The median TTP in such patients was 13 months, and the 2-year progression rate was 70% [18]. These patients should no longer considered as SMM but as MM according to the current IMWG criteria. In conclusion, for each newly diagnosed SMM patient, it is necessary to identify the risk of progression. So far, the Mayo Clinic and the Spanish models have been used and validated in prospective trials. However, the two models do not overlap and there are many patients that are differently classified according to the two models. In addition, many other models have been generated in the last years although all of them need to be validated [19] (Table 1). In any case, the probability of each SMM patient to evolve in MM should be defined by taking into account all the available data rather than defining the risk according to a fixed model. In general, according to the available models and to the aforementioned risk factors, SMM patient can be divided in three categories of risk of progression [19]: a) *low risk:* these patients have a probability of progression at 5 years of 8% and should be followed similarly to MGUS patients. b) *intermediate risk:* with a risk of progression of 42% at 5 years. They represent the true SMM patients and should be followed every 6 months. c) *high risk:* half of these patients will progress to MM within 2 years from diagnosis and the key question is whether they should be treated at diagnosis or at progression. Some interventional trials are ongoing in this group of patients and nowadays there are no clear indications on the correct choice. In this uncertainty, clinicians are invited to include these patients in clinical prospective trials in order to better understand the natural course of the disease and the real survival benefits of an early treatment.

Table 1. Risk models for SMM.[19]

Risk model	Risk of progression to MM	
Mayo Clinic		Median TTP
· ≥ 10% clonal PCBM infiltration	1 risk factor	10 years
· ≥ 3 g/dL of serum M-protein	2 risk factors	5 years
· serum FLC ratio between <0.125 or >8	3 risk factors	1.9 years
Spanish myeloma		Median TTP
· ≥ 95% of aberrant PCs by MFC	No risk factors	NR
· immunoparesis	1 risk factor	6 years
	2 risk factors	1.9 years
Heidelberg		5 years TTP
· Tumor mass using the Mayo Model	T-mass low + CA low risk	15%
· t(4;14), del 17p or + 1q	T-mass low + CA high risk	42%
	T-mass high + CA low risk	64%
	T-mass high + CA high risk	55%
SWOG		2 years TTP
· Serum M-protein ≥ 2 g/dL	No risk factors	30%
· Involved FLC > 25 mg/dL	1 risk factor	29%
· GEP risk score > - 0.26	≥ 2 risk factors	71%
Pcm		2 years TTP
· ≥ 40% clonal PCBM infiltration	No risk factors	16%
· sFLC ratio ≥ 50	1 risk factor	44%
· Albumin ≤ 3.5 mg/dL	≥ 2 risk factors	81%
Japanese		2 years TTP
· Beta 2-microglobulin ≥ 2.5 mg/L	2 risk factors	67.5%
· M-protein increment rate > 1 mg/dL/day		
Czech & Heidelberg		2 years TTP
· immunoparesis	No risk factors	5.3%
· serum M-protein ≥ 2.5 g/dL	1 risk factor	7.5%
· involved/uninvolved s FLC > 30	2 risk factors	44.8%
	3 risk factors	81.5%
Barcelona		2 years TTP
· evolving pattern = 2 points	0 points	2.4%
· serum M-protein ≥ 3 g/dL = 1 point	1 point	31%
· immunoparesis = 1 point	2 points	52%
	3 points	80%

References

1. Kyle RA, Greipp PR. Smoldering multiple myeloma. N Engl J Med 1980; 302: 1347-1349.
2. Alexanian R. Localized and indolent myeloma. Blood 1980; 56: 521-525.
3. Kyle R, Gertz M, Witzig T et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003; 78: 21 - 33.
4. Kristinsson SY, Holmberg E, Blimark C. Treatment for high-risk smoldering myeloma. N Engl J Med 2013; 369: 1762-1763.
5. Kyle RA, Remstein ED, Therneau TM et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. N Engl J Med 2007; 356: 2582-2590.
6. Kyle RA, Therneau TM, Rajkumar SV et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med 2002; 346: 564-569.
7. Kastritis E, Terpos E, Moulopoulos L et al. Extensive bone marrow infiltration and abnormal free light chain ratio identifies patients with asymptomatic myeloma at high risk for progression to symptomatic disease. Leukemia 2013; 27: 947-953.
8. Rajkumar SV, Dimopoulos MA, Palumbo A et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014; 15: e538-548.
9. Perez-Persona E, Vidriales MB, Mateo G et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. Blood 2007; 110: 2586-2592.
10. Dispenzieri A, Kyle RA, Katzmann JA et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. Blood 2008; 111: 785-789.
11. Larsen JT, Kumar SK, Dispenzieri A et al. Serum free light chain ratio as a biomarker for high-risk smoldering multiple myeloma. Leukemia 2013; 27: 941-946.
12. Bianchi G, Kyle RA, Larson DR et al. High levels of peripheral blood circulating plasma cells as a specific risk factor for progression of smoldering multiple myeloma. Leukemia 2013; 27: 680-685.
13. Neben K, Jauch A, Hielscher T et al. Progression in smoldering myeloma is independently determined by the chromosomal abnormalities del(17p), t(4;14), gain 1q, hyperdiploidy, and tumor load. J Clin Oncol 2013; 31: 4325-4332.
14. Rajkumar SV, Gupta V, Fonseca R et al. Impact of primary molecular cytogenetic abnormalities and risk of progression in smoldering multiple myeloma. Leukemia 2013; 27: 1738-1744.
15. Dhodapkar MV, Sexton R, Waheed S et al. Clinical, genomic, and imaging predictors of myeloma progression from asymptomatic monoclonal gammopathies (SWOG S0120). Blood 2014; 123: 78-85.
16. Khan R, Dhodapkar M, Rosenthal A et al. Four genes predict high risk of progression from smoldering to symptomatic multiple myeloma (SWOG S0120). Haematologica 2015.
17. Moulopoulos LA, Dimopoulos MA, Smith TL et al. Prognostic significance of magnetic resonance imaging in patients with asymptomatic multiple myeloma. J Clin Oncol 1995; 13: 251-256.
18. Hillengass J, Fechtner K, Weber MA et al. Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. J Clin Oncol 2010; 28: 1606-1610.
19. Mateos MV, San Miguel J. V. Smoldering multiple myeloma. Hematol Oncol 2015; 33 Suppl 1: 33-37.

GENE THERAPY FOR THALASSEMIA: STATE OF THE ART

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Severe β-thalassemia (β-thal) is a form of congenital anemia caused by reduced or absent production of the β-globin chains of the adult hemoglobin (HbA), a tetramer made of two α and two β-globin chains. It is a heterogeneous disorder and more than 200 mutations in the β globin gene locus have been described causing a B-thal phenotype (Higgs *et al.*, 2012), characterized by a variety of clinical manifestations. B-thal patients' bone marrow contains 5-6 times the number of erythroid precursors than normal donors[1], with a number of apoptotic cells at the differentiative stage of polychromatic or ortochromatic erythroblast about 15 times greater. The reason of this condition might depend on the fact that the reduced or absent β-globin chain synthesis leads to an excess and imbalance of α-chains which, in turn, is responsible of two phenomena closely related: the increased peripheral destruction of circulating red blood cells (hemolytic anemia) and the death of erythroid precursors within the bone marrow (ineffective erytropoiesis or intramedullary hemolysis). Patients affected by B-thal present severe anaemia in the first years of life, stigmata of chronic haemolysis, hepatosplenomegaly, skeletal abnormalities due to rapid expansion of erythroid bone marrow and complications related to the iron overload such as cardiopathies, hepatic dysfunction and endocrine disorders. Treatment of B-thal is essentially supportive. Patients require lifelong transfusions combined with iron chelation therapy to reduce hemosiderosis that is ultimately fatal if not continuously treated. Optimal clinical management, based on regular blood transfusions and iron chelation therapy, have greatly improved the survival and quality of life of β-thalassemia major patients converting a previously fatal disease into a chronic, progressive disease with a life expectancy into adulthood. Indeed, B-thal remains a challenge in developing areas where children have poor access to safe blood products and iron chelat-