Sarcoma Research - International

Open Access

Austin Publishing Group

Mini Review

Overall Survival as Primary End Point in Advanced Soft Tissue Sarcoma and its Surrogates: A Bemusing Mirage

Rastogi S[1]*, Mishra SV[2] and Aggarwal A[3]

[1]Assistant Professor, Medical Oncology, AIIMS, New Delhi, India

[2]Department of Biotechnology, AIIMS, New Delhi, India

[3]Consultant, Radiation Oncology, Fortis Hospital, Noida, India

***Corresponding author:** Sameer Rastogi, Assistant Professor, Department of Medical Oncology, Dr. BRA Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India

Received: July 05, 2016; **Accepted:** July 29, 2016; **Published:** August 01, 2016

Abstract

Advanced soft tissue sarcoma is extremely complex and heterogenous disease with dismal outcomes. The advent of newer drugs like pazopanib, trabectedin and most recently eribulin has enabled a flexible and more individualized approach to the treatment of advanced soft tissue sarcoma. However, given their modest benefit, it becomes essential to evaluate if we are using appropriate end points in the current trials and how the equation between progression free survival and overall survival might change in future.

Keywords: Soft tissue sarcoma; Surrogacy; Eribulin

Introduction

The progress in advanced soft tissue sarcoma as compared to other common tumors like lung and breast cancer has been painfully slow. However, gradually the hope seems evident in the face of newly approved drugs in last few years. All these trials show at best the modest improvement in outcomes leaving an unmet need for more effective therapies. There is no consensus with regard to the best end point in advanced soft tissue sarcoma trials. This debate of end point has been sparked by the recently published systematic review for trial level surrogacy by Zer et al in Journal of clinical Oncology highlighting that PFS and RR can be appropriate surrogates for Overall Survival (OS) in advanced Soft Tissue Sarcoma (STS) [1]. This along with the editorial published by Zhao et al in the same issue emphasize in general the objective, accurate and reliable nature of OS with the caveat that OS requires long follow up and is often affected by post progression therapies and cross over [2]. Here we have highlighted how OS is gradually losing its importance as a primary end point and how it is increasingly difficult to establish the surrogacy between OS and PFS, exemplified by recent trials especially in STS. Though Progression free survival as an end point is not free of flaws but it is the best practical end point we might have with us right now.

Why OS is no More an Appropriate End Point?

Traditionally, the OS in treatment naive metastatic STS had been around one year and post progression survival after first line therapy was only few months as typified by EORTC 62012 trial where combination of ifosfamide and doxorubicin was compared to single agent doxorubicin in a randomized manner [3]. Median PFS for combination arm was 7.4 months *vs.* 4.6 months in single agent arm while OS was 14.3 months *vs.* 12.8 months respectively. After the advent of newer drugs (pazopanib, trabectedin and eribulin) , as in the regulatory trials leading to FDA approval of all three drugs, OS has been consistently shown to be two to four times the PFS and is comparable to EORTC 620102 trial which was unanticipated in the heavily treated population enrolled in these trials [4-6]. Thus it is apparent that availability of multiple lines of therapy has dispelled the nihilism of the post progression therapy even in patients who have already progressed after two or more lines of therapy. Other than post progression therapies, this difference might be attributed to selection bias for fit patients in the trials testing second or third line therapies and lesser extent to histology specific trial population. However, in such a scenario there is a high likelihood that results of OS are increasingly confounded by post progression salvage therapies. The gap between OS and PFS is very much evident in the randomized trial of eribulin *vs.* dacarbazine, where patients who had already received two or more lines of therapies were enrolled. PFS in both arms was 2.6 months while OS in eribulin *vs.* dacarbazine was 13.5 months *vs.* 11.5 months respectively. This conspicuous gap between PFS and OS in this heavily treated population further points out that post progression therapies could play a major role and lack of benefit of OS or significant benefit of eribulin, both, could be erroneous. Analogically, the treatment with eribulin is akin to the first 200metres of a 1km race and that the lead taken or getting behind might not be truly representative of the end result. OS might be an apt endpoint in more pragmatically designed trials with post progression predefined sequential therapies or diseases like pancreatic cancer where salvage chemotherapy is still not available. In nutshell, with the availability of multiple lines of chemotherapy and targeted therapies, it is increasingly difficult to rely on OS as an end point.

Loss of Surrogacy between OS and PFS – De ja vu

Besides this gradually increasing gap between PFS and OS, there is a discernible loss of surrogacy in PFS and OS in most recent trials [4-6].This could be partly due to the effect of post progression therapies causing dampening of trial level association between OS and PFS. The same phenomenon has been previously seen in metastatic colon cancer trials and melanoma trials. In malignant melanoma, a number of initial trials which compared effective investigational agent with earlier standard of care, dacarbazine revealed statistically significant improvement in PFS translating into OS benefit (OS correlation coefficient 0.96) [7]. However once highly effective agents became available as subsequent lines of therapy after progression on investigational agents, the association of PFS and OS dwindled

Citation: Rastogi S, Mishra SV and Aggarwal A. Overall Survival as Primary End Point in Advanced Soft Tissue Sarcoma and its Surrogates: A Bemusing Mirage. Sarcoma Res Int. 2016; 3(2): 1031.

(correlation coefficient 0.55) [7]. Similarly in colorectal cancer, when targeted agents were not available, PFS was found to be a valid surrogate for OS but this association has diminished in recent trials when multiple agents are available for salvage therapy [8,9]. Taken further, it might also be a possibility that end points might be therapy specific and depend upon therapy as well and not all treatments can be clubbed together. It might be a possibility in case of eribulin where absence of PFS benefit is standing out in the presence of OS benefit both in breast cancer and STS [4,10]. In designing future trials we must pre-empt that surrogacy between PFS and OS might not hold true. We believe in the study by Zer et al PFS seemed to be surrogate for OS because most of the trials had post progression survival less than 12 months, which might not be the case when conventional chemotherapy along with newer drugs pazopanib, trabectedin and eribulin would be used as subsequent different lines.

Conclusion

In nutshell, though PFS evaluation might be rife with assessment time bias, bias due to symptomatic (i.e., non radiologic) disease progression, subjective assessment bias and bias due to missing data but it is the most practical and feasible end point in soft tissue sarcoma in current scenario. Besides, as seen in current trials surrogacy would be difficult to establish in between OS and PFS.

References

1. Zer A, Prince RM, Amir E, Abdul Razak A: Evolution of Randomized Trials in Advanced/Metastatic Soft Tissue Sarcoma: End Point Selection, Surrogacy, and Quality of Reporting. J Clin Oncol. 2016; 34: 1469-1475.
2. Zhao F: Surrogate End Points and Their Validation in Oncology Clinical Trials. J Clin Oncol. 2016; 34: 1436-1437.
3. Judson I, Verweij J, Gelderblom H, Hartmann JT, Schöffski P, Blay JY, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol. 2014; 15: 415-423.
4. Schöffski P, Chawla S, Maki RG, Italiano A, Gelderblom H, Choy E, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet. 2016; 387: 1629-1637.
5. Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Arthur Staddon, et al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. J Clin Oncol. 2015.
6. Van der Graaf WT, Blay JY, Chawla SP, Dong-Wan Kim, Paolo G Casali, Patrick Schöffski, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012; 379: 1879-1886.
7. Flaherty KT, Hennig M, Lee SJ, Paolo A Ascierto, Reinhard Dummer, Alexander M M Eggermont, et al. Surrogate endpoints for overall survival in metastatic melanoma: a meta-analysis of randomised controlled trials. Lancet Oncol. 2014; 15: 297-304.
8. Buyse M, Burzykowski T, Carroll K, Michiels S, Sargent DJ, Miller LL, et al. Progression-free survival is a surrogate for survival in advanced colorectal cancer. J Clin Oncol. 2007; 25: 5218-5224.
9. Shi Q, de Gramont A, Grothey A, John Zalcberg, Benoist Chibaudel, Hans-Joachim Schmoll, et al. Individual patient data analysis of progression-free survival versus overall survival as a first-line end point for metastatic colorectal cancer in modern randomized trials: findings from the analysis and research in cancers of the digestive system database. J Clin Oncol. 2015; 33: 22-28.
10. Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011; 377: 914-923.

Citation: Rastogi S, Mishra SV and Aggarwal A. Overall Survival as Primary End Point in Advanced Soft Tissue Sarcoma and its Surrogates: A Bemusing Mirage. Sarcoma Res Int. 2016; 3(2): 1031.