See original article on page 515

New alternatives in the treatment of myeloma kidney

M. Antonia Álvarez-Lara, Alejandro Martín-Malo, Pedro Aljama-García

Servicio de Nefrología. Hospital Universitario Reina Sofía. Córdoba (Spain)

Nefrologia 2013;33(4):443-7
doi:10.3265/Nefrologia.pre2013.Jun.12138

Multiple myeloma (MM) is a clonal proliferation of plasma cells that produces a certain immunoglobulin or a fraction thereof. Although renal involvement in MM is around 40%, only 12%-20% of the cases develop acute renal failure (ARF) and it is a poor prognostic factor for patient survival,[1,2] probably because the disease is more aggressive.[3-5] Approximately 10% of patients with ARF due to MM require haemodialysis (HD).[3,6] The mean survival of patients with MM on HD is 12 to 24 months, with one year survival rates ranging between 30% and 84% according to different series.[7]

The most common cause of ARF is an excessive production of free light chains (FLC), which causes a cast nephropathy known as myeloma kidney. These casts are composed of cell fragments, FLC and Tamm-Horsfall protein. Factors such as a low glomerular filtration rate, the acidic environment of the distal nephron and the presence of electrolytes such as sodium chloride facilitate coaggregation of FLC with the Tamm-Horsfall protein and its precipitation causes tubular obstruction. Most of the casts produce lumen obstruction of the distal tubule on a microscopic level and often induce a local inflammatory reaction with the creation of giant multinuclear cells typical of myeloma kidney.[8] Glomerular involvement, which is due to amyloidosis AL (10%-15% of the cases), FLC deposits at this level or type I cryoglobulinaemia, is less common. Other mechanisms of renal injury are hypercalcaemia, hyperuricaemia and hyperviscosity syndrome.[9]

The objective of myeloma kidney treatment is to reduce the production of, and therefore exposure of the kidney to FLC. Until the middle of this decade, when we began to have access to a specific laboratory test, it was not possible to determine FLC and consequently, the latter could not be routinely measured in the follow-up of these patients. Studies carried out since 2008 show for the first time the relationship between the reduction of plasma levels of FLC by different methods and renal function recovery.[10-12] Furthermore, not only is the reduction in plasma FLC significant but the rate of reduction is also important, and as such, patients who achieve a sustained reduction in the first three weeks of treatment have a significantly higher likelihood of recovering renal function than those who do not.[13] New chemotherapeutic agents and combinations of techniques that increase FLC clearance have improved the survival of patients with myeloma kidney and the recovery of renal function in many cases.

NEW CHEMOTHERAPEUTIC AGENTS

In recent years, the chemotherapeutic treatment of MM has changed with the introduction of new drugs that have increased the mean survival of patients from 30 to 45 months.[14] Current regimens include, in addition to dexamethasone, proteasome inhibitors such as bortezomib and immunomodulators such as thalidomide and lenalidomide. Bortezomib, through a series of mechanisms including blocking the activation of nuclear factor ?B, promotes apoptosis of plasma cells and sensitises them to the chemotherapeutic action of other agents.[15] Since no dose adjustment is required in renal failure, it has become a first-line treatment in patients with myeloma kidney in combination with dexamethasone and other agents. Approximately 20%-30% of patients on dialysis recover renal function during treatment with bortezomib[10,16] and this usually occurs early, during the first two or three cycles.[17-19]

Immunomodulators such as thalidomide and lenalidomide are generally used with other chemotherapeutic agents,

Correspondence: M. Antonia Álvarez Lara
Servicio de Nefrología. Hospital Universitario Reina Sofía.
Avda. Menéndez Pidal s/n. 14004 Córdoba. (Spain).
malvarezlaras@senefro.org
mariaa.alvarezlara.sspa@juntadeandalucia.es

although there are studies that show that, in combination with high-dose dexamethasone, thalidomide is associated with improvement of renal function in patients with myeloma kidney.[20,21] Thalidomide is not eliminated by the kidney and therefore no dose adjustment is required, although in patients on dialysis, there may be hyperkalaemia, and therefore, it should be used with caution.[22] Lenalidomide, a second generation derivative, is eliminated by the kidney, and as such, it is necessary to adjust the dose in patients with renal failure. Most studies with lenalidomide exclude patients with renal failure, although one trial with small numbers of patients showed an improvement in renal function.[23] Compared with immunomodulator-based regimens, it seems that bortezomib is more effective recovering renal function and furthermore, the latter occurs earlier.[24] In addition to its chemotherapeutic effect, its anti-inflammatory effect through the inhibition of nuclear factor ?B could help prevent inflammation and renal fibrosis.[5] The International Myeloma Working Group recommends using bortezomib-based regimens as the first choice in patients with myeloma kidney. Adding thalidomide to these regimens seems to improve response, but there have not yet been any conclusive studies.[25]

ELIMINATION OF FREE LIGHT CHAINS IN PLASMA

Kappa and lambda FLC are normally found in serum as monomers or dimers with a molecular weight of 22.5kDa and 45kDa respectively, with a half-life of 3 to 6 hours. In MM, in addition to the great overproduction of FLC, the latter form high molecular weight multimers. If there is renal failure, the half-life of these multimers increases to 2-3 days, which prolongs exposure of the kidney to FLC and increases renal toxicity, even if the response to chemotherapy is good. In patients presenting with severe renal failure and requiring dialysis, there is minimal renal clearance of FLC and the possibility of non-recovery of renal function is very high.[26] For this reason, it is necessary to use additional therapies to eliminate FLC from plasma in these patients.

The first attempts at FLC elimination were made with plasmapheresis. Although initial studies seemed promising, in 2005 Clark published a randomised controlled study with 104 patients with MM and ARF that does not show substantial clinical benefits (substantial reduction in mortality, dependence from dialysis or an improved glomerular filtration rate) after plasmapheresis treatment associated with chemotherapy.[27] By contrast, another study in 2008 demonstrated that plasmapheresis is effective for recovery of renal function if the FLC level is reduced by 50%[12] and a more recent observational study on a small number of patients demonstrated that when bortezomib is used and plasmapheresis is performed daily, high renal recovery rates can be achieved.[28] Although the idea of eliminating FLC by plasmapheresis is attractive, body distribution of FLC, balanced between intra-and extravascular compartments, with 80% in the latter compartment, results in poor elimination with a regular exchange of plasma volume (1.5 times in about 2-3 hours). Given the very high cut-off of plasma filters, higher rates of plasma exchange have the disadvantage that they are associated with loss of other higher molecular weight proteins that are essential for the body and, therefore, it is not advisable to use these aggressive therapies.

In recent years, several studies have been published on the efficacy of eliminating FLC from very high patency, high-cut-off (HCO) dialysis membranes designed for this purpose. HCO membranes have large pores with a cut-off of 45-60kD, therefore allowing both kappa and lambda FLC filtration. Hutchison et al. have shown that when used in patients with dialysis-dependent ARF due to MM in combination with bortezomib-based chemotherapy regimens, renal function recovery rates of 60%-74% are achieved.[11,29-31] Dialysis with HCO membranes is more effective the earlier the diagnosis and treatment of MM.[3,32] Furthermore, a linear relationship exists between the early treatment and the rate of renal function recovery, which is associated with survival,[13] and this is probably due to reduced renal exposure to FLC. In subsequent studies, on a smaller number of patients, similar results were obtained, although a higher rate of FLC reduction has not been directly associated with renal recovery.[33] In all published studies, long dialysis sessions of about 8-12 hours are carried out. At the beginning, the Theralite® (Gambro) HCO 1100 dialyzer with a 1.1m^2 area was used and, as the dialyzer clotted over time, two or more dialyzers were used per session. The 2.1m^2 Theralite® (Gambro) HCO 2100 dialyzer is currently used. Its clearance is more effective due to its larger area and only one filter is required. The main drawback of HCO membranes is that they cause a substantial loss of albumin, especially if associated with convective transport, and as such, replacement of the latter is required. Moreover, they can lead to decreased levels of chemotherapeutic agents that have a high rate of protein binding. Another drawback is their high price, to which albumin replacement must be added.

Recently, HFR (haemodiafiltration with ultrafiltrate regeneration by adsorption in resin) has been introduced as an extrarenal clearance technique that combines convection, adsorption and diffusion. It uses a dual chamber dialyzer: the first with a superflux polyphenylene membrane, with a cut-off of 42kD in which ultrafiltration is performed, and the second has the same membrane, but with low penetration, in which diffusion takes place. The ultrafiltrate obtained from the first chamber passes through a resin cartridge where adsorption occurs and it is reinfused before reaching the second chamber. This

technique is employed in HD patients due to its high protein bound toxins adsorption capacity, with the great advantage that it does not adsorb albumin.[34] Since the cut-off of 42kD theoretically allows the passage of FLC, especially kappa FLC, HFR may also be useful for eliminating FLC. A study has recently shown that HFR effectively removes kappa FLC in dialysis patients with both monoclonal and polyclonal gammopathies[35] and our group is obtaining very promising preliminary results in patients with ARF due to MM who require HD.[36]

In this issue of the journal, Borrego et al. report five cases of ARF due to MM treated by HD with HCO, with excellent results.[37] In association with a bortezomib-based chemotherapy regimen, all patients were treated with long dialysis sessions with a HCO membrane of 1.1m^2 in one case and 2.1m^2 in the others. Four of the five patients recovered renal function and became independent of dialysis and survival varied between 12 and 26 months at the end of the study. These results are comparable with those obtained by other authors[26,33] and show that the elimination of circulating FLC is essential for the recovery of renal function in patients with myeloma kidney. It must be highlighted that this study also confirms that early treatment is fundamental for reducing FLC, as was already described,[13] since the only patient who did not recover renal function was the patient in whom HCO dialysis was delayed. Another point that has been ruled out is the excessive loss of albumin, which requires it to be replaced, further increasing the cost of this therapy. The main limitations of the study by Borrego et al. are the small number of patients and the heterogeneity of the sample, as is the case in the majority of studies published, which furthermore, lack a control group. The multi-centre, randomised and controlled EuLITE (European Trial of Free Light Chain Removal by Extended Haemodialysis in Cast Nephropathy) study, is currently being carried out and is headed by Hutchison.[38] It compares the effect of extended HD with HCO with that of high-flux HD in patients with ARF due to *de novo* diagnosed MM and treated with the same bortezomib-based chemotherapy regimen. The primary objective is independence from dialysis after three months and the secondary objectives are length of time on dialysis, reduction of FLC, myeloma response and survival. We impatiently await the results of this study that will surely shed much light on the hitherto gloomy outlook for myeloma kidney.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

REFERENCES

1. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple mieloma. Mayo Clin Proc 2003;78:21-33.
2. Knudsen LM, Hjorth M, Hippe E. Renal failure in multiple myeloma: reversibility and impact on prognosis. Eur J Haematol 2000;65:175-81.
3. Khalafallah AA, Loi SW, Love S, Mohamed M, Mace R, Khalil R, et al. Early application of high cut-off haemodialysis for de-novo myeloma nephropathy is associated with long-term dialysis-independency and renal recovery. Mediterr J Hematol Infect Dis 2013;5(1):e2013007.
4. Lameire NH, Flombaum CD, Moreau D, Ronco C. Acute renal failure in cancer patients. Ann Med 2005;37:13-25.
5. Ying WZ, Wang PX, Aaron KJ, Batuman V. Immunoglobulin light chains activate nuclear factor-{kappa} B in renal epithelial cells through a Src-dependent mechanism. Blood 2011;117:1301-7.
6. Darmon M, Ciroldi M, Thiery G, Schlemmer B, Azoulay E. Clinical review: specific aspects of acute renal failure in cancer patients. Crit Care 2006;10(2):211.
7. Bladé L, Fernández-Llama R, Bosch E, Montolíu J, Lens XM, Montoto S, et al. Renal failure in multiple myeloma: presenting features and predictors of outcome in 94 patients from a single institution. Arch Intern Med 1998;158:1889-93.
8. Isaac J, Herrera del Castillo G. El riñón en el mieloma y en las enfermedades de cadenas ligeras y pesadas. En: Hernando L,

KEY CONCEPTS

1. The recovery of renal function in patients with myeloma kidney requires an energetic and early reduction of FLC in plasma.
2. Bortezomib, administered with high doses of dexamethasone, with or without immunomodulators, is the drug of choice in these patients and furthermore, it requires no dose adjustment.
3. In patients who require dialysis, the reduction of FLC in plasma, through clearance techniques with a high cut-off membrane, seems to improve prognosis. More studies are necessary to demonstrate this hypothesis and evaluate other techniques.

Aljama P, Arias M, et al. Nefrología Clínica. 3.ª ed. Madrid: Panamericana; 2008. p. 450-60.
9. Cobo MA, Miquel R, González A. Afectación renal en las enfermedades sistémicas. En: Lorenzo V, López JM. Nefrología al día. 1.ª ed. Barcelona: Grupo Editorial Nefrología; 2010. p. 47-80.
10. Roussou M, Kastritis E, Migkou M, Psimenou E, Grapsa I, Matsouka C, et al. Treatment of patients with multiple myeloma complicated by renal failure with bortezomib-based regimens. Leuk Lymphoma 2008;49(5):890-5.
11. Hutchison C, Bradwell A, Cook M, Basnayake K, Basu S, Harding S, et al. Treatment of acute renal failure secondary to multiple myeloma with chemotherapy and extended high cut-off hemodialysis. Clin J Am Soc Nephrol 2009;4:745-54.
12. Leung N, Gertz MA, Zeldenrust SR, Rajkumar SV, Dispenzieri A, Fervenza FC, et al. Improvement of cast nephropathy with plasma exchange depends on the diagnosis and on reduction of serum free light chains. Kidney Int 2008;73:1282-8.
13. Hutchison C, Cockwell P, Stringer S, Bradwell A, Cook M, Gertz MA, et al. Early reduction of serum-free light chains associates with renal recovery in myeloma kidney. J Am Soc Nephrol 2011;22:1129-36.
14. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008;111:2516-20.
15. Boccadoro M, Morgan G, Cavenagh J. Preclinical evaluation of the proteasome inhibitor bortezomib in cancer therapy. Cancer Cell Int 2005;5:18.
16. Ludwig H, Drach J, Graf H, Lang A, Meran JG. Reversal of acute renal failure by bortezomib-based chemotherapy in patients with multiple myeloma. Haematologica 2007;98:1411-4.
17. Dimopoulos MA, Roussou M, Gavriatopoulou M, Zagouri F, Migkou M, Matsouka C, et al. Reversibility of renal impairment in patients with multiple myeloma treated with bortezomib-based regimens: identification of predictive factors. Clin Lymphoma Myeloma 2009;9:302-6.
18. Dimopoulos MA, Richardson PG, Schlag R, Khuageva NK, Shpilberg O, Kastritis E, et al. VMP (bortezomib, melphalan, and prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: cohort analysis of phase III VISTA study. J Clin Oncol 2009;27:6086-93.
19. Ludwig H, Adam Z, Hajek R, Greil R, Tóthová E, Keil F, et al. Light chain-induced acute renal failure can be reversed by bortezomibdoxorubicindexamethasone in multiple myeloma: results of a phase II study. J Clin Oncol 2010;28:4635-41.
20. Kastritis E, Anagnostopoulos A, Roussou M, Gika D, Matsouka C, Barmparousi D, et al. Reversibility of renal failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone-containing regimens and the impact of novel agents. Haematologica 2007;92:546-9.
21. Tosi P, Zamagni E, Tacchetti P, Ceccolini M, Perrone G, Brioli A, et al. Thalidomide-dexamethasone as induction therapy before autologous stem cell transplantation in patients with newly diagnosed multiple myeloma and renal insufficiency. Biol Blood Marrow Transplant 2010;16:1115-21.
22. Harris E, Behrens J, Samson D, Rahemtulla A, Russell NH, Byrne JL. Use of thalidomide in patients with myeloma and renal failure may be associated with unexplained hyperkalaemia. Br J Haematol 2003;122:160-1.
23. de la Rubia J, Roig M, Ibáñez A, García I, Vera JA, Aguilar C, et al. Activity and safety of lenalidomide and dexamethasone in patients with multiple myeloma requiring dialysis: a Spanish multicenter retrospective study. Eur J Haematol 2010;85:363-5.
24. Roussou M, Kastritis E, Christoulas D, Migkou M, Gavriatopoulou M, Grapsa I, et al. Reversibility of renal failure in newly diagnosed patients with multiple myeloma and the role of novel agents. Leuk Res 2010;34:1395-7.
25. Dimopoulos MA, Terpos E, Chanan-Khan A, Leung N, Ludwig H, Jagannath S, et al. Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the International Myeloma Working Group. J Clin Oncol 2010;28:4976-84.
26. Hutchison C, Cockwell P, Reid S, Chandler K, Mead GP, Harrison J, et al. Efficient removal of inmunoglobulin free light chains by hemodialysis for multiple myeloma: in vitro and in vivo studies. J Am Soc Nephrol 2007;18:886-95.
27. Clark WF, Stewart AK, Rock GA, Sternbach M, Sutton DM, Barrett BJ, et al. Plasma exchange when myeloma presents as acute renal failure: a randomized, controlled trial. Ann Intern Med 2005;143:777-84.
28. Burnette BL, Leung N, Rajkumar SV. Renal improvement in myeloma with bortezomib plus plasma exchange. N Engl J Med 2011;364:2365-6.
29. Hutchison CA, Basnayake K, Cook M, Bradwell AR, Cockwell P. Free light chain hemodialysis increases renal recovery rate and improves patient survival in patients with cast nephropathy. Nephrol Dial Transplant 2008;1(Suppl 2):ii9a.
30. Bachmann U, Schindler R, Storr M, Kahl A, Joerres A, Sturm I. Combination of bortezomib-based chemotherapy and extracorporeal free light chain removal for treating cast nephropathy in multiple myeloma. NDT Plus 2008;1:106-8.
31. Hutchison CA, Heyne N, Airia P, Schindler R, Zickler D, Cook M, et al. Immunoglobulin free light chain levels and recovery from myeloma kidney on treatment with chemotherapy and high cut-off haemodialysis. Nephrol Dial Transplant 2012;27(10):3823-8.
32. Gaballa MR, Laubach JP, Schlossman RL, Redman K, Noonan K, Mitsiades CS, et al. Management of myeloma-associated renal dysfunction in the era of novel therapies. Expert Rev Hematol 2012;5:51-66.
33. Martín-Reyes G, Toledo-Rojas R, Torres-de Rueda Á, Sola-Moyano E, Blanca-Martos L, Fuentes-Sánchez L, et al. Tratamiento con hemodiálisis del fracaso renal agudo en el mieloma múltiple con filtros de alto poro (High Cut Off). Nefrologia 2012;32(1):35-43.
34. Wratten ML, Ghezzi PM. Hemodiafiltration with endogenous reinfusion. Contrib Nephrol 2007;158:94-102.
35. Testa A, Dejoie T, Lecarrer D, Wratten M, Sereni L, Renaux JL. Reduction of free immunoglobulin light chains using adsorption properties of hemodiafiltration with endogenous reinfusion. Blood Purif 2010;30:34-6.

36. Pendón-Ruiz de Mier MV, Ojeda-López R, Álvarez de Lara-Sánchez MA, Martín-Malo A, Aljama-García P. Eficacia de la HFR SUPRA en la insuficiencia renal por mieloma múltiple. Nefrologia 2013;33(3):426-8.
37. Borrego-Hinojosa J, Pérez-del-Barrio MP, Biechy-Baldan MM, Merino-García E, Sánchez-Perales MC, García-Cortés MJ, et al. Tratamiento con hemodiálisis larga con filtros de alto *cut-off* en la nefropatía por cilindros del mieloma: nuestra experiencia. Nefrologia 2013;33(4):515-23.
38. Hutchison CA, Cook M, Heyne N, Weisel K, Billingham L, Bradwell A, et al. European trial of free light chain removal by extended haemodialysis in cast nephropathy (EuLITE): a randomised control trial. Trials 2008;9:55.

Enviado a Revisar:18 Mar. 2013 | Aceptado el: 4 Abr. 2013