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Medac at the EBMT 2018

Highly effective with reduced toxicity – Treosulfan-based regimen is a promising new conditioning therapy for MDS and AML

- **Allogeneic haematopoietic stem cell transplantation is the only potentially curative treatment option in MDS and AML, which are among the most common malignant blood diseases in adults**
- **Conditioning therapy is essential for treatment success, yet it is still associated with high rates of morbidity and mortality**
- **New phase III study data presented at the EBMT¹ demonstrate the considerable clinical benefit of a treosulfan-based reduced-toxicity conditioning regimen with regard to overall survival**

Lisbon, Portugal / Wedel, Germany (18 March 2018). “There is a great need for conditioning therapies with maximum antileukaemic effect and, at the same, reduced toxicity”, Prof. Arnon Nagler, Tel Hashomer/Israel, emphasised during the Medac Satellite Symposium at this year’s 44th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT). The treosulfan-based reduced-toxicity conditioning (RTC) from Medac is a promising new treatment option. This treosulfan therapy is distinguished by its high intensity – similar to that of the myeloablative process – and antileukaemic effect, while at the same time having significantly reduced levels of toxicity.^{2,3,4}

¹ Medac Satellite Symposium “New clinical trial data on treosulfan-based conditioning therapy”, 18 March 2018, as part of the 44th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT) in Lisbon, Portugal.

² Ruutu T et al. *Haematologica*. 2011;96(9):1344-50.

³ Casper J et al. *Bone Marrow Transplantation*. 2012;47(9):1171-77.

⁴ Shimoni A et al. *Bone Marrow Transplant*. 2012;47(10):1274-82.

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Allogeneic haematopoietic stem cell transplantation (HSCT) is the only potentially curative treatment option for many malignant and non-malignant diseases.⁵ It is imperative that transplantation be preceded by preparatory conditioning therapies. The standard in this respect is conditioning with high-dose, toxic myeloablative regimens which, however, are not suitable for at-risk groups.⁶ For some time now, research has therefore been conducted into so-called reduced-intensity conditioning therapies (RIC).^{7,6}

The RIC procedures to date have made it possible for more at-risk patient groups, such as elderly and comorbid patients, to be treated with stem cell transplantation. This has led to an increase in the number of allogeneic HSCTs carried out worldwide.^{5,8} This also applies to acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)⁵, common malignant blood diseases that are primarily diagnosed in elderly – often also comorbid – adults. These diseases are usually associated with a poor prognosis, which deteriorates further with increasing age.⁹ However, the currently established RIC regimens are disadvantaged by the fact that, although they are associated with a reduced transplant-related mortality rate (TRM), they also carry an increased risk of relapse and/or transplant failure.^{5,8}

Conditioning with treosulfan – clinically relevant survival benefit

As part of the Symposium, Prof. Dietrich Beelen, Essen/Germany, presented data from what is to date the largest international prospective phase III study on conditioning therapy with treosulfan.¹⁰ This comparative study investigated a treosulfan/fludarabine-based conditioning regimen as an alternative to reduced-intensity conditioning therapy with busulfan/fludarabine in 476 predominantly elderly and in some cases comorbid AML and MDS patients, in whom allogeneic HSCT was indicated. In addition to the early achievement of the primary study objective, the study results are also noteworthy

⁵ Niederwieser D et al. Bone Marrow Transplant. 2016;51(6):778-85.

⁶ Bacigalupo A et al. Biol Blood Marrow Transplant. 2009;15(12):1628-33.

⁷ Sakellari I et al. Biol Blood Marrow Transplant. 2017;23:445-51.

⁸ Mohty B, Mohty M. Blood Cancer J. 2011;1(4):e16.

⁹ Juliusson G et al. Blood. 2009;113(18):4179-87.

¹⁰ ClinicalTrials.gov. Clinical Phase III Trial to Compare Treosulfan-based Conditioning Therapy With Busulfan-based Reduced-intensity Conditioning (RIC) Prior to Allogeneic Haematopoietic Stem Cell Transplantation in Patients With AML or MDS Considered Ineligible to Standard Conditioning Regimens. NCT0082239. URL: <https://clinicaltrials.gov/ct2/show/NCT00822393> (version: 16.03.2018).

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for the outstanding results of the secondary endpoints, particularly concerning the overall survival and transplant-related mortality. For example, the overall survival in the treosulfan group was considerably higher at 71.3% than in the busulfan-based conditioning therapy group at 56.4%. At the same time, the TRM for the treosulfan-based regimen was 12.1%, and therefore significantly lower than the 28.2% for the busulfan comparator arm. Beelen concluded: *“We are talking about a considerable clinical benefit of the treosulfan-based conditioning regimen. For those patients investigated, the treosulfan-based regimen therefore represents a promising new conditioning therapy that has the potential to become the new standard.”*

Effective and well-tolerated – even in children and non-malignant diseases

Very good results for the treosulfan-based conditioning therapy have also been demonstrated in other indications. Lauri Burroughs, MD, Seattle/USA, presented new data from a phase II study with 72 patients who had undergone transplantation for non-malignant diseases, such as congenital immunodeficiencies or metabolic diseases. These confirm the efficacy and safety of the treosulfan/fludarabine-based conditioning regimen and, according to Burroughs, also point towards improved survival rates in these patient groups.

The data from a phase II study with 70 paediatric patients aged from 28 days to 18 years – which were presented for the first time during the Symposium – also confirmed the high level of efficacy and safety of conditioning with treosulfan in children with malignant blood diseases. Prof. Krzysztof Kalwak, Wroclaw/Poland, pointed out that the good results – also regarding the non-relapse mortality rate (NRM) – favour the use of treosulfan-based conditioning therapy in children. As part of his population pharmacokinetic modelling of treosulfan, Theo Reimers, PhD, Breda/Netherlands, extrapolated dosage recommendations for the different age groups of these particular paediatric patients based on individual body surface area (BSA).

Based on the presented results, the highly effective treosulfan-based conditioning regimen with its low toxicity profile can be considered the new conditioning therapy.

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