Title
Multiple myeloma triplet therapies: baseline characteristics and control groups

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will happen after the COVID-19 pandemic, which is far from over, to prepare for any possible pandemics in the future.[4]

Health-care providers and research institutions worldwide should engage in a veritable reflection of practical ethics to adapt their guidelines to the clinical and scientific reality during this time and to improve the experience of doctors and scientists. Over the past few months, these specialists have been confronted with an entirely new situation that merits the development of an ethical vision of actions. The legitimate needs and fears of populations also need to be factored in, without forgetting the constraints inherent in an increasingly globalised world.

This reflection should lead to the embodiment of practical ethics that can mediate tensions between health and economics, and between individuals and the community, by distinguishing cultural and temporal aspects. Indeed, identifying identical solutions for all countries and transforming heterogeneous health systems is difficult. A practical, pragmatic, and rational ethical reflection is therefore needed to include these different elements.

At the start of the COVID-19 pandemic, it was time to act and apply guidelines.[2] Almost a year later, the goal is to define an ethical vision capable of bringing countries together, while considering their specific characteristics. Now is the time to call into question the subsidiarity of health at a worldwide level to arrive at useful functional coexistences between systems on the basis of different standards and cultural values.

We declare no competing interests.

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For more on the **PMNCH** see https://www.who.int/pmnch/en/

For the **PMNCH call to action** see https://www.who.int/pmnch/media/news/2020/call-to-action-on-COVID-19/en/

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Women, children, and adolescents in the post-pandemic world

Mahomed Patel and Christine Phillips[1] offer compelling arguments for a post-COVID-19 world that breaks with business as usual. I wholeheartedly agree. An early study[2] of the indirect impact of COVID-19 on maternal and child mortality estimated 2 million additional deaths in 2020–21 compared with pre-pandemic figures because of the disruptions to essential health services.

The world after the pandemic offers a unique opportunity for radical change by placing women, children, and adolescents at the heart of investments in health and opportunities for socioeconomic repair and resilience.

New solutions can be discovered to advance health—eg, by challenging the dominance of biomedical and technical frameworks that detract from the effect of power relations on health outcomes. We also need a global investment framework that includes women, children, and adolescents at its core, and features components on preparedness and response.

To ensure that the experiences of women and young people drive policy and research in this area, the Partnership for Maternal, Newborn and Child Health (PMNCH) issued a seven-point call to action in 2020, to direct investment and policy towards the unequal social, economic, and political factors driving the impact of COVID-19 and its future consequences. Commitments by ten countries to women's, children's, and adolescents' health—totalling US$20 billion—will be amplified by the PMNCH as part of this call.

I urge the global health community to support Patel and Phillips' call for a moral imagination that makes us think about how we frame solutions to old and new problems. We are morally obliged to heed that call.

I declare no competing interests.

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Multiple myeloma triplet therapies: baseline characteristics and control groups

Given that the bortezomib and dexamethasone combination treatment has been shown to be inferior to contemporary treatments in clinical trials well before the BOSTON trial began enrolling,[1] why did Sebastian Grosicki and colleagues[2] consider bortezomib and dexamethasone for the control group for patients in the USA? How many patients from the USA were enrolled?

The investigators claim that the BOSTON trial[2] included patients with cardiac and other major organ dysfunctions. What percentage of the patients enrolled in this study actually had cardiac or major organ dysfunction? Given that triplet therapy being administered at diagnosis is standard in the USA, what percentage of patients at first relapse had previously received a triplet

bortezomib-containing regimen such as bortezomib, lenalidomide, and dexamethasone? What were the outcomes for those patients for the control and intervention?

As crossover was allowed, 63 patients crossed over from bortezomib and dexamethasone to selinexor, bortezomib, and dexamethasone at progression. The investigators report that 49% of patients who crossed over did not get subsequent treatment. Is it ethical to permit patients to cross over to a triplet therapy containing two of the drugs that have already been administered many times before (especially if patients are unable to receive anything afterwards)? Was the receipt of highly effective agents, such as daratumumab, delayed?

The results of this study should indeed change the practice of the medical community, and not because of the efficacy, safety, or novelty of selinexor. This study should change the practice of enrolling patients onto antiquated control groups that have already been repeatedly shown to be inferior.[3]

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1 Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone (Kd) *vs* bortezomib and dexamethasone (Vd) in patients (pts) with relapsed multiple myeloma (RMM): results from the phase III study ENDEAVOR. *J Clin Oncol* 2015; **33:** 8509.

2 Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. *Lancet* 2020; **396:** 1563–73.

3 Hilal T, Sonbol MB, Prasad V. Analysis of control arm quality in randomized clinical trials leading to anticancer drug approval by the US Food and Drug Administration. *JAMA Oncol* 2019; **5:** 887–92.

Sebastian Grosicki and colleagues[1] reported the results of a randomised study among patients with previously treated multiple myeloma comparing selinexor, bortezomib, and dexamethasone versus standard bortezomib and dexamethasone. The primary endpoint was progression-free survival, and the investigators observed improved progression-free survival in the selinexor, bortezomib, and dexamethasone group. However, we are concerned about whether the presence of extramedullary plasmacytomas was well balanced between the two groups.

The incidence of extramedullary plasmacytomas at the diagnosis of multiple myeloma has been reported as 16·3%.[2] Previous research has shown that the presence of extramedullary plasmacytomas was significantly associated with a shorter progression-free survival in a retrospective study (median time 27 months *vs* 38 months, p=0·006),[3] as well as in a longitudinal study (hazard ratio 1·46, p=0·04).[4] Furthermore, radiation therapy is one of the most useful therapeutic options for extramedullary plasmacytomas,[5] but Grosicki and colleagues[1] did not mention radiation therapy for extramedullary plasmacytomas. As such, because patients with extramedullary plasmacytomas have poorer progression-free survival than those without it, and require different treatment strategies, it might have skewed the study results if the presence and the radiation therapy of extramedullary plasmacytomas was not balanced between the two groups.

Did the investigators observe improved progression-free survival among patients with extramedullary plasmacytomas treated with selinexor, bortezomib, and dexamethasone?

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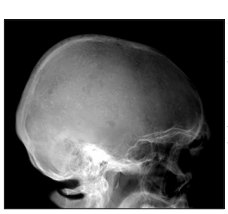
Authors' reply

We thank Ghulam Mohyuddin and colleagues for their interest in our Article[1] but respectfully disagree with their labelling of the bortezomib and dexamethasone group in our study as an inferior control group. First, according to their own definition, an inferior or suboptimal control group uses a treatment that is not standard of care, with standard of care being a treatment recommended by current guidelines and review papers.[2] The bortezomib and dexamethasone doublet drug regimen is a standard-of-care treatment for patients with relapsed or refractory multiple myeloma, because it is recommended by the 2021 edition of the National Comprehensive Cancer Network guidelines, by the current European Society for Medical Oncology guidelines, and by the current American



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