALYs), and a willingness to pay (WTP) threshold. The key findings were: 1) Polivy-CHP is provisionally cost-effective compared with R-CHOP for the frontline treatment of DLBCL at a WTP of $150 000/QALY. 2) The cost-effectiveness of Polivy-R-CHP depends on its long-term outcomes (a 5-year PFS of at least 66.1% is needed to remain cost-effective) [19]. Scheffer and Pandya argued that the advantage of the study was the ability to quantify saved costs concerning PFS[20]. The in-group PFS was also seen as an advantage. PFS was said to be a more reliable surrogate in DLBCL than in other malignancies. They also compared Polivy-CHP's cost-effectiveness to the extremely expensive next therapy, CAR-T cell therapy (>$700,000 per patient, cost of care included). Polivy-CHP, according to the analysis, can only lose its cost-effectiveness if CAR T-cell therapy prices were reduced to match the cost of ASCT and Polivy-CHP at a WTP threshold of $100 000/QALY. This is called the "New Math of Cost-Effectiveness," whereby one drug or strategy is only cost-effective as a result of the price of an alternate therapy[21]. This cost-effectiveness model could have plausible and cryptic acceptability for approval, especially for the POLARIX study. While this model may work in some advanced countries, it will hardly receive a glance in most LMICs because of its inherent financial toxicity, even in its basic management. There is, however, an acknowledgement of the controversy over the intrinsic value of PFS in the absence of OS among haematologists, haemato-oncologists, and oncologists. Thus, in the case of Polivy-R-CHP vs R-CHOP without any advantage in complete response rate and OS, I can say that Polivy-R-CHP is not an improvement on R-CHOP per se. PFS may also not be worthwhile if quality of life, and treatment-associated toxicities are not significantly improved. This is best exemplified in the E2100 trial[11]. Kovic et al, in their study, did not find any significant association between health-related quality of life (HRQoL) and PFS[22]. Thus, “cost-effectiveness” of PFS without improvement in QoL may not be a true reflection of value.

The crossroads: PFS, OS, QoL and suggestions for future oncology studies

The current reality is that most cancers are in a chronic disease state with many treatment options available, along with different protocols/regimens in different lines of combinations, each with its advantages. Thus, proving a significant benefit in OS may be a difficult endpoint to reach, so other objective criteria like PFS, QoL, and drug safety can be used. This is best exemplified in the BELLINI clinical trial (NCT02755597), a phase 3, double-blind, randomized, controlled trial of bortezomib and low-dose dexamethasone with or without venetoclax in patients with relapsed and refractory multiple myeloma who have received 1 to 3 prior lines of therapy. While the median PFS (95% CI) was 22.4 months (15.3, -) for the venetoclax arm and 11.5 months (9.6, 15.0) for the placebo arm, the interim analysis for overall survival was 41/194 (21.1%) deaths on the venetoclax-containing investigational arm and 11/97 (11.3%) deaths on the placebo arm. The hazard ratio (HR) of the venetoclax-containing investigational arm compared to the placebo arm was 2.03 (95% CI: 1.04, 3.94), increasing the relative risk of death by approximately two-fold compared to the placebo arm[23]. The FDA had to issue a warning against the investigational use of venetoclax in the management of multiple myeloma[24]. Very recently, AbbVie, the makers of ibrutinib, voluntarily withdrew ibrutinib from the US market for the management of mantle cell lymphoma and marginal zone lymphoma as a result of the confirmatory phase 3 SHINE (NCT01776840) and SELENE (NCT01974440) trials, where SHINE, though meeting the PFS endpoint, had increased adverse events compared to the control regimen[25][26]. The most recent essay by Meirson et al in the Lancet on the validity of adjuvant abemaciclib in HER2-negative breast cancer patients of the monarchE trial and the response by Johnston et al mean the debate is far from over[27][28]. These disconnects need to be addressed by the regulatory authorities urgently. While Polivy + R-CHP might have shown a significant PFS over R-CHOP, and also proved "cost-effective" against the alternative, its long-term effects including QoL indices would need to be determined over time.

Conclusion

In conclusion, while an OS may not be a feasible endpoint in all clinical trials, a significant PFS is not enough when QoL is adversely affected especially on follow-up as in the case of the PARP inhibitors in some cancers[29]. Data on OS must also be carefully analyzed as part of the whole data, just like the BELLINI trial, and informed decisions on the risk and benefit of the cancer drug are properly assessed. QoL should thus be part of the "currency" to measure cost-effectiveness. Of what value is it to live longer if it is full of pain and misery?

List of abbreviations

- OS: Overall survival
- PFS: Progression-free survival
- ICER: Incremental cost-effectiveness ratio
- WTP: Willingness to pay
- QALYs: Quality-adjusted life years
- QoL: Quality of life
- FDA: Food and Drug Administration
- PARP: Poly-ADP ribose polymerase

Availability of data and materials

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Competing interests

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Authors' information

The author is a consultant haematologist practising in Nigeria.

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