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Letter to Editor
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Geddis Trial and Its Primary End Point- There is An Elephant in the Room!

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Letter to Editor

We read with immense interest the GeDDiS trial [1] and its editorial commentary [2] published in Lancet oncology and congratulate the authors for the same. The GeDDiS trial was a multicentre randomized controlled trial and included treatment naïve advanced soft tissue sarcoma. Patients were randomized in 1:1 fashion between six cycles of intravenous doxorubicin 75 mg/m^2 on day 1 every 3 weeks, or intravenous gemcitabine 675 mg/m^2 on days 1 and 8 and intravenous docetaxel 75 mg/m^2 on day 8 every 3 weeks. The primary endpoint was the proportion of patients alive and progression free at 24 weeks in the intention-to-treat population. With a total of 257 patients randomized in the trial (129 to doxorubicin and 128 to gemcitabine and docetaxel) and median follow up of 22 months, The proportion of patients alive and progression free at 24 weeks (the primary end point) did not differ between those who received doxorubicin versus those who received gemcitabine and docetaxel (46.3% *vs* 46.4%). We would like to highlight some relevant points pertaining to this trial. The authors of the trial have concluded that doxorubicin should remain first line for most of the patients with advanced soft tissue sarcoma.

Firstly, the choice of end point i.e. progression free rate (PFR) at 24 weeks is unique for a phase 3 trial. Progression free rate in soft tissue sarcoma (STS) was originally approved for phase 2 trial end point to test cytostatic drugs in advanced sarcoma as response rates might not be conspicuous. [3] In the meta analysis published by Zer et al PFR at 3 months and 6 months failed to show surrogacy with progression free survival or overall survival. [4] PFR at a fixed end point like 6 months progression free rate is more likely to be biased as compared to overall hazard for the same event (PFS). Besides, it does not take censuring and further event into consideration and can be unreliable in the kind of uneven (converging but not crossing)PFS curves in this study. Though authors have also shown that median progression free survival of the study was not significantly different between the arms but we must remember that the study was not powered for the same.

Secondly with this invalid end point and with only 50% patients with leiomyosarcoma it is certainly not possible to rule out better or worse activity in leiomyosarcoma based on subgroup analysis. We further believe that in the trial sarcoma pathologies like clear cell sarcoma and epithelioid sarcoma shouldn't have been included in such sarcoma trials as it dilutes the results and clouds interpretation.

However, we appreciate the inclusion of health related quality of life assessment in this trial as the 12 week assessment which shows numerical adjusted lower mean global health status score in Gem/docetaxel group as compared to doxorubicin group. It is definitely encouraging to see clinical trials in advanced soft tissue sarcoma including quality of life so as to helping with the ease of decision making for the clinicians. [5,6] Besides, it would be interesting to know in further trials the appropriate timings of measurements of quality of life and what difference can be helpful for making clinical decisions. Simultaneously it would be great to see quality of life as primary end point in such future trials with minimal difference expected in terms of quantity of life.

In nutshell, there might be more to gemcitabine and docetaxel regimen and in further trials collaborative effort must go on and try to delineate the subgroup that is benefitted by both drug regimens individually with the help of biomarkers.

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