Antibody-drug conjugates: when chemotherapy meets immuno-oncology

Commentary

Antibody–Drug Conjugates: When Chemotherapy Meets Immune-Oncology

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RM and FG equally contributed to the intellectual content, drafted the manuscript, revised and finally approved the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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RM has received honoraria from Sanofi, Celgene, Takeda and Janssen; has served on the advisory boards for Sanofi, Takeda, Janssen, and Bristol-Myers Squibb; has received consultancy fees from Janssen.
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Immunomodulatory (IMiD) agents and proteasome inhibitors (PIs) ignited the transition from conventional chemotherapy, mainly based on cytotoxic drugs interfering with DNA repair and cell proliferation, to targeted therapies specifically sabotaging plasma-cell functioning and eliciting the immune system against tumour cells. Another revolution in the therapeutic approach to multiple myeloma (MM) was the introduction of monoclonal antibodies (mAbs) that, being directed against cell-surface targets, increased on-target activity while sparing normal cells. Anti-CD38 mAbs played a major role in this process and now represent, with PIs and IMiD agents, the backbone of the majority of anti-MM regimens adopted at diagnosis or at relapse.
However, given the highly heterogeneity of MM cell biology and the lack of efficacy of current drugs in completely eradicating the disease, treatment-resistant clones will inevitably emerge, thus fostering the development of refractory disease. Resistance mechanisms to anti-CD38 mAbs are not completely understood, and data on retreatment with different agents targeting the same surface antigen are lacking. Therefore, patients refractory to anti-CD38 therapies currently represent an unmet medical need, and the development of new compounds with different targets and/or mechanisms of action is warranted.

Indatuximab ravtansine (BT062) is an antibody–drug conjugate (ADC) consisting of a chimerized IgG4 mAb (nBT062) targeting CD138, a transmembrane receptor involved in cell-cell adhesion upregulated in malignant plasma cells,[1] and a microtubule-binding agent (maytansinoid DM4),

which, after being internalized into target cells, may induce direct apoptosis.[2] In vitro studies suggested synergy between indatuximab ravtansine and lenalidomide,[3] despite the limited anti-MM activity shown by single-agent BT062 in a phase I study enrolling relapsed/refractory (RR)MM patients (overall response rate [ORR] 5·9%).

In *The Lancet Haematology*, Kelly and colleagues[4] present the results of a phase I/IIa study to determine maximum tolerated dose (MTD), safety, and efficacy of BT062 combined with lenalidomide-dexamethasone (Len/Dex) or pomalidomide-dexamethasone (Pom/Dex) in RRMM patients. The MTD of BT062 combined with either Len/Dex or Pom/Dex was 100 mg/m^2. The most common toxicities, mainly of grade 1-2, were fatigue (73%), diarrhoea (72%), and hypersensitivity reactions (63%). Of note, peripheral neuropathy was observed in 36% of patients, while infusion-related reactions were uncommon (3%).

In patients receiving BT062/Len/Dex, the ORR was 79%. Importantly, 74% of these patients were already exposed to lenalidomide, including a 35% of lenalidomide-refractory patients in whom the ORR was 63%. While data on lenalidomide rechallenge in refractory patients are scarce, and while most of the studies that led to the approval of Len/Dex-based triplets excluded lenalidomide-refractory patients, the data reported by Kelly et al. suggest that the synergy between BT062 and lenalidomide can at least partially revert lenalidomide refractoriness. However, these data should be considered with caution, since a substantial difference in terms of progression-free survival (PFS) was observed between lenalidomide-refractory (9 months) and non-refractory (42 months) patients.
Pom/Dex was approved for patients failing treatment with both lenalidomide and bortezomib, based on an ORR of 30% and a median PFS of approximately 4 months.[5] With an ORR of 71% and a median PFS of 16.6 months associated with BT062/Pom/Dex, the data presented by Kelly et al. compare favourably with those related to Pom/Dex and other Pom/Dex-based combinations.
The main limitation of this study is the previous treatment exposure of patients enrolled. Despite the high number of prior lines (4), only 1 patient had previously received daratumumab. Given the current wide use of daratumumab and the unmet medical need represented by patients refractory to anti-CD38 mAbs, the results reported by Kelly et al. should be confirmed by further studies also including this patient population.

Several treatment options have recently emerged for the management of MM: ADCs, bispecific T-cell engagers (BiTEs), and chimeric antigen receptor (CAR) T-cell therapy. ADCs are attractive treatment options due to their off-the-shelf availability, ease of administration, and absence of risk of cytokine release syndrome or central neurological toxicity and consequent need for hospitalization. Currently, only one anti-B-cell maturation antigen (BCMA) ADC (belantamab mafodotin) has been approved. BCMA is also the target of the majority of BiTEs and CAR-T cell therapies. Other cell-surface antigens can be potential targets for new therapies and may represent new options in the sequential or combination treatment of RRMM. By targeting CD138, BT062 could potentially fill the treatment 'void' experienced by patients while relapsing not only after treatment with anti-CD38 mAbs, but also after BCMA-directed therapies. Future research may thus focus on newer combinations with agents, such as the new cereblon E3 ligase modulators (CELMoDs), that are not commonly used in the first lines and that are also active in patients who already failed IMiD-based treatment.

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