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Fixed-duration lenalidomide maintenance: considering environmental value in multiple myeloma

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Author contributions

MP and ST performed the calculations. MP wrote the first draft of the manuscript. MP and ST reviewed and edited the manuscript and approved the final version.

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ST is the founder and director of Ecovamed, a consulting company specializing in carbon-footprint assessment for the pharmaceutical industry. MP has no conflicts of interest to disclose.

Comment

Kumar et al. recently reported the results of the ENDURANCE maintenance randomization, comparing indefinite lenalidomide with a fixed 2-year duration in patients with standard-risk newly diagnosed multiple myeloma who were not undergoing upfront autologous stem-cell transplantation.[1] Continuous maintenance improved progression-free survival but did not improve overall survival, while grade ≥3 nonhematologic adverse events were more frequent.[1] These findings contribute to the ongoing discussion regarding the optimal duration of maintenance therapy. We suggest that they also illustrate a broader and largely unmeasured consequence of treatment de-escalation: its potential environmental co-benefits.

The environmental burden of health care is increasingly recognized as a contributor to pollution-related health damage, and pharmaceuticals represent an important component of this footprint.[2,3] Treatment duration is therefore not environmentally neutral. This may be particularly relevant in hematology, where maintenance strategies can expose large numbers of patients to anticancer medicines for several years. De-escalation trials consequently provide an opportunity to identify strategies that preserve patient outcomes while reducing treatment burden and resource consumption.

To illustrate the potential magnitude of this effect in ENDURANCE, we reconstructed incremental lenalidomide exposure from the published supplementary treatment-exposure data.[1] For each 3-cycle interval beyond cycle 24 in the indefinite-maintenance arm, the number of patients remaining on treatment was multiplied by the number of cycles and by the dose-specific cradle-to-pharmacy-gate carbon footprint of a 21-capsule lenalidomide box. Dose-specific footprints were derived from a hybrid life-cycle assessment approach previously developed for oral medicines.[4] On this basis, fixed-duration maintenance would avoid approximately 526 kg (95% uncertainty interval 190-1,347) carbon dioxide equivalents (CO_2e) per patient compared with indefinite treatment. At the population-level, an illustrative U.S. scenario of approximately 8,000 potentially relevant patients annually, corresponding to roughly 4,200 metric tons CO_2e avoided each year. Applying ReCiPe 2016 egalitarian health-damage factors, these avoided emissions would correspond to approximately 53 disability-adjusted life-years of future health damage avoided annually.[2] These estimates are intended to contextualize the potential environmental magnitude of treatment duration rather than to modify the clinical interpretation of ENDURANCE.

We deliberately restricted this illustration to lenalidomide exposure. Drug exposure could be reconstructed directly from published trial data and combined with product-level life-cycle estimates. By contrast, reliably estimating the environmental consequences of adverse events, dose modifications, toxicity monitoring, hospital care, or management of second primary cancers would require patient-level resource-use data that were not reported. Incorporating these components using generic assumptions would introduce substantial model dependence and imply a degree of precision unsupported by the available data. Their exclusion therefore

provides a deliberately narrow estimate of the directly quantifiable drug-related effect while potentially omitting additional environmental differences between the strategies. Subsequent anticancer therapy could partially offset these savings, although nonprotocol treatment was only modestly more frequent after fixed-duration maintenance.[1]

Environmental considerations should not determine treatment duration when clinically meaningful benefits are at stake. In ENDURANCE, the progression-free-survival benefit of continued maintenance must be considered together with the absence of an overall-survival benefit, treatment toxicity, second primary cancers, treatment burden, quality of life, and patient preferences.[1] Environmental impact should enter this discussion as an additional dimension of treatment value, rather than as a substitute for established clinical outcomes.

The implications extend beyond lenalidomide and beyond greenhouse-gas emissions. De-escalation may reduce pharmaceutical production, packaging and transportation, but also monitoring, patient travel, waste generation, supportive care, and other health-care resource use. These changes may affect climate change as well as resource depletion, ecotoxicity, air pollution, and other environmental endpoints. Yet these consequences remain largely invisible in conventional clinical trials. Recent work in oncology has highlighted several clinically validated strategies, including shorter treatment duration, dose reduction, reduced visit frequency, biomarker-guided treatment selection, and treatment omission, that may generate environmental co-benefits even though these outcomes were not prospectively assessed.[5]

Future maintenance and de-escalation trials could address this gap with relatively modest additional data collection. Treatment exposure, dose modifications, hospitalizations, outpatient visits, laboratory and imaging procedures, patient travel, and major supportive-care interventions are frequently already collected or could be captured prospectively. Combined with transparent life-cycle inventories and standardized environmental impact factors, these data could allow environmental outcomes to be evaluated alongside survival, toxicity, quality of life, and cost. Carbon footprint provides an intuitive starting point, but sustainability assessment should ultimately evolve toward a broader life-cycle perspective rather than equating environmental impact with greenhouse-gas emissions alone.

The ENDURANCE results therefore raise a question extending beyond the optimal duration of lenalidomide maintenance: when therapeutic strategies achieve similar survival, should we systematically assess which achieves that outcome with less treatment burden and lower environmental impact? Doing so would not lower the evidentiary standard for hematologic care. It would broaden our understanding of treatment value and help identify strategies that are simultaneously clinically sound, patient-centered, economically responsible, and environmentally sustainable.

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