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Original Research

Comparative effectiveness and safety of thalidomide and lenalidomide in patients with multiple myeloma in the United States of America: A population-based cohort study☆

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Survival

Abstract ***Background:*** The comparative effectiveness of thalidomide and lenalidomide in the treatment of multiple myeloma has not been established. We conducted an observational cohort study of multiple myeloma patients receiving either thalidomide or lenalidomide in routine care in the United States of America to assess their comparative survival and rates of peripheral neuropathy.

Methods: Myeloma patients were identified and followed using administrative claims data from a large national health insurance provider (UnitedHealth). Patients were eligible if they initiated treatment with either lenalidomide or thalidomide between 2004 and 2013. Propensity score stratified Cox proportional hazards regression was used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for death and new-onset peripheral neuropathy (defined by International Classification of Disease, Ninth Revision codes or a new prescription intended to treat neuropathic pain).

Findings: Our cohort included 1264 myeloma patients who initiated either thalidomide or lenalidomide. Among 406 new users of thalidomide, 142 (35%) developed peripheral neuropathy during a mean 499 person-days of follow-up. Among 858 new users of lenalidomide, 244 (29%) developed neuropathy during 587 person-days. Compared with thalidomide initiators, lenalidomide initiators had a reduced risk of peripheral neuropathy (HR 0.71, 95% CI: 0.56–0.92). We found no difference in rates of death (HR 1.00, 95% CI: 0.71–1.41).

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Interpretation: Our results agree with the findings of recently published trials suggesting that thalidomide and lenalidomide are equivalent with respect to survival outcomes but different with respect to neurotoxicity in clinical practice settings.

1. Introduction

For many years, multiple myeloma was an invariably deadly plasma cell cancer; its main treatment was poorly effective chemotherapeutic agents or a stem cell transplant, a dangerous and potentially life-threatening procedure. Management of multiple myeloma was transformed in the early 2000s when it was shown that thalidomide (Thalomid), an old, unpatented drug found in the 1960s which cause birth defects when used as a sedative or anti-emetic during pregnancy, could induce response rates in patients with myeloma despite previous treatment with high-dose chemotherapy [1]. Thalidomide was approved by the US Food and Drug Administration (FDA) to treat newly diagnosed multiple myeloma in combination with dexamethasone in 2006. The manufacturer of thalidomide, Celgene, has since received approval for two derivatives of the drug for multiple myeloma: lenalidomide (Revlimid), also in 2006, and pomalidomide (Pomalyst) in 2013. Another unrelated drug, bortezomib (Velcade), was approved for the frontline treatment of multiple myeloma in 2008 [2,3].

These four drugs are now routinely used in induction and maintenance strategies for both newly diagnosed and relapsed or refractory multiple myeloma [4–7]. Among patients who have not received prior myeloma therapy, the 2015 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology recommends both thalidomide and lenalidomide as part of category 1 (preferred) treatment regimens [8]. However, controversy remains over their comparative effectiveness and safety, especially in routine care settings. In dexamethasone or placebo-controlled randomised trials, lenalidomide was associated with high rates of progression-free survival (PFS) and complete response, although these were highly-selected populations that met trial entry criteria [9–11]. To our knowledge, only three published trials have included patients taking both thalidomide and lenalidomide. The industry-funded trial (Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide) compared continuous lenalidomide-dexamethasone (LD) against melphalan-prednisone-thalidomide (MPT) among newly diagnosed myeloma patients who were either older than 64 years of age or not eligible for autologous stem cell transplantation. Although patients in the continuous LD arm had improved PFS, the shape of the PFS curves were similar when comparing MPT against a group who did not receive continuous lenalidomide; suggesting that maintenance therapy with an immunomodulator was an important driver of the improved outcomes seen in this trial [6,12]. Two more recently published randomised phase III non-inferiority trials (Eastern Cooperative Oncology Group [ECOG] EA106 and HOVON87/NMSG18) compared lenalidomide directly against thalidomide (melphalan, prednisone, thalidomide with thalidomide maintenance [MPT-T] versus melphalan-prednisone-lenalidomide with lenalidomide maintenance [MPR-R]) in myeloma patients and found no difference in either PFS or overall survival, although those randomised to maintenance therapy with thalidomide had higher rates of peripheral neuropathy, higher rates of discontinuation due to neuropathy and a lower quality of life [13,14].

One of the most common and debilitating side-effects of myeloma treatment is peripheral neuropathy, which affects patients' quality of life and can limit treatment intensity and duration [15,16]. Drugs approved for multiple myeloma may differ in their peripheral neuropathy rates, and although there is limited evidence from head-to-head clinical trials such as EA106 or HOVON87, expert opinion suggest that lenalidomide is less neurotoxic than thalidomide [17,18].

Though thalidomide is a decades-old product, generic competition has been prevented in the United States of America (USA) by Celgene's patents on its restricted distribution system intended to prevent the drug from falling into the hands of pregnant women [19]. Thalidomide's market exclusivity may expire soon, and lower-cost versions may become available; by contrast, patent-protected lenalidomide costs approximately $160,000/year in the USA and the prospect of generic competition remains in the future [20]. As a result, thalidomide-based regimens may be encouraged by payors and strongly considered by patients with high-deductible health insurance plans or by those in resource-limited settings [21]. To better understand the comparative safety and effectiveness of thalidomide and lenalidomide in routine clinical use, and in light of the mixed survival results from the three head-to-head trials, we conducted an observational cohort study of myeloma patients in the USA to examine the risk of death and of peripheral neuropathy with each regimen.