AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Immunotherapy: the next step in the treatment of myeloma

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1557634> since 2016-03-09T14:52:43Z

Published version:

DOI:10.1016/S2352-3026(15)00226-4

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

UNIVERSITÀ DEGLI STUDI DI TORINO

This is an author version of the contribution published on:

Questa è la versione dell'autore dell'opera:

Lancet Haematol. 2015 Dec;2(12):e504-5. doi: 10.1016/S2352-3026(15)00226-4

The definitive version is available at:

La versione definitiva è disponibile alla URL:

<http://www.sciencedirect.com.offcampus.dam.unito.it/science/article/pii/S2352302615002264/pdf?md5=b6ecc834ca0f2396193a61872b0a2896&pid=1-s2.0-S2352302615002264-main.pdf>

Immunotherapy, the next step in the treatment of myeloma

The improved understanding of the molecular pathways involved in cancer development has allowed for the rational design of drugs that target and selectively interfere with oncogenic signaling pathways, thus moving from the “one size fits all” approach to a more personalized therapy. As a consequence, cancers, including multiple myeloma, are now treated effectively, with prolonged survival.¹ Nevertheless, nearly all myeloma patients will experience acquired resistance arising from a number of alterations, such as gene mutation, amplification or alternative splicing, and different mechanisms may be in operation in different cells due to intra-tumor heterogeneity. In addition, the tumor and its microenvironment may lead to immunosuppression in the bone marrow,² causing a loss of tumor immunosurveillance and providing protection to targeted cell death.³ In this scenario, recent findings suggest the central role of immunotherapeutic agents, including monoclonal antibodies, with a dual mechanism of action, as they can act directly against cancer cells and regulate cellular immune response.⁴

This is indeed the model of action of elotuzumab. Elotuzumab is a humanized monoclonal antibody targeted against Signalling Lymphocytic Activation Molecule Family member 7 (SLAMF7). It has a novel dual mechanism of action, as it binds to SLAMF7 on myeloma cells, while also binding to CD16 on natural killer (NK) cells, activating NK cells to lyse the antibody-bound tumor cells, thus with selective killing of myeloma cells and minimal effects on normal tissue. In addition, elotuzumab directly activates NK cells by binding to SLAMF7 on their surface and improves their antimyeloma activity through the interaction with signaling intermediary EAT-2.⁵ Based on this knowledge, elotuzumab is under evaluation in clinical trials and it showed to be safe and effective as single agents, as well as in combination with other agents such as bortezomib and lenalidomide.⁴

In the *Lancet Haematology*, the authors present final results from a phase 1b/2 randomized study of elotuzumab – 10 mg/kg or 20 mg/kg - in combination with lenalidomide and dexamethasone in relapsed myeloma patients who received one to three prior lines of therapy.⁶ Twenty-nine patients were enrolled in the phase 1 and 73 in the phase 2. In the latter, 36 patients were randomized to receive elotuzumab at 10 mg/kg and 37 patients to elotuzumab at 20 mg/kg. The overall response rate was 84%, including a very good partial response rate of 42%, and the median progression-free survival was 28.6 months. No significant differences in outcome were detected between elotuzumab at 10 or 20 mg/kg. Although cross trial comparisons should be considered with caution, the efficacy

of this combination was also confirmed in the phase 3 ELOQUENT-2 trial,⁷ where patients receiving elotuzumab plus lenalidomide-dexamethasone had a relative reduction of 30% in the risk of disease progression or death compared with the control group. Of note, in the subgroup of patients receiving elotuzumab and who achieved a very good partial response or better the median progression-free survival was not reached. Thus, elotuzumab plus lenalidomide-dexamethasone showed to be particularly effective with reduced tumor mass.

The phase 1b-2 study showed that the elotuzumab combination was well tolerated, and the most common, all grade adverse events were diarrhea (66%), muscle spasms (62%) and fatigue (56%). The good safety profile was confirmed in the phase 3 ELOQUENT-2 study,⁷ which found no significant difference between elotuzumab-lenalidomide-dexamethasone and the control group in terms of rates of grade 3-4 toxicities: neutropenia was 34% versus 44%, thrombocytopenia 19% versus 20%, and anemia 19% versus 21%, in the elotuzumab and in the control groups, respectively. Elotuzumab induced an increase in lymphocytopenia (77% versus 49%), which may reflect alterations in lymphocyte trafficking, including NK cells, with no evidence of autoimmunity or other sequelae of immune dysregulation.

The results of the phase 1b-2 study, and in particular those of the ELOQUENT-2 study, suggest that the combination of elotuzumab plus lenalidomide-dexamethasone can be considered one of the new standards of care for relapsed/refractory myeloma patients, with no additional toxicity. Longer follow-up is needed to assess whether a subgroup of patients may have a very prolonged remission duration. Further evidence is needed to support the role of treatment strategies that combine cytoreduction and tumor immunosurveillance in multiple myeloma, as already demonstrated in other tumors.

Antonio Palumbo, Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Italy.

appalumbo@yahoo.com

AP has received honoraria and consultancy fees from Bristol-Myers Squibb and Celgene.

References

1. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell* 2015;**161**:205-14.
2. Abdi J, Chen G, Chang H. Drug resistance in multiple myeloma: latest findings and new concepts on molecular mechanisms. *Oncotarget* 2013;**4**:2186-207.
3. Pratt G, Goodyear O, Moss P. Immunodeficiency and immunotherapy in multiple myeloma. *Br J Hematol* 2007;**138**:563:79.
4. Donato F, Gay F, Brighen S, et al. Monoclonal antibodies currently in Phase II and III trials for multiple myeloma. *Expert Opin Biol Ther* 2014;**14**:1127-44.
5. Palumbo A, Sonneveld P. Preclinical and clinical evaluation of elotuzumab, a SLAMF7-targeted humanized monoclonal antibody in development for multiple myeloma. *Expert Rev Hematol* 2015;**8**:481-91.
6. Richardson PG, Jagannath S, Moreau P, et al. Elotuzumab in combination iwth lenalidomide and dexamethasone in patients with relapsed multiple myeloma : final results from the 1703 phase 1b/2, open-label, randomized study. *Lancet Haematol* 2015 XXXX
7. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. *N Engl J Med* 2015;**373**:621-31.