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Epidemiology and outcomes research for MGUS, myeloma and amyloidosis

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ABSTRACT

The epidemiology of plasma cell dyscrasias clearly links to a complicated multi-factorial pathogenic pathway that at the individual patient level gives no clear indication of why the malignant process has occurred but factors in the environment and within the genome give clues and are discussed. MGUS is a pre-malignant disorder characterised by monoclonal plasma cell proliferation in the bone marrow and no end-organ damage; the patients are asymptomatic. Primary amyloidosis is a rare disorder that is characterised by deposition of amyloid fibrils composed of immunoglobulin light chain fragments; symptoms relate to the affected organ. Multiple myeloma is a malignant disease of plasma cells and with improvements in treatment, patients can now expect a doubling of median survival to 5 years, a 20% chance of surviving >10 years and a 50% chance of complete remission (CR), morphological and biochemical. The challenge is now to determine exactly what this means to the individual myeloma patient in terms of benefit, and to society as a whole and this is the basis of 'outcomes research' which is discussed in this review.

1. Epidemiology of plasma cells diseases

Almost the first question patients ask when told of their diagnosis is 'what was the cause?' and clinicians involved in busy myeloma clinics are aware that, unlike in say lung cancer, there are no obvious pre-disposing or laboratory-based results that answer this question. However, there has been an exponential increase in our biological understanding of the pathogenesis and treatment of plasma cell diseases to such a point that there are now hints to the complicated multi-causal pathway that leads to these dysplasias.

In a significant number of cases, multiple myeloma is preceded by a pre-malignant condition called monoclonal gammopathy of undetermined significance (MGUS) which occurs in increasing numbers in patients over the age of 50 years[1] reaching 5% in people over the age of 80 years[2,3] and with very sensitive immuno-fixation techniques, the detection of monoclonal bands may be much higher in this age group.

Thus, age is the dominant risk factor resulting in increased incidence of myeloma with advancing age. Myeloma develops from MGUS at the rate of roughly 1% per year. This is similar to the significantly increased incidence rates reported for lymphoma with age.[4–6]

However, it is clear that one single oncogenic event does not lead to myeloma in the same way as seen in chronic myeloid leukaemia and it is more likely that there are multiple oncogenic events like karyotypic instability, primary or secondary Ig translocations and mutations leading to a multi-step transformation process.[7]

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2. Descriptive epidemiology

2.1. Age/Race

Myeloma is rare under the age of 30 (less than 0.3%) but the disease even in young people, in general, appears to have the same clinico-pathological features although there is a suggestion there may be a high incidence of extra medullary involvement.[8–11] In a series of 4081 patients from the Mayo Clinic, with a median age of 63 years, only 2% were less than 40 years. The incidence of extra-medullary involvement was 20% and 40% in those less than 40 and 30 years respectively.[10]

The perception that myeloma is getting more common is almost certainly real because the median age of the population is increasing in western societies. However, although many studies have attempted to show that there is an absolute increase in age corrected incidence, on balance this seems unlikely.[12–18] SEER (US Surveillance Epidemiology and End Results Programme) data incidence age-adjusted rates from 1992 to 1998 show an overall incidence of 4.5 per 100,000 per year, with the incidence among caucasians at 4.2 per 100,000 per year and among blacks 9.3 per 100,000 per year. Male to female ratio is 1.4–1, and the median age at diagnosis of myeloma is 71 years. Fig. 1 shows the increasing incidence of myeloma in older patients (SEER). The age-adjusted incidence-rate was 5.5 per 100,000 men and women per year. These rates are based on cases diagnosed in 1998–2002 from 13 SEER geographic areas, the incidence rates by race and sex are shown in Table 1.

In the European Union, the incidence of multiple myeloma is 5.72 per 100,000 people.[19] It is estimated that around 21,500 patients will be diagnosed with multiple myeloma in the pre-expansion EU in 2004.[19] Currently, around 70,000 people are living with multiple myeloma in the pre-expansion EU. The incidence of multiple myeloma in black populations is lower than that for Caucasians and is lower still for those of Chinese heritage.[19,20]

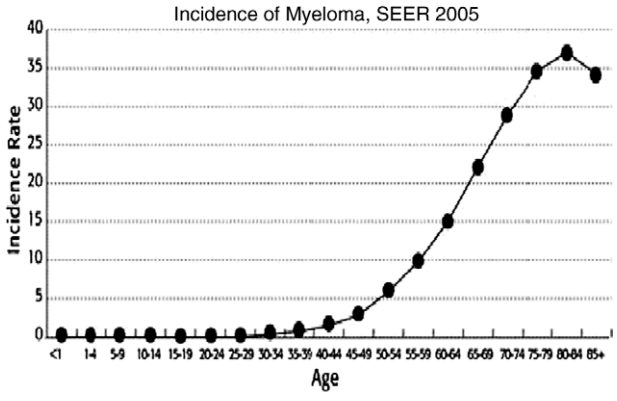

Fig. 1 – The horizontal axis shows the age at diagnosis of Americans who develop myeloma. Age is grouped into 5-year periods. The vertical axis represents the number of new cases of myeloma per 100,000 people in a particular 5-year age grouping. The risk of myeloma is about ten times greater (29 cases per 100,000) in those 70 to 74 years of age compared to those 45 to 49 years of age (three cases per 100,000). The data are from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program, 2005.

Table 1 – Incidence rates of myeloma by race and sex (SEER data)

Race/Ethnicity	Men	Women
All races	6.9 per 100,000 men	4.5 per 100,000 women
White	6.7 per 100,000 men	4.1 per 100,000 women
Black	13.1 per 100,000 men	9.5 per 100,000 women
Asian/Pacific islander	3.9 per 100,000 men	2.9 per 100,000 women
American Indian/ Alaskan native	3.7 per 100,000 men	4.3 per 100,000 women
Hispanic	6.2 per 100,000 men	4.4 per 100,000 women

2.2. Environmental agents

There are increasing numbers of studies suggesting that there may be environmental factors which may interact with underlying genetic factors that lead to increased myeloma risk.

2.3. Ionising radiation

Exposure to radiation exposure is a well recognised leukaemogen though there have been conflicting reports among the survivors of atomic bomb exposures and also those residing close to nuclear facilities about correlation between incidence of myeloma and radiation dose.[21–24] For example, a survey of Chinese diagnostic X-ray workers showed no increased incidence of myeloma over a 30-year period,[25] while other studies have shown a lower rate of myeloma amongst people employed at nuclear facilities than that observed in the general population.[26] Another study has shown an increased risk of myeloma in workers at nuclear processing plants[27] and an excess of myeloma deaths among American radiologists was also reported three decades ago.[28] In contrast, some studies show no evidence of an increased risk of myeloma in relation to residential proximity to nuclear facilities,[23,29] and although an increase in the multiple myeloma incidence has been observed amongst British military personnel who participated in atmospheric nuclear tests, no increase was seen amongst New Zealand military participants in the same tests.[24,30]

Also, a statistically significant relationship between the incidence of myeloma at radiation dose estimates of more than 1 Gy was shown in Japanese survivors of an atomic bomb though a follow up study by Preston et al showed that in 59 patients whose first cancer diagnosis was myeloma and whose dose estimates were less than 4 Gray, the relative risk for developing myeloma was not significant.[22,31] The different conclusions between the two datasets were attributed to a more complete follow up, stringent diagnostic criteria, and exclusion of myeloma cases defined as second primaries. Hence, it is not possible to confirm ionising radiation as a definitive cause of myeloma.

The frequency of monoclonal gammopathy does not appear to be increased in survivors of the atomic bombs, and nor is the relative risk of an M-protein significantly increased with increasing radiation dose.[32]

2.4. Chronic immune antigenic stimulation

There is evidence in experimental models that chronic antigenic stimulation may produce a plasma cell expansion and this led to considerable interest in the Kaposi's sarcoma-associated herpes virus infection of bone marrow dendritic cells from multiple myeloma patients, but this association was not substantiated and it now seems unlikely that chronic immune stimulation is likely to increase the risk of myeloma.[33,34]

2.5. Relationship between rheumatoid arthritis and myeloma

Early work showed an occurrence of malignant neoplasms including myeloma in patients with rheumatoid arthritis.[35,36] This has been added to by the observation that there is an increasing number of rheumatoid autoantibodies in the sera of patients with paraproteins.[37]

2.6. Occupation exposure (farming and petrochemical industries)

Examinations of the general occupational substances usually linked to carcinogenesis do not fulfill the criteria of reproducibility and dose response linking any of them to myeloma. There is some suggestion that individuals involved in the agricultural occupations may have an increased risk of myeloma but the specific agents responsible have remained unknown,[38–40] though the use of pesticides (phenoxyacetic acid and DDT) has been implicated.[41] In a recent Japanese case-control study, the occupational category of agriculture and fishery showed a significant association with increased risk of developing myeloma (OR = 5.89, 95% CI = 1.24–28.04) and exposure to chemical products including organic solvents or petroleum also showed a significant association with increased risk (OR = 8.05, 95% CI = 1.01–64.45).[42] Another population-based case-control study examined the relationship between occupation, living or working on a farm, pesticide exposure, and the risk of multiple myeloma.[43] The study included 573 newly-diagnosed patients with myeloma and 2131 controls. This study showed that farmers and farm workers had odds ratios of 1.9 (95% CI 0.8–4.6) and 1.4 (95% CI 0.8–2.3), respectively. An odds ratio of 1.7 (95% CI 1.0–2.7) was observed for sheep farm residents or workers, whereas no increased risks were found for cattle, beef, pig, or chicken farm residents or workers. A modestly increased risk was observed for pesticides (OR 1.3, 95% CI 0.9–1.8). the authors felt that the increased risk for sheep farm residents or workers indicates that certain animal viruses may be involved in myeloma risk.[43]

In the dioxin industrial accident in Italy, the risk of myeloma in the subsequent ten years was elevated in both men (relative risk 3.2; 95% confidence level 0.8 to 13.3) and in women (relative risk 5.2; 95% confidence 1.2 to 22.6).[44] However, other studies have not confirmed a relationship between a history of exposure to pesticides and myeloma.[38,40] Statistical associations have also been made between employment in metal, rubber, plastics, wood, textile industry and myeloma[40,45,46] though given the current evidence, such an association is unlikely to be significant.[47,48] Workers in the petroleum industry are exposed to a variety of known carcinogens, including polycyclic aromatic hydrocarbons. The factors studied by Cuzick and de Stavola in a case controlled study evaluating occupation, chemical exposure, radiation exposure, prior diseases, immunisations, chronic infections and markers for defects in immune regulation showed no association with occupation.[49] Another study showed that some domestic animals (cattle, horses, goats) and pesticides increased the risk of myeloma but there was no increased risk for workers in the petroleum industry.[41]

2.7. Benzene

Although previously there has been an accepted association of benzene with myeloma,[50] more recently updating of the cohort mortality study from the National Institute for Occupational Safety and Health culminating in an analysis of published case controlled literature in 1996 by Bezabeh and colleagues[51–53] makes any association now more unlikely.

2.8. Obesity, smoking and alcohol

There is no evidence that smoking or alcohol consumption increases the incidence of myeloma but obesity may be linked.[54,55] In a large epidemiologic population-based case-control study of 21,022 incident cases with 19 types of cancer and 5039 controls aged 20–76 people with a body mass of $\geqslant 30$ mg/m^2 compared with <25 kg/m^2, had an increased risk of multiple myeloma (odds ratio of = 2.06, 95% CI 1.46–2.89).[56] It has been hypothesised that oestrogen and oestrogen receptors may play a role in initiation and progression of the myeloma in obese post menopausal women where overproduction of oestrogen in adipose tissue may up regulate oestrogen receptors in plasma cells.[57] This needs to be confirmed by others, hence is not a well documented risk factor.

3. Monoclonal gammopathy of undetermined significance (MGUS)

MGUS is a pre-malignant disorder characterised by a clonal plasma cell proliferation in the bone marrow producing a monoclonal paraprotein without end-organ damage such as osteolytic bone lesions, anaemia, hyperviscosity, hypercalcemia or renal failure.[58] The abbreviation MGUS is used to describe a benign proliferation of an M component (monoclonal) of the serum proteins according to Kyle's criteria (see below), with a potential to be malignant that is indicated by clinical, biochemical and haematological parameters. The criteria for diagnosing MGUS are the presence of a serum monoclonal (M) protein <3 g/dL, fewer than 10% plasma cells in the bone marrow, absent or a small amount of protein in the urine and absence of anaemia, hypercalcemia, lytic bone lesions, or renal insufficiency related to the plasma cell proliferative process.[59,60] MGUS is the most common plasma cell dyscrasia, present in approximately 2% of the general population 50 years of age and older 23 and 3% of those $\geqslant 70$ years.[1] The prevalence increases with age. Patients with MGUS are at an increased risk for progression to either myeloma or amyloidosis.

3.1. Pathogenesis of progression of MGUS to MM

The malignant transformation of MGUS to MM is a multi-step transformation process[7] and not well understood, but because angiogenesis increases progressively with various stages of myeloma progression, this could be one of the mechanisms responsible for the process.[61,62] Approximately 50% of patients with MGUS have primary translocations in the clonal plasma cells involving the immunoglobulin heavy chain (IgH) locus on chromosome 14q32[63] and one of five partner chromosomes, 11q13 (CCND1 [cyclin D1 gene]), 4p16.3 (FGFR-3 and MMSET), 6p21 (CCND3 [cyclin D3 gene]), 16q23 (c-maf), and 20q11 (mafB).[64–66] These cytogenetic changes may play an important role in the pathogenesis of MGUS to myeloma. Kyle et al recently published large epidemiologic study with a median follow-up of 15.4 years which showed the constant rate of progression of MGUS to multiple myeloma.[5] The overall risk of progression was about 1% per year and patients were at risk even after 25 years or more of stable MGUS making life-long follow-up necessary. The risk was similar regardless of the known duration of antecedent MGUS.

3.2. Risk factors for progression of MGUS

It is increasingly important to identify patients with a low risk of developing multiple myeloma from MGUS, not only for the patient's peace of mind but also to avoid unnecessary investigations like skeletal survey and bone marrows. But patients with high risk MGUS should be identified because this is a vital research area for prophylactic approaches and clinical trials. In the recently published Kyle et al study on more than 1000 patients with MGUS, only the size and type of M protein (IgM and IgA subtypes) were predictive of progression.[5] Bone marrow plasma cell infiltration and an abnormal serum free light chain (FLC) ratio at baseline have also been shown to be an important risk factor for progression of MGUS to myeloma, amyloidosis or non-Hodgkin's lymphoma.[67,68]

Fig. 2 shows a new risk stratification system that has been developed by the Mayo clinic group to predict the risk of progression of MGUS based on three risk factors: size of the serum M protein, the type of immunoglobulin, and the serum FLC ratio. Patients with an abnormal serum FLC ratio, non-IgG MGUS, and a high serum M protein level ($\geqslant$1.5 gm/dL) had a risk of progression of 58% at 20 years (high-risk MGUS), compared to 5% when none of the risk factors were present (low-risk MGUS). The low-risk MGUS subset (constituting almost 40% of the cohort) carries a lifetime risk of only 2% when competing causes of death are taken into account. The authors suggest that the patients with low-risk MGUS can be reassured and can be monitored less frequently than once a year, perhaps only if symptoms of myeloma or related disorder become apparent.[68]

3.3. Treatment strategies for MGUS

The treatment strategy for MGUS is based on the observation that most patients with MGUS will die of other unrelated causes in a normal life span and treatment should only be designated for those who will benefit. Patients with MGUS require indefinite life-long follow-up given their risk of progression to multiple myeloma or related malignancy. Currently, no treatment is recommended though risk stratification should help guide follow-up of these patients.[67–69] Trials with chemo prophylactic agents such as dehydroepiandrosterone (DHEA), anakinra, bisphosphonates and celecoxib are underway and patients in the high-risk group should be encouraged to participate.

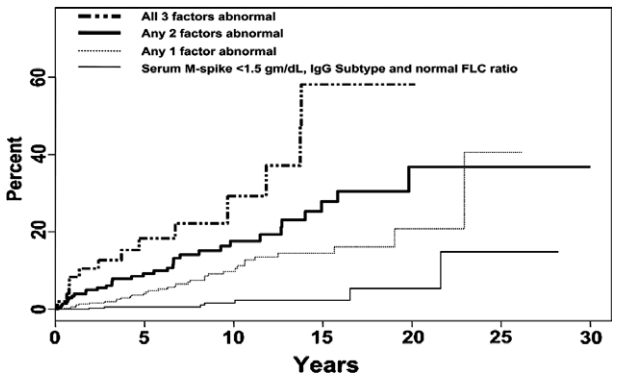

Fig. 2 – Risk of progression of MGUS to myeloma or related disorder using a risk-stratification model that incorporates the FLC ratio and the size and type of the serum monoclonal protein. The top curve illustrates risk of progression with time in patients with all three risk factors- abnormal serum kappa-lambda FLC ratio (<0.26 or >1.65), a high serum monoclonal protein level ($\geqslant$15 g/L), and non–IgG MGUS; the 2nd gives the risk of progression in patients with any two of these risk factors; the third curve illustrates the risk of progression with one of these risk factors; the bottom curve is the risk of progression for patients with none of the risk factors (permission taken from Blood).

4. Amyloidosis

Systemic (primary) amyloidosis (AL) is a plasma cell dyscrasia with an over production of Ig light chains, which form insoluble amyloid fibrillar deposits in the kidneys, heart, liver, and autonomic and peripheral nerves. Eighty-five percent of patients have evidence of a monoclonal plasma cell dyscrasia with serum and/or urine monoclonal proteins and with low-level bone marrow plasmacytosis showing clonal dominance by either kappa or lambda light chain isotypes.[70–72] The remaining 15% have clinically detectable amyloid deposits but no other detectable evidence of monoclonality although as tests become more sensitive, it is likely that all patients will be shown to have a monoclonal plasma cell dyscrasia. Highly sensitive immunoassays for free light chains in the serum may aid in the demonstration of a clonal excess of plasma cells, as well as assessing response to treatment.[73,74] AL should be distinguished from other forms of amyloidosis such as secondary, familial, or senile amyloidosis because the management is entirely different.[72,75,76] The chromosomal abnormalities described in patients with AL are: monosomy of chromosome 18, trisomy of a variety of chromosomes, t(11;14)(q13;q32), a transloca-

tion frequently seen in multiple myeloma, and a del(13q14), an abnormality associated with a poor prognosis in multiple myeloma.[77,78] A minority of patients have, or develop, multiple myeloma.[76,79]

4.1. *Pathogenesis/epidemiology*

AL is a rare disease with an estimated age-adjusted incidence of 5.1–12.8 cases per million person-years.[80]

AL fibrils are derived from the variable region of lambda light chains in approximately 75% of cases, and kappa in 25% of patients.[81–83] These fibrils bind Congo red (leading to green birefringence under polarised light) and thioflavine-T (producing an intense yellow-green fluorescence). Amyloid fibrils also bind serum amyloid P (SAP) component; this has led to the evaluation of the use of radio labeled SAP to detect tissue amyloid deposits non-invasively- SAP scan.[84]

It is unclear what determines the site of tissue deposits. The clinical presentation in AL amyloidosis depends on the number and nature of the organs affected. In some patients only one organ is affected, while in others there is extensive multi-system involvement. However, even in patients with more than one organ affected, it is usually possible to identify one organ as the 'dominant' site of involvement. The most common clinical presentations of AL amyloidosis include-nephrotic syndrome with or without renal insufficiency, restrictive cardiomyopathy, peripheral neuropathy which can be associated with autonomic neuropathy, carpal tunnel syndrome, hepatomegaly with elevated liver enzyme levels and macroglossia. Approximately 10% of patients have co-existing multiple myeloma.[72,76]

Patients with AL who do not have myeloma at the time of, or soon after, diagnosis only rarely progress to myeloma. In a series of 1596 patients with AL amyloidosis reported from Mayo Clinic, only 0.4% patients had delayed progression to myeloma.[79] This usually occurred in patients without cardiac or hepatic amyloidosis who lived long enough to develop myeloma.

4.2. *Therapy and prognosis*

Untreated patients with AL have a median survival of 10–14 months from the time of diagnosis and for those presenting with cardiomyopathy and congestive cardiac failure, the survival is less than 5 months.[72] The clonal origins shared by AL and multiple myeloma have provided the rationale for chemotherapy treatment for AL patients.

The optimal intensity of chemotherapy in AL amyloidosis remains contentious. Unlike myeloma, traditional low dose oral melphalan and prednisolone therapy is ineffective in most patients, whereas high dose ablative therapy with melphalan followed by autologous stem cell rescue, whilst effective, carries substantial procedure related mortality[85–88] presumably because of compromised organ function. The options to improve results are either to reduce dose of melphalan or select good risk patients. Reducing the melphalan dose appears to render more AL patients eligible for stem cell transplantation but sacrifices the degree of response.[89]

4.3. *Autologous stem cell transplants*

Selecting good risk patients to receive autologous bone marrow transplants has recently been reported with good results and the largest series available to date is thus a highly selected group of 312 patients (out of a total of 701 evaluated patients) treated with high-dose melphalan (100–200 mg/m^2) followed by autotransplant.[90] This study showed that the CR rate was 40% and this was associated with prolonged survival. The 100-day treatment-related mortality was 13% with a median survival of 4.6 years for the entire group of transplanted patients, and was 1.6 versus 6.4 years for those with or without cardiac involvement, respectively. It is possible that these low risk patients may also do well with chemotherapy alone. A higher dose of melphalan (200 mg/m^2) was associated with a higher CR rate and improved overall survival.

A prospective, randomised trial was designed to look at the timing of stem cell transplant for patients with AL whereby patients were randomised to high-dose melphalan and autotransplant as initial therapy (arm 1) or following two cycles of oral melphalan and prednisone (arm 2). The study showed that, the overall survival was not significantly different between the two treatment arms ($P = 0.39$). The hematological response and organ system improvements after treatment did not differ between the two groups. Fewer patients received autotransplant in arm 2 because of disease progression during the oral chemotherapy phase of the study, rendering them ineligible for subsequent high-dose therapy.[91] Hence, newly diagnosed patients with AL amyloidosis eligible for an autotransplant did not benefit from initial treatment with oral melphalan and prednisone, and there was a survival disadvantage for patients with cardiac involvement if autotransplant was delayed by initial oral chemotherapy. It has also been shown that treatment of patients with AL with high-dose melphalan and autotransplant produces measurable and sustained improvements in quality of life, particularly in those patients who achieve hematological CR.[92]

4.4. *Other treatments for AL/prognosis*

The Southwest Oncology Group studied a non-stem cell transplant-containing regimen consisting of high dose pulse dexamethasone (40 mg/day PO on days 1–4, 9–12, 17–20 every 35 days for 3 cycles) followed by dexamethasone (40 mg/day PO for 4 days every 4 weeks) together with interferon alpha (5 mU s/c three times per week) for the first 2 years, followed by interferon alpha alone for next 3 years. Improvement in amyloidosis-related organ dysfunction was noted in 45%, with an estimated 2-year overall survival of 60% for all patients and 78 and 56% for those considered eligible or not eligible for hematopoietic cell transplantation, respectively. Major toxicities were cardiovascular /fluid overload secondary to dexamethasone, and neuropsychiatric manifestations secondary to interferon.[93]

Thalidomide, which has been successfully employed in multiple myeloma, has been poorly tolerated in patients with AL amyloid though better results were obtained when thalidomide was combined with dexamethasone.[94,95] In this latter trial of 31 patients with AL amyloid whose disease was refractory to, or had relapsed after, first-line therapy, complete and

overall responses were noted in 19 and 48%, respectively. Treatment-related toxicity was seen in 65%; symptomatic bradycardia was a common adverse reaction (25%).[95] To minimise toxicities, we recommend that when using thalidomide in patients with amyloidosis (alone or in combination with dexamethasone), patients should commence on a lower dose of thalidomide (50–100 mg/day) and the maximum dose should not exceed 200 mg/day depending upon patients tolerability.

The extent of cardiac involvement in patients with AL is the most important determinant of clinical outcome. Other adverse predictors of survival include increased number of organ systems involved, time to referral centre, bone marrow plasmacytosis greater than 30%, circulating plasma cells in the peripheral blood, elevated bone marrow plasma labelling index, Howell Jolly bodies on peripheral blood film and beta-2 microglobulin.[74,87,88,96,97] It has also been shown that serum Cardiac Troponins and N-Terminal Pro-Brain Natriuretic Peptide are independent predictors of survival in patients with AL amyloidosis and can be incorporated into simple prognostic staging systems.[98,99]

4.5. *Treatment recommendations for AL amyloidosis*

Currently, there are insufficient data to indicate the optimal treatment of patients with AL; hence all patients should if possible be treated within the context of a clinical trial. Therapeutic options have been described above. The quality of life (QoL) data using a quantitative and well validated instrument shows that treatment with high-dose melphalan followed by an autotransplant improves QoL in nearly half the patient s who survive one year after treatment with improvements being seen in both CR and non-CR patients.[92]

5. Multiple myeloma

Multiple myeloma remains an incurable neoplasia in the truest definition for cure, despite treatment with conventional and/or high-dose chemotherapy. In particular, high-dose therapy with stem cell transplantation and novel targeted therapies (thalidomide and its more potent analogues, proteasome inhibitors) represent two approaches for overcoming resistance of myeloma cells to conventional therapies. Gene expression profiling will help to improve the management of myeloma by identifying prognostic subgroups and also defining molecular pathways associated with these subgroups, which may eventually become additional possible targets for future therapies.[100–103]

The first step in managing patients with myeloma is to determine if the patient needs therapeutic intervention. For example, patients with smoldering myeloma can be observed without therapy and close follow-up is recommended. This is supported by evidence from a study that showed many smoldering myeloma patients lived for several years without evidence of progression[104] and delaying therapy and treating patients at the time of progression does not adversely affect survival.[105] Patients with smoldering myeloma should be encouraged to participate in clinical trials with less toxic drugs like thalidomide in low doses or bisphosphonates investigating the delay to myeloma progression.

Patients with a solitary plasmacytoma, with no evidence of other bone or extramedullary lesions are usually treated with involved field radiotherapy followed by close observation. These patients are at risk for developing myeloma, particularly if they have a residual monoclonal protein after radiation therapy.[102]

Once MGUS, smoldering myeloma, and solitary plasmacytoma have been excluded, the treating physicians must determine if the patient is a potential candidate for an autotransplant as this will influence the initial treatment.[102,103] Treatment of myeloma needs to be tailored according to each patient with consideration of following variables in order of importance, patients choice, co-morbidities, evidence of end-organ damage, goals of treatment, age, type number and response to previous therapy. Treatment for myeloma has been discussed in detail in the previous chapters.

5.1. *Outcomes research in cancer*

Until recently, outcomes in cancer were usually only expressed in terms of overall survival and disease free survival and organisations such as the National Institute of Clinical Excellence (NICE) used only survival data as a measure of treatment success. There is now emerging an area of research that is looking into a more global impact of all aspects of treatment benefit that can act as an endpoint for the parties involved in taking decisions about whether treatments have really improved outcome. This includes the health care workers and patients and also the health care purchasers, and facilitators such as NICE. Factors that now make up part of outcome research besides survival and disease free survival are also quality of life assessment, often disease specific, and the economic implications for the individuals involved and the society as a whole.

To this end, a monograph was published in the Journal of the National Cancer Institute[106] in which the aim was to provide a review and evaluation of peer reviewed literature in cancer outcomes research. It was clear at this time that there was no consensus definition of outcomes research much less cancer outcomes research but a recent statement by the US Agency of Health Care Research and Quality (AHRQ) and the NCI in which it defines outcome research as an understanding of the end results of particular health care practises and intervention of which a key is the ability to function.[106,107] Thus at NCI, outcomes research describes, interprets and predicts the impact of various influences especially (but not exclusively) interventions on the final endpoints that matter to the decision makers who include patient's families, individuals at risk of cancer, providers, purchasers, regulatory authorities, health care accreditation organisations and the society at large. Final outcomes differ from intermediate outcomes, i.e. did somebody stop smoking, and clinical outcomes (did the patient go into remission?)?

5.2. *Outcome research in myeloma*

It is clear that our understanding of current myeloma outcomes is naïve and a long way from the global description above. For example, it is clear that health-related QoL mea-

surements in routine clinical practice, as distinct from its use in clinical trials, are currently rarely done.[107] The decision making process for myeloma care will require us to pursue descriptive studies that correlate the publication of myeloma practice guidelines with the subsequent changes in patterns of care. Following this, we will need to identify which particular outcomes research findings change the decision making process to further improve the global benefit for myeloma prevention and treatment and in turn, this will help design better ways of undertaking myeloma outcomes research. Tunis and Stryer produced an outcomes research pyramid with level one being the impact on further research, level two the impact on policies, level three impact on clinical practice and level four impact on health care outcomes.[108]

It is into this background we can see that myeloma lags a long way behind in addressing these issues. A single centre series of 195 consecutive newly diagnosed untreated myeloma patients under 70 years, seen between September 1986 and March 1994, were analysed to assess the impact of current intensive treatment methods upon remission rate, response rate and subsequent outcome.[109] They were predominantly an unselected population based group of patients (other than by age) that could be used by purchasers of health care as a model for outcome assessment. All patients were scheduled to receive a care plan which included a sequential package of treatment consisting initially of courses of infusional chemotherapy followed by an autotransplant. The complete remission rate was 53% for the whole group and 74% for those receiving high-dose melphalan and an autograft.[109] The median OS and PFS for the whole group of 195 patients was 4.5 years and 25 months, respectively. The 112 patients receiving the melphalan autografts fared significantly better than the rest of the patients with OS and PFS (from high-dose treatment) of 6.6 years and 27 months, respectively ($P < 0.005$). Outcome data from unselected patients are now expected by purchasers and presented in this way, help qualify the activity impact of advances made from research trials for the treatment of population-based cancer problems.

In a population-based survey covering two geographically distinct UK regions, Morris et al have shown that 57% of age-eligible myeloma patients were not transplanted.[110] Early death and co-morbidity accounted for nearly half of the non-transplanted patients. This study provides previously unavailable population-based epidemiological data on the availability and uptake of transplantation for younger myeloma patients in two distinct UK regions. The observed transplant rate of 43% for patients aged 65 years or under was considerably lower than that reported in a Nordic population-based survey (63%) in patients aged 60 years.[111] The main reasons for which the patients in the UK study did not receive an autotransplant were co-morbidity (34%), early death (15%), patient decision (11%), refractory disease (15%), failed mobilisation (10%) and others including complications during therapy, pancytopenia, planned allograft. Such studies can direct the efforts of health-care providers to change modifiable factors that would impact directly on clinical practice and thus health care outcomes.

5.3. *Quality of life (QoL) assessment in myeloma*

Without clear guidelines, clinicians and health care providers are often uncertain how to interpret QoL scores. To facilitate the interpretation, QoL scores of multiple myeloma patients at diagnosis were compared with the scores of a reference population, and the clinical significance of QoL score differences and of changes in scores over time was assessed by the Nordic group and the conclusion was that comparison with a reference population eases the interpretation of QoL scores and prevents overestimation of symptoms and underestimation of subjective treatment response.[112] To this end, a multiple myeloma-specific QoL questionnaire module has been designed in collaboration with the EORTC QoL Study Group to be used in clinical trials with the EORTC QLQ-C30, a general cancer questionnaire. The provisional questionnaire and the EORTC QLQ-C30 were administered to patients with multiple myeloma in each participating country with further semi-structured interviews to refine the content and design of the questionnaire. A review of the results obtained in each stage of development resulted in a 24-item myeloma-specific module, the EORTC QLQ-MY24, which assesses disease-specific symptoms and their impact on everyday life, treatment side-effects, social support, and future perspective. The module is currently undergoing further international field-testing to assess its psychometric properties.[113] Response to myeloma therapy has been directly linked to improvement in QoL.[114]

5.4. *Improvements in survival in myeloma*

Oral melphalan was first used to treat myeloma nearly 50 years ago and in combination with prednisolone still remains standard treatment for some (generally elderly) patients even now. The response rate is 40–60% but complete remission is rare and median survival is 24–30 months.[115] Various combination chemotherapy regimens including continuous infusions of vincristine and doxorubicin have been developed but none at present show a survival advantage over melphalan and prednisolone.[116] The treatment options for myeloma have expanded significantly since the paper was published in 1968 and we now have available six broad treatment packages that are different in their strategy and sensitivities. These are:[100–103,117] 1. Infusional chemotherapy (VAD/VAMP/C-VAMP). 2. Thalidomide, cyclophosphamide and dexamethasone (CTD). 3. Velcade alone or with an alkylating agent and dexamethasone. 4. Revlimid, dexamethasone (and recently addition of an alkylating agent). 5. High dose Melphalan/autologous peripheral blood stem cell transplant. 6. Allogeneic full or non-myeloablative transplant. 7. Other biological agents, i.e. Pegylated Interferon, monoclonal antibodies etc.

Thus, the whole strategy for treating myeloma has changed. The median survival for studies conducted at least 5 years ago, in which actual median survival figures therefore available give a median overall survival are approaching 5 years; this was before the impact of all of the above treatments began to occur. Table 2 shows the improvements in overall survival over the last four decades.[109,118–124] Because the majority of patients are now living longer, and early death due to either disease or treatment related problems is

Table 2 – Improvements in overall survival with changing therapy trends (first-line therapy)

Study/Trial	Therapy arm	Conditioning of transplant	Maintenance therapy	Number of patients	Overall survival
MacLennan et al. (1992) (UK MRC study)	ABCM	None	None	314	Median 32 mo
	Intermittent melphalan			316	Median 24 mo
Attal et al. (1996) (French IFM)	Conventional therapy	MEL140 +TBI	None	100	Median 44 mo
	One transplant		None	100	Median 57 mo
Powles et al. (1997) (UK single-centre)	One transplant	MEL200 in 57%, Other HDT in 15%	29% received IFN	195	Median 54 mo
Barlogie et al. (1999) (US single centre)	Two transplants	1st: MEL200 2nd: MEL200; Cy/TBI added if <PR	IFN	231	Median 68 mo
Child et al. (2003) (UK MRC)	Conventional therapy		IFN	200	Median 54.1 mo
	One transplant	MEL200	IFN	201	Median 42.3 mo
Attal et al. (2003) (French IFM)	One transplant	MEL140+TBI	IFN	199	Median 48 mo, at 7-y 21%
	Two transplants	1st: MEL140 2nd: MEL140+TBI	IFN	200	Median 58 mo, at 7-y 42%
Segeren et al. (2003) (HOVON study)	Intensified therapy		IFN	129	Median 50 mo
	One transplant	Cy-TBI	IFN	132	Median 47 mo
Sirohi et al. (2005) (UK single centre)	One transplant	MEL200	IFN	451	Median 68.4 mo, at 7-y 42%, at 10-y 31.4%

Abbreviations: ABCM : adriamycin, BCNU, cyclophosphamide, melphalan; UK MRC :United Kingdom Medical Research council; mo: months; y: years ; MEL140: Melphalan 140 mg/m^2; MEL200: Melphalan 200 mg/m^2; TBI: total body irradiation; Cy- cyclophosphamide; IFN: interferon ; PR: partial response.

decreasing, it means that almost all patients will be eligible for most of the above treatment options provided that the sequence of treatment is selected so that a treatment option does not by its nature, preclude other options later, for e.g. a patient planned to have an autotransplant should receive a stem-cell sparing regimen as first-line therapy.

Therefore, current studies looking at treatment options for induction of first response, or response to failed patients although giving clear indications of efficacy do not contribute to the understanding of the overall contribution to the total patient pathway unless an outcomes research approach is incorporated.

In addition, it may be that median survival estimations although giving clear indications of treatment responses fail to give us any idea about what may be happening to long term survivors. Potential outcomes that need to be incorporated into the large randomised clinical trials are outlined in Table 3.

Table 3 – Potential outcomes of treatment in myeloma

Treatment outcome	Definition
QoL	Quality of life with various questionnaires.
Cure	Complete and lasting recovery from disease (could be patients in first complete remission for longer than 10 years with normal quality of life).
Molecular complete response	No evidence of disease using the most sensitive techniques available. These techniques continue to evolve and become more sensitive, so this definition is constantly changing and becoming more stringent.
Complete response (CR)	No detectable M protein in the serum and urine using negative immunofixation test and normal percentage of plasma cells in the bone marrow or absence of myeloma cells by staining techniques.
Near complete response	As listed for CR, but with a positive immunofixation test.
Very good partial response (PR)	Greater than 90% decrease in M protein.
PR	Greater than 50% decrease in M protein.
Minimal response	Less than 50% decrease in M protein. Some myeloma groups consider minimal response s part of stable disease.
Stable disease (SD)	Stable disease parameters (including number and extent of bone lesions).
Progressive disease	Greater than 25% increase in M protein, new bony lesions, or a new plasmacytoma.
Overall Survival	5-year and 10-year survival.
Progression-free/event-free survival	

5.5. *Long term survival in myeloma/operational cure*

For patients who have myeloma, the chances of true cure, i.e. eradication of the last myeloma cell are low, although with auto transplantation, which has a low risk of treatment related mortality (2–3%),[120,125] a substantial proportion of patients survive for more than ten years.[124] We have described a group of myeloma patients receiving modern treatment who might have disease detectable by molecular methods but have been in long lasting first CR for >10 years lead normal lives and are free from symptoms relating to myeloma or its complications.[126] Patients with a minimum follow-up of 10 years (all diagnosed before 1993) were evaluated for prognostic factors and it was shown that patients with a pre-therapy B2M <3 mg/L and age <55 years ($n = 39$; 23%) had a median OS of 9.1years (95% CI 6.5–11.5) and 10-year survival of 43.4%. On addition of therapy variables, patients with B2M <3 mg/L, age <55 years, in CR/PR post induction therapy and those who received high-dose therapy ($n = 28$; 16%) had a 10-year survival of 50% (Fig. 3).[127] 10-year survival might therefore become increasingly important as an endpoint when testing new treatment strategies, but probably requires the platform of CR for effective treatment.

It is hoped that with a better understanding of the biology of myeloma, we might soon be able to define at the individual patient level a tailor-made sequence of treatment at the time of diagnosis. To suppose that the biological opportunities presenting themselves in myeloma should be the basis of our research in the immediate future seems reasonable and it is already likely that the median survival of the patient currently being treated outside of the context of research trials is already significantly longer than 5 years. We feel therefore that randomised trials with the advances in treatment might need to be focused not only on changes in median disease free survival but also on increasing the proportion of patients surviving at 10 years with a normal quality of life because this endpoint could be the way to lead us either to a true cure or already to a group of patients who are in long-term first complete remission and will die with their disease rather than of it.

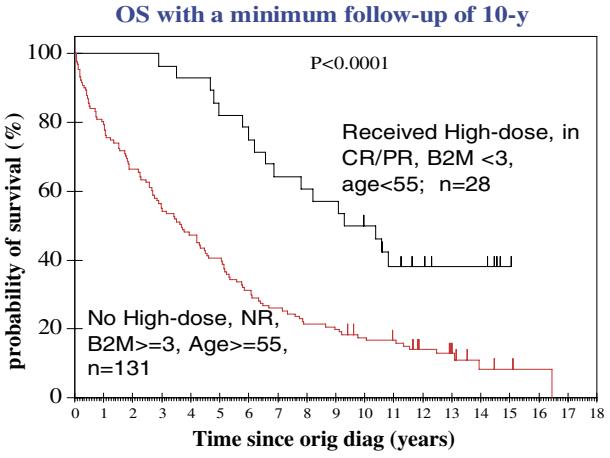

Fig. 3 – Log rank comparison of OS of patients with a minimum follow-up of 10 years (all diagnosed before 1993). The top curve illustrates patients who received high-dose therapy, were in CR/PR after induction therapy, had B2M <3 mg/L and were <55 years ($n = 28$). The bottom curve includes patients who did not receive high-dose therapy or did not respond to induction therapy or had B2M $\geqslant$3 mg/L or were $\geqslant$55 years.[127]

6. Future directions

This chapter has looked at both the epidemiology and outcomes research for plasma cell dyscrasias, and in the case of epidemiology it is quite clear that there are many years of research required before we can fully understand the dynamics of the interplay of the multi-factorial gene and environmental pathway that leads to the malignant switch from MGUS to myeloma or the pathogenesis of de-novo myeloma but the cryo-preservation of clinical material in the IMF 'bank on a cure' program would at least be a step in this direction. However, analysing within the malignant cell and within the host, the interplay of relevant proteins that are affecting the initiation and outcome of the disease seems daunting but biological treatments that are now available at least give us the opportunity to glimpse at the extraordinary biology that seems to be occurring in patients living with their myeloma. Concerning outcomes research, it is becoming increasingly apparent that most patients with myeloma will never be cured of their disease but may well live a normal life span dying of other causes and to this end, all of the factors that interplay and contribute to the quality of outcome and its impact on the patient and society are central to making a meaningful understanding of progress in treatment.

Conflict of interest statement

None declared.

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