British Journal of Haematology, 1998, **102**, 1115–1123

Annotation

CRITERIA FOR EVALUATING DISEASE RESPONSE AND PROGRESSION IN PATIENTS WITH MULTIPLE MYELOMA TREATED BY HIGH-DOSE THERAPY AND HAEMOPOIETIC STEM CELL TRANSPLANTATION

Multiple myeloma (MM) is a malignant plasma cell disorder accounting for about 10% of haematological malignancies. The disease is characterized by the clonal proliferation of plasma cells which produce a monoclonal immunoglobulin heavy and/or light chain (paraprotein, M-protein or M-component). This patient-specific paraprotein is present in the serum and/or urine of all patients except in the 1–2% of patients with non-secretory myeloma. Typical clinical and laboratory features in patients with MM include bone pain (due to lytic lesions or osteoporosis), anaemia, renal insufficiency, hypercalcaemia, increased susceptibility to infection and constitutional symptoms resulting in poor performance status. Less common complications include cord compression due to extramedullary plasmacytomas or vertebral collapse, peripheral neuropathy, amyloidosis and hyperviscosity syndrome (Malpas, 1998).

Prior to the introduction of alkylating agents, the median survival of patients with MM was less than a year (Korst *et al*, 1964; Holland *et al*, 1966). Approximately 60% of patients respond to initial treatment with conventional chemotherapy, but although survival is prolonged by treatment the median survival remains approximately 3 years (Bergsagel, 1998). Complete remissions are rare and all patients ultimately relapse, resulting in *c* 25% survival at 5 years and <10% survival at 10 years. Criteria by which different treatment regimens can be evaluated include the proportion of patients achieving an objective response, the duration of response, and survival.

Over the past 10–15 years high-dose therapy followed by haemopoietic stem-cell rescue, either allogeneic or autologous, has been increasingly employed in the treatment of multiple myeloma. For a number of reasons the existing criteria for the assessment of disease response have not proved entirely satisfactory for the analysis of disease outcome after high-dose therapy. In particular, there has been no generally agreed definition of complete response. Agreed definitions of response and progression are essential to ensure consistency of reporting within the transplant registries and to enable comparison of results from different studies and/or different treatment centres. New criteria for response and progression have therefore been developed as a result of discussions between representatives of the Myeloma Subcommittee of the Chronic Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT) and representatives of the Myeloma Working Committee of the Autologous Blood and Marrow Transplant Registry (ABMTR) and the International Bone Marrow Transplant Registry (IBMTR). These criteria will now form the working definitions of response and progression for the purposes of data collection and registry-based studies.

Currently none of the registries include specific diagnostic criteria, although all record the relevant investigations performed at diagnosis. However, we wish to emphasize that all patients undergoing high-dose therapy should have proven myeloma which requires treatment. At present high-dose therapy is not recommended for patients with equivocal myeloma or those with stage I disease. We have not at this stage reviewed the criteria for the diagnosis of myeloma, but there may be a requirement for this in the future. For example, because of the increasing use of high-dose therapy for the treatment of primary amyloidosis, it will be important to establish clear guidelines for the differential diagnosis between this condition and multiple myeloma with amyloid.

Correspondence: Dr Diana Samson, Department of Haematology, Hammersmith Hospital, London W12 0NN.

The existing response criteria

The definition of response. Changes in the level of the serum paraprotein and/or urinary light chain excretion form the basis of assessing the response to therapy and monitoring the progress of the disease. In a minority of patients disease progression will be manifested by increasing marrow or skeletal involvement, or development of other complications, without a rise in paraprotein. In non-secretory myeloma it is difficult to monitor disease accurately. Serial bone marrow examinations are helpful, although the patchy nature of marrow involvement in myeloma makes it difficult to accurately interpret small changes in the percentage of plasma cells present.

The currently used response criteria are shown in Tables I–IV. Response criteria were first developed by the Committee of the Chronic Leukemia and Myeloma Task Force (CLMTF) of the U.S. National Cancer Institute in 1968 and were reviewed by the same group in 1973 (Chronic Leukemia and Myeloma Task Force, 1968, 1973). The main response parameter is a reduction in the paraprotein of at least 50% (Table I). In 1972 the Southwest Cancer Chemotherapy Study Group, now the Southwest Oncology Group (SWOG), defined 'objective response' as a reduction of at least 75% in the calculated serum paraprotein synthetic rate (rather than paraprotein concentration) and/or a decrease of at least 90% in urinary light-chain excretion, sustained for at least 2 months (Alexanian *et al*, 1972). Patients with a reduction in serum paraprotein synthetic

Table I. Criteria of response in multiple myeloma: Chronic Leukemia and Myeloma Task Force (1968, 1973).

Effect on direct manifestations of myeloma: one or more of the following:
1. Serum M-protein: reduction to 50% or less of the pretreatment value.
2. Urinary M-protein: decrease to 50% or less of the pretreatment value if the amount was greater than 1 g/24 h; a fall to less than 0·1 g/24 h if the pretreatment value was between 0·5 and 1 g/24 h; if the pretreatment value was less than 0·5 g/24 h, this parameter should not be considered as a reliable indicator of response.
3. Reduction of 50% or more in the product of the two largest diameters of palpable or X-ray visualized plasmacytomas.
4. Radiographic evidence of skeletal healing.

Effect on indirect manifestations of myeloma (may be helpful in grading response):
1. Significant rise in Hb level (at least 2 g/dl).
2. Weight gain (at least 4 kg) with no evidence of oedema.
3. Correction of hypercalcaemia.
4. Normalization of renal function.
5. Recovery.of normal immunoglobulins.
6. Normalization of serum albumin.
7. Reduction in the percentage of bone marrow plasma cells to less than 5% if the pretreatment value was 20% or more.

Table II. Criteria of response in multiple myeloma: Southwest Cancer Chemotherapy Study Group (Alexanian *et al*, 1972).

Objective response (all of the following criteria sustained for at least 2 months):
1. Decrease in the synthetic index of serum M-protein to 25% or less of the pretreatment value and to less than 25 g/l.
2. Decrease in light-chain urine protein excretion to less than 10% of the pretreatment value and to less than 0·2 g/24 h.
3. Improvement in bone pain and performance status.
4. In all responsive patients the size and number of lytic skull lesions must not increase and serum calcium remain within normal limits.
5. Correction of anaemia (Hb >9 g/dl, and hypoalbuminaemia (>30 g/l) if they are considered to be secondary to myeloma.

Improvement:

Decline in the M-protein synthesis index to less than 50% but not less than 25% of the pretreatment value.

rate of between 50% and 74% were considered to have improved (Table II). A review of the literature indicates that the CLMTF or SWOG criteria have been used in most subsequent clinical trials, albeit frequently with some modifications of the original proposals. The relative merits of these two sets of criteria in defining outcomes has never been formally assessed, i.e. there is no evidence to indicate whether a 75% reduction in paraprotein synthetic rate has a better prognostic significance than a 50% reduction in serum paraprotein level. Most groups have used paraprotein concentration to define response because of simplicity. The terms partial response or partial remission are also frequently used. Some groups have added additional response categories, such as good or very good partial response and minimal response, again based on the degree of paraprotein reduction. An exception is the United Kingdom Medical Research Council (MRC) Myelomatosis trials, which have evaluated the efficacy of treatment not by the degree of paraprotein reduction but by the proportion of patients achieving plateau (Table III) (MacLennan *et al*, 1992). Plateau phase consists of a period of stability after chemotherapy in which tumour progression does not occur despite the persistence of measurable disease. The definition of plateau does not require any specific degree of paraprotein reduction. The minimum period of stable observation required to define plateau was 6 months in the early MRC trials but more recently has been reduced to 3 months (MacLennan *et al*, 1992). Although the concept of plateau phase was introduced almost 20 years ago (Durie *et al*, 1980), it has not been extensively used for the evaluation of response in multiple myeloma.

Table III. Definition of plateau phase in MRC Myelomatosis Trials (MacLennan *et al*, 1992).

Satisfaction of all the following criteria for a period of at least 6 months in the Vth MRC Myelomatosis trial, and for 3 months in all subsequent trials:
1. Stabilization of the M-protein without further tumour regression despite continued treatment.
2. Few or no symptoms from myeloma.
3. No blood transfusion requirement.

Complete remission. Neither the CLMTF nor the SWOG response criteria include a definition of complete response/complete remission (CR), since CR was rarely observed with existing treatments. With the introduction of new regimens such as VAD (vincristine, adriamycin and dexamethasone) and high-dose melphalan (140 mg/m^2) without stem cell support, measurable paraprotein disappeared in a significant proportion of patients and criteria for complete remission were formulated (Selby *et al*, 1987; Gore *et al*, 1989; Samson *et al*, 1989). As the use of high-dose therapy has increased

Table IV. Published criteria for complete remission in multiple myeloma.

Reference	Study	Method of paraprotein detection (negative result)	Bone marrow plasma cells	Other criteria	Required duration of negative results
Selby *et al*, 1987	HDM	EP	No specified %; normal marrow morphology	None	1 month
Gore *et al*, 1989	HDM and ABMT	EP and stain of urine with colloidal gold	<5%; normal morphology	None	3 months
Samson *et al*, 1989	VAD	EP	<4%	None	None
Gahrton *et al*, 1991	EBMT data	EP or IF accepted	<5%; normal morphology	None	None
Anderson *et al*, 1993	Allo/auto-BMT	IF	<5%; polyclonal	None	3 months
Dimopoulos *et al*, 1993	Autologous transplant	IF	No monoclonal plasma cells	None	2 months
Bjorkstrand *et al*, 1995a	Double ABMT	IF	<5%; normal morphology	None	None
Attal *et al*, 1996	ABMT *v* CCT (IFM 90)	EP	<5%; normal morphology	None	None
Vesole *et al*, 1996	Autologous transplant	IF	<1% light-chain restricted	None	2 months
Barlogie *et al*, 1997	Tandem transplant	IF	<1% light-chain restricted	None	2 months
Ballester *et al*, 1997	Intensive induction	IF	<4%	None	None
Joshua *et al*, 1997	CCT ± IFN	IF	<5%; normal morphology	Asymptomatic No transfusion	None
Schiller *et al*, 1998	CD34+selected PBPCT	IF or IEP	<5%	No progression of bone disease	None

Abbreviations: HDM: high-dose melphalan; ABMT: autologous bone marrow transplant; CCT: combination chemotherapy; PBPCT: peripheral blood progenitor cell transplant; IFM: Intergroupe Français du Myelome; EP: routine electrophoresis; IF: immunofixation; IEP: immunoelectrophoresis; EBMT: European Group for Blood and Marrow Transplantation; VAD: vincristine, adriamycin and dexamethasone.

there has been a consequent increase in the number of patients entering CR, and other groups have published their own definitions of CR; as shown in Table IV (Gahrton *et al*, 1991; Anderson *et al*, 1993; Dimopoulos *et al*, 1993; Bjorkstrand *et al* 1995b; Attal *et al*, 1996; Vesole *et al*, 1996; Barlogie *et al*, 1997; Ballester *et al*, 1997; Joshua *et al*, 1997; Schiller *et al*, 1998). All groups agreed that there should be no detectable paraprotein in serum or urine together with a normal number of plasma cells in the marrow (i.e. <4–5%), but differed according to whether the absence of paraprotein is based on routine electrophoresis (EP) alone or whether a more sensitive method such as immunoelectrophoresis (IEP) or immunofixation (IF) was required. In the earliest reports either no method was specified or only EP was required. More recently there has been a trend towards a more stringent definition of CR requiring a negative IF. Some groups have also required the plasma cells in the marrow to be of normal morphology whereas others have not included morphological assessment, and some groups have included factors such as transfusion independence and lack of symptoms. It is perhaps surprising that many groups do not exclude transient responses by specifying a minimum duration of time for which the paraprotein must remain undetectable to fulfil the definition of CR.

CR has hitherto been defined by the EBMT Myeloma Transplant Registry as absence of detectable paraprotein in serum and urine and < 5% plasma cells in marrow, without specifying the method to be used for excluding the presence of paraprotein, nor the time period for which results must remain negative. The IBMTR and ABMTR have not hitherto used a standard definition of CR. The current North American National Cancer Institute Intergroup (SWOG, INT, CALGB and ECOG) Myeloma Trial, comparing conventional versus high-dose therapy, defines CR as absence of paraprotein in serum and urine by EP and IF on at least two measurements for a minimum of 6 weeks, and <4% plasma cells in the bone marrow.

The definition of progression. There are also currently no generally accepted criteria for the definition of disease progression or relapse and papers reporting the results of different treatment regimens do not always specify the criteria used to define progression (MacLennan *et al*, 1992; Ballester *et al*, 1997; Barlogie *et al*, 1997). Bergsagel *et al* (1979) defined progression as a progressive increase in serum paraprotein of at least 10 g/l or a 100% increase in urinary light chain excretion. Belch *et al* (1988) also used a minimum increase of 10 g/l in serum paraprotein but required an increase of 2·0 g/24 h in urinary light chain excretion. In recent reports most groups have defined progression as an increase in serum paraprotein or urinary light chain excretion by 25% (Oivanen *et al*, 1997) or 50% (Samson *et al*, 1989; Bjorkstrand *et al* 1995a; Attal *et al*, 1996; Joshua *et al*, 1997). Other indicators of progressive disease such as increasing marrow infiltration or an increase in the number of lytic bone lesions are also included in the definition of disease progression by most groups. For patients in CR a reappearance of paraprotein, by whatever method, is generally accepted to constitute relapse. The EBMT has hitherto defined progression as a 50% increase of

measurable paraprotein levels (Bjorkstrand *et al*, 1995b; Gahrton *et al*, 1995). The IBMTR and ABMTR have not previously utilized any defined criteria, but a number of groups recently reporting results of high-dose therapy studies have used a 25% increase for defining progression (Attal *et al*, 1996; Schiller *et al*, 1998; Barlogie *et al*, 1997) and the current North American Intergroup trial adopts the same definition.

Response and survival. In the pioneer study dealing with response to treatment in multiple myeloma, the median survival of patients who responded to melphalan was 41 months compared with 9 months in patients who did not respond (Bergsagel, 1975) and Alexanian *et al* (1972) reported that the survival of patients treated with combination chemotherapy was directly correlated with the extent of reduction of paraprotein synthesis. This has been a frequently quoted reference supporting the relationship between the degree of response and subsequent survival. However, a similar survival analysis carried out by Palmer *et al* (1989) failed to show such a correlation. Several other studies have also reported a lack of correlation between response and survival (Baldini *et al*, 1991; Marmont *et al*, 1991; Joshua *et al*, 1991; Blade *et al*, 1994). Even with regimens such as high-dose melphalan 140 mg/m^2 and VAD, which produced CR in up to 25% of newly diagnosed patients, duration and survival were not prolonged in patients reaching CR as compared with those achieving PR (Selby *et al*, 1987; Samson *et al*, 1989).

With conventional chemotherapy, stabilization of tumour load is a more powerful prognostic factor than the degree of tumour reduction in predicting survival (Durie *et al*, 1980; Joshua *et al*, 1991; MacLennan *et al*, 1992, 1994; Blade *et al*, 1994; Oivanen, 1996). Since the survival of patients who achieve a partial or minimal response is similar to that of those fulfilling more stringent response criteria, all patients attaining a stable state should be considered in plateau phase regardless of the level of paraprotein. The MRC has been unique among those carrying out clinical trials in multiple myeloma in using stable plateau phase to define treatment efficacy rather than response criteria based on a given degree of paraprotein reduction. In some patients the paraprotein does not fall with treatment but does not increase and may remain stable for months or years. These patients have non-responding but non-progressive disease and may be considered to be in plateau phase at diagnosis. Although these patients are classified as non-responders according to the CLMTF and SWOG criteria, the disease does not progress and such patients in fact usually have a long survival (Blade *et al*, 1986; Joshua *et al*, 1991). This situation is similar to that observed in patients with smouldering myeloma (Kyle & Greipp, 1980).

In summary, few patients treated with conventional chemotherapy enter CR and the correlation between the degree of tumour response and ultimate survival is questionable. In contrast, up to 50% of patients enter CR after high-dose therapy (with CR being defined on the basis of negative EP). Furthermore, after high-dose therapy a correlation between the degree of tumour response and survival has been demonstrated. Thus, myeloma patients who enter CR post-transplant have a significantly longer progression-free and overall survival than those who enter or remain in PR or who fail to respond (Gahrton *et al*, 1991, 1995; Bjorkstrand *et al*, 1995a; Attal *et al*, 1996; Barlogie *et al*, 1997). This cannot be explained entirely by the increasing use of more stringent criteria for CR in more recent studies of high-dose therapy since in some of these reports CR was based on negative EP without negative IF (Gahrton *et al*, 1991, 1995; Bjorkstrand *et al*, 1995a). It seems more likely that there is a difference in the quality of CR after conventional chemotherapy and after high-dose therapy; in other words the level of minimal residual disease is presumably lower in patients in CR post-transplant than in those who are in CR after non-myeloablative therapy.

The new EBMT, IBMTR and ABMTR criteria for response, progression and relapse

The proposed new criteria are shown in Table V. They are based on existing criteria, with modifications. As they will form the basis for data reporting from a large number of centres throughout the world, a pragmatic approach was essential; the investigations required are therefore those which are felt to be the minimum necessary to assess response and to diagnose progression or relapse. Serum paraprotein levels and urinary light chain excretion form the basis for the assessment of response, progression and relapse. Paraprotein levels must remain stable for a minimum of 6 weeks to fulfil the criteria for a given category of response. The response criteria for both serum paraprotein and free urinary light chain must be met in patients in whom both are present.

Bone marrow examinations are essential only to confirm complete response or to evaluate response in non-secretory myeloma. It is recognized that there are occasional patients who develop increasing bone marrow plasmacytosis despite a falling paraprotein level (hyposecretory or non-secretory progression), but this is not sufficiently common to justify mandatory marrow examinations in all patients and will become evident on further follow-up. In patients known to have non-secretory myeloma, however, marrow examination is essential to document response. In these patients it was also felt justifiable to require a repeat examination to ensure that the response is not transient and because of the patchy nature of myeloma infiltration. Trephine biopsy of the marrow is not essential, but if biopsy is performed then the marrow plasma cell percentage must independently meet the proposed criteria.

Similarly, skeletal X-rays are not required for the definition of response, but if performed there must be no evidence of progression of bone disease. Follow-up X-rays to confirm continuing response are also not mandatory, although periodic radiological examinations are recommended. If radiological examinations are performed as part of routine follow-up, or for other clinical indications, and show evidence of progressive disease, this will constitute relapse or progression even in the absence of any other criteria. It is strongly recommended therefore that a full skeletal survey be performed immediately prior to conditioning in order to ensure that any apparently new lesions subsequently seen

Table V. EBMT, IBMTR and ABMTR criteria for definition of response, relapse and progression in patients with multiple myeloma treated by high-dose therapy and stem cell transplantation.

Complete response (CR) requires all of the following:
1. Absence of the original monoclonal paraprotein in serum and urine by immunofixation, maintained for a minimum of 6 weeks. The presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.
2. < 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed. If absence of monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow, except in patients with non-secretory myeloma where the marrow examination must be repeated after an interval of at least 6 weeks to confirm CR.
3. No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).
4. Disappearance of soft tissue plasmacytomas.

Patients in whom some, but not all, the criteria for CR are fulfilled are classified as PR, providing the remaining criteria satisfy the requirements for PR. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

Partial response (PR) requires all of the following:
1. ⩾50% reduction in the level of the serum monoclonal paraprotein, maintained for a minimum of 6 weeks.
2. Reduction in 24 h urinary light chain excretion either by ⩾90% or to <200 mg, maintained for a minimum of 6 weeks.
3. For patients with non-secretory myeloma only, ⩾50% reduction in plasma cells in a bone marrow aspirate and on trephine biopy, if biopsy is performed, maintained for a minimum of 6 weeks.
4. ⩾50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
5. No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).

Patients in whom some, but not all, the criteria for PR are fulfilled are classified as MR, provided the remaining criteria satisfy the requirements for MR.

Minimal response (MR) requires all of the following:
1. 25–49% reduction in the level of the serum monoclonal paraprotein maintained for a minimum of 6 weeks.
2. 50–89% reduction in 24 h urinary light chain excretion, which still exceeds 200 mg/24 h, maintained for a minimum of 6 weeks.
3. For patients with non-secretory myeloma only, 25–49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 weeks.
4. 25–49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
5. No increase in the size or number of lytic bone lesions lesions (development of a compression fracture does not exclude response).

MR also includes patients in whom some, but not all, the criteria for PR are fulfilled, provided the remaining criteria satisfy the requirements for MR.

No change (NC)
1. Not meeting the criteria of either minimal response or progressive disease.

Plateau
1. Stable values (within 25% above or below value at the time response is assessed) maintained for at least 3 months.

Time point for assessing response
1. Response to the transplant procedure will be assessed by comparison with results immediately prior to conditioning.
2. If transplant is part of a treatment programme response to the whole treatment programme will be assessed by comparison with the results at the start of the programme.

Relapse from CR requires at least one of the following:
1. Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal immune reconstitution.
2. ⩾5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.
3. Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression).
4. Development of hypercalcaemia (corrected serum calcium >11·5 mg/dl or 2·8 mmol/l) not attributable to any other cause.

Progressive disease (for patients not in CR) requires one or more of the following:
1. >25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/l and confirmed by at least one repeated investigation.
2. >25% increase in the 24 h urinary light chain excretion excretion, which must also be an absolute increase of at least 200 mg/24 h and confirmed by at least one repeated investigation.
3. >25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.
4. Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
5. Development of new bone lesions or soft tissue plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate progression).
6. Development of hypercalcaemia (corrected serum calcium >11·5 mg/dl or 2·8 mmol/l) not attributable to any other cause.

were not in fact present at the time of the transplant. It is also emphasized that the development of a new vertebral compression fracture(s) may result from pre-existing bone damage (lytic lesions or osteoporosis) and does not necessarily preclude response nor constitute relapse. Magnetic resonance imaging (MRI) data have not been included in the definitions of response and progression because experience with this technique is still limited and the significance of different MRI patterns is not yet defined.

Complete response. CR is defined on the basis of negative IF on both serum and urine, maintained for a minimum of 6 weeks. Patients who have no detectable paraprotein on EP without a negative IF result (IF either positive or not performed) will no longer be classified as CR. A bone marrow aspirate containing <5% plasma cells is also required for the confirmation of CR. Although it is recognized that in patients with secretory myeloma it would be very unusual to have disappearance of the paraprotein with persisting marrow infiltration, it was felt important to exclude this possibility. Normal morphology of the plasma cells is not specified because morphological assessment was felt to be too subjective. It is not essential to perform a trephine biopsy, but if a biopsy is performed this must also contain <5% plasma cells. In non-secretory myeloma the marrow must be repeated after a 6-week interval to confirm CR.

The main requirement in the above definition is the absence of detectable paraprotein by IF as well as by EP. Since CR is a prerequisite for potential cure in myeloma, it is logical that CR should require absence of paraprotein by the most sensitive method in routine use. Studies of minimal residual disease at the molecular or cytogenetic level may prove informative in patients without detectable paraprotein (Bird *et al*, 1993; Bjorkstrand *et al*, 1995b) but the results of such studies are not yet clearly interpretable and are not routinely available; in consequence cytogenetic and molecular data cannot at present be included in the criteria for CR.

There are potential problems in the use of IF to determine remission status. The requirement for regular monitoring by IF imposes additional laboratory workload and expense and many laboratories do not routinely perform IF when EP is negative. Therefore it is the treating physician's responsibility specifically to request that IF be performed if EP is negative. A patient is classified as in CR only when a negative IF has been documented on serial samples at a minimum interval of 6 weeks. In patients achieving CR, IF must also be performed at all subsequent evaluations in order to document the time of disease relapse. Most clinicians would repeat IF every 3–4 months post-transplant in these patients.

Whether using IF rather than EP to define CR will prove clinically relevant will depend on the evaluation of outcomes utilizing CR as a prognostic variable. To this end the EBMT and ABMTR/IBMTR follow-up forms will record both EP and IF results and will retrospectively compare outcomes in patients in CR and those who are EP-negative but IF-positive or unknown.

Partial response. A 50% decrease in serum paraprotein is required for PR, as in the CLMTF criteria. However, a 50% decrease in urinary light chain excretion was not considered adequate to define PR. Most free light chains are catabolized by the kidney and the urinary excretion therefore represents only the excess that escapes renal catabolism. Therefore a given degree of tumour reduction has a more marked effect on urinary light chain excretion than on serum paraprotein level. McLaughlin & Alexanian (1982) observed that in a series of patients with both serum paraprotein and free urinary light chains a 50% decrease in serum paraprotein level was always accompanied by a decrease of >90% in urinary light chain excretion. We have therefore used the SWOG criterion of ⩾90% decrease in urinary light chain excretion to define PR. However, in contrast to the SWOG criteria, it is not necessary for urinary light chain excretion to fall below 200 mg/24 h if there has been a ⩾90% reduction. Conversely, urinary light chain excretion may decrease by <90% and still qualify for PR if it falls to < 200 mg/24 h, since it is difficult to accurately measure amounts of light chain excretion <200 mg/24 h, which would be necessary to document a reduction of >90% in patients with an initial light chain excretion of 2 g/24 h or less.

Duration of response required for the definition of CR/PR. To avoid recording a transient response as CR or PR a minimum period of negative results or stable paraprotein level needs to be specified, although this is shorter than that required to fulfil the criteria for plateau (see below). It has been agreed that 6 weeks will be the minimum required period; this enables assessment of response to be made at day 100 post-transplant, which corresponds with the Registries' initial data collection forms. Some patients will reach their maximum response after day 100, and in this case the final response will be recorded on the first annual follow-up form.

Reference point for assessment of response. The post-transplant paraprotein level must be compared with a previous reference point in order to accurately assess response. A simple approach is to use the paraprotein level immediately prior to transplant as the reference point. However, this may lead to the paradox of a patient transplanted as consolidation of a chemotherapy-induced remission being termed a non-responder if the paraprotein level does not decrease by a further 50%. Patients in CR pre-transplant who remain in CR post-transplant would similarly be classified as non-responders. Therefore when transplant has been performed as consolidation of a chemotherapy-induced remission the overall response will be assessed by comparing the pre- and post-transplant paraprotein levels with those immediately prior to the previous chemotherapy programme. Thus a patient may move from PR to CR, or from PR to continuing PR, or from non-responsive disease to PR or CR. Patients in CR pre-transplant who remain in CR post-transplant will be designated as being in continuous complete response. Patients who have not responded to initial chemotherapy nor to subsequent transplant will be classified as having no response. For patients who have not received chemotherapy within the 6 months prior to transplant the response to the transplant alone will be assessed solely by comparing post-transplant paraprotein levels with those immediately prior to

transplant. Such patients will include some patients transplanted with primary refractory disease or in untreated relapse, as well as those who have remained stable for >6 months after completion of chemotherapy.

Plateau. The attainment of plateau is an important prognostic indicator for the outcome of patients treated with conventional chemotherapy. It may therefore be important to determine if patients in plateau before transplant have a better prognosis in relation to transplant outcome. However, this may be difficult to determine, since transplant is now often performed as the final cycle of a planned treatment programme and insufficient time may have elapsed for stable plateau to be reached before the transplant procedure. It may also be important to know whether reaching plateau post-transplant is also of prognostic significance in those patients who do not achieve CR, and whether the establishment of plateau is more important than the degree of partial response achieved. It has been agreed that plateau phase will be defined on the basis of stable paraprotein levels for a minimum of 3 months, as in the current MRC trials. Plateau will require observations to be within 25% of the value when response is assessed, a rise above 25% being one of the criteria for disease progression.

Progression and relapse. We have used the term progression to describe a definite increase in disease activity in patients in partial remission or plateau phase, whereas the term relapse applies to a recurrence of evident disease in patients previously in CR. Progression is usually defined as an increase of >25% in serum paraprotein or urinary light chain excretion, with reference to the levels documented at the time of response. However, the paraprotein level or urinary light chain excretion post-transplant is often at a very low level, and it would not be appropriate to consider a change in serum paraprotein from a level of 6–8 g/l, for example, as definite evidence of progression. We have therefore defined progression as an increase of >25% in paraprotein or urinary light chain excretion (or marrow plasma cell percentage in the marrow), but in addition we have stipulated minimum absolute increases in these parameters. These criteria have been established to reliably identify a definite increase in disease activity; it is recognized that many patients will be asymptomatic and may not necessarily require treatment at this stage. Progression may also be defined on the basis of increasing marrow infiltration or skeletal disease, but, as noted, it is not essential to repeat these investigations unless there is a clinical indication to do so.

Relapse is defined as reappearance of detectable paraprotein or other manifestation of disease in patients previously in CR. Relapse is a more appropriate term than progression in these patients as there was no evidence of disease when they were in CR. Since a negative IF is the criterion for the definition of CR, then recurrence of positivity on IF (confirmed on at least one repeat sample) constitutes relapse, whether or not the paraprotein becomes detectable again by EP. This is a very stringent definition of relapse, especially since recurrence of IF positivity is not always immediately followed by an increase in paraprotein level, and such patients may remain asymptomatic for a prolonged period (Bjorkstrand *et al*, 1995b). Furthermore, the IF result may only be intermittently positive in some patients, a situation analogous to that of patients with CML in whom PCR for bcr-abl mRNA may be intermittently, but not consistently, positive (Cross *et al*, 1993). In other words, recurrence of IF positivity does not necessarily lead, at least in the short-term, to clinical disease progression. This sensitive definition of relapse in CR patients could, at least theoretically, lead to a paradoxically shorter remission duration in CR patients than those who do not enter CR. It will therefore be important to record the time when treatment was instituted after progression or relapse, in order to evaluate whether the proposed criteria are predictive of subsequent disease evolution.

Conclusion

These proposed criteria for response, progression and relapse have been developed with the aim of improving the evaluation of new therapeutic approaches in multiple myeloma, specifically high-dose therapy with haemopoietic stem cell rescue. It is recognized that re-assessment and subsequent modification of these criteria, again using an international forum, may be necessary in the future as they are implemented in clinical practice and as new technologies evolve. For the present, these consensus criteria for complete remission, relapse and progression should provide a useful framework for clinical trials and registry analysis.

ACKNOWLEDGMENTS

J. Bladé was supported by a grant from the Fondo de Investigationes Sanitarias de la Seguridad Social FIS 96/0397 and Gosta Gahrton by the Cancer Society of Stockholm.

*On behalf of the Myeloma Subcommittee of the EBMT (European Group for Blood and Marrow Transplant) Chronic Leukaemia Working Party and the Myeloma Working Committee of the IBMTR (International Bone Marrow Transplant Registry) and ABMTR (Autologous Blood and Marrow Transplant Registry)**

Joan Bladé
Diana Samson
Donna Reece
Jane Apperley
Bo Björkstrand
Gösta Gahrton
Morie Gertz
Sergio Giralt
Sundar Jagannath
David Vesole

*Authors' affiliations: Joan Blade: Department of Haematology, Hospital Clinic, IDIBAPS (Institut d'Investigations Biomediques August Pi y Sunyer, Barcelona, Spain. Diana Samson, Jane Apperley: Department of Haematology, Imperial College School of Medicine, London, U.K. Donna Reece: Markey Cancer Center, University of Kentucky, U.S.A. Bo Bjorkstrand, Gosta Gahrton: Departments of Medicine and Haematology, Karolinska Institute, Huddinge University Hospital, Huddinge, Sweden. Morie Gertz: Department of Hematology, The Mayo Clinic, Rochester, Minnesota, U.S.A. Sergio Giralt: M. D. Anderson Cancer Center, University of Texas, U.S.A. Sundar Jagganath: St Vincent's Comprehensive Cancer Center and New York Medical College, U.S.A. David Vesole: Department of Medicine, Medical College of Wisconsin, U.S.A.

REFERENCES

Alexanian, R., Bonnet, J., Gehan, E., Haut, A., Hewlett, J., Lane, M., Monto, R. & Wilson, H. (1972) Combination chemotherapy for multiple myeloma. *Cancer*, **30,** 382–389.

Anderson, K.C., Andersen, J., Soiffer, R., Freedman, A.S., Rabinowe, S.N., Robertson, M.J., Spector, N., Blake, K., Murray, C., Freeman, A., Coral, F., Marcus, K.C., Mauch, P., Nadler, N.M. & Ritz, J. (1993) Monoclonal antibody-purged bone marrow transplantation therapy for multiple myeloma. *Blood*, **82,** 2568–2576.

Attal, M., Harousseau, J.L., Stoppa, A.-M., Sotto, J.-J., Fuzibet, J.-G., Rossi, J.P.F., Casassus, P., Maisonneuve, H., Facon, T., Ifrah, N., Payen, C. & Bataille, R., for the Intergroup Francais du Myelome (1996) A prospective randomised trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *New England Journal of Medicine*, **335,** 91–97.

Baldini, L., Radaelli, F., Chiorboli, O., Fumagalli, S., Cro, L., Segala, M., Cesana, B.M., Polli, E.E. & Maiolo, A.T. (1991) No correlation between response and survival in patients with multiple myeloma treated with vincristine, melphalan, cyclophosphamide and prednisone. *Cancer*, **68,** 62–67.

Ballester, O.F., Moscinski, L.C., Fields, K.K., Hiemenz, J.W., Zorsky, P.E., Goldstein, S.C., Saba, H.I., Spiers, A.S.D., Kronisj, L., Sullivan, P. & Elfenbein, G.J. (1997) Dexamethasone, cyclophosphamide, idarubicin and etoposide (DC-IE): a novel, intensive induction chemotherapy regimen for patients with high-risk multiple myeloma. *British Journal of Haematology*, **96,** 746–748.

Barlogie, B., Jagannath, S., Vesole, D.H., Naucke, S., Cheson, B., Mattox, S., Bracy, D., Salmon, S., Jacobson, J., Crowley, J. & Tricot, G. (1997) Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. *Blood*, **89,** 789–793.

Belch, A., Shelley, W., Bergsagel, D., Wilson, K., Klimo, P., White, D. & Willan, Q. (1988) A randomised trial of maintenance versus no maintenance melphalan and prednisone therapy in responding multiple myeloma patients. *British Journal of Cancer*, **57,** 94–99.

Bergsagel, D.E. (1975) Plasma cell myeloma: prognostic factors and criteria of response to therapy. *Cancer Therapy: Prognostic Factors and Criteria of Response* (ed. by M. J. Staquet), pp. 73–87. Raven Press, New York.

Bergsagel, D.E. (1998) Chemotherapy of myeloma. *Multiple Myeloma: Biology and Management* (ed. by J. S. Malpas, D. E. Bergsagel, R. A. Kyle and K. C. Anderson), pp. 269–302. Oxford University Press.

Bergsagel, D.E., Bailey, A.J., Langley, G.R., Macdonald, R.N., White, D.F. & Millar, A.B. (1979) The chemotherapy of myeloma and the incidence of plasma cell leukemia. *New England Journal of Medicine*, **301,** 743–748.

Bird, J.M., Russell, N.H. & Samson, D. (1993) Minimal residual disease after bone marrow transplantation for multiple myeloma: evidence of cure in long-term survivors. *Bone Marrow Transplantation*, **12,** 651–654.

Bjorkstrand, B., Ljungman, P., Bird, J.M., Samson, D., Brandt, L., Alegre, A., Auzanneau, G., Blade, J., Brunet, S., Carlson, K., Cavo, M., Ferrant, A., Gravett, P., de Laurenzi, A., Prentice, H.G., Proctor, S., Remes, K., Troussard, X., Verdonck, L.F., Williams, C. & Gahrton, G. (1995a) Autologous stem cell transplantation in multiple myeloma: results of the European Group for Bone Marrow Transplantation. *Stem Cells, Daytona*, **13,** (Suppl. 2), 140–146.

Bjorkstrand, B., Ljungman, P., Bird, J.M., Samson, D. & Gahrton, G. (1995b) Double high-dose therapy with autologous stem cell transplantation can induce molecular remissions in multiple myeloma. *Bone Marrow Transplantation*, **15,** 367–371.

Blade, J., Lopez-Guillermo, A., Bosch, F., Cervantes, F., Montserrat, E. & Rozman, C. (1994) Impact of response to treatment on survival in multiple myeloma: results in a series of 243 patients. *British Journal of Haematology*, **88,** 117–121.

Blade, J., Rozman, C., Montserrat, E., Cervantes, F., Feliu, E., Granena, A., Marin, P. & Nomdedeu, B. (1986) Treatment of alkylating agent resistant multiple myeloma with vincristine, BCNU, doxorubicin and prednisone (VBAP). *European Journal of Cancer and Clinical Oncology*, **22,** 1193–1197.

Chronic Leukemia and Myeloma Task Force of the National Cancer Institute (1973) Proposed guidelines for protocol studies. II. Plasma cell myeloma. *Cancer Chemotherapy Reports*, **4,** 145–158.

Chronic Leukemia and Myeloma Task Force (1968) Proposed guidelines for protocol studies. II. Plasma cell myeloma. *Cancer Chemotherapy Reports*, **1,** 17.

Cross, N.C.P., Lin, F., Chase, A., Bungey, J., Hughes, T.P. & Goldman, J.M. (1993) Competitive polymerase chain reaction to estimate the number of bcr-abl transcripts in chronic myeloid leukemia after bone marrow transplantation. *Blood*, **82,** 1929–1936.

Dimopoulos, M.A., Alexanian, R., Przepiorka, D., Hester, J., Andersson, B., Giralt, S., Mehta, R., van Biesen, K., Delasalle, K.B., Reading, C., Deisseroth, A.B. & Champlin, R.E. (1993) Thiotepa, busulfan and cyclophosphamide: a new preparative regimen for autologous marrow or blood stem cell transplantation in high-risk multiple myeloma. *Blood*, **82,** 2324–2328.

Durie, B.G.M., Russell, D.H. & Salmon, S.E. (1980) Reappraisal of plateau phase in myeloma. *Lancet*, **ii,** 65–68.

Gahrton, G., Tura, S., Ljungman, P., Belanger, B., Brandt, L., Cavo, M., Facon, T., Granena, A., Gore, M., Gratwohl, A., Lowenberg, B., Nikoskelainen, J., Reiffers, J., Samson, D., Verdonck, L. & Volin, L. (1991) Allogeneic bone marrow transplantation in multiple myeloma using HLA-matched sibling donors. *New England Journal of Medicine*, **325,** 1267–1272.

Gahrton, G., Tura, S., Ljungman, P., Blade, J., Brandt, L., Cavo, M., Facon, T., Gratwohl, A., Hagenbeek, A., Jacobs, P., de Laurenzi, A., Van Lint, M., Michallet, M., Nikoskelainen, J., Reiffers, J., Samson, D., Verdonck, L.F., de Witte, T. & Volin, L. (1995) Prognostic factors in allogeneic transplantation in multiple myeloma. *Journal of Clinical Oncology*, **13,** 1312–1322.

Gore, M.E., Selby, P.J., Viner, C., Clark, P.I., Meldrum, M., Millar, B., Bell, J., Maitland, J.A., Milan, S., Judson, I.R., Zuiable, A., Tillyer, C., Slevin, M., Malpas, J.S. & McElwain, T.J. (1989) Intensive treatment of multiple myeloma and criteria for complete remission. *Lancet*, **ii,** 879–881.

Holland, J.F., Hosley, H., Scharlau, C., Carbone, P.P., Frei, E., Brindley, C.O., Hall, T.C., Shmider, B.I., Gold, G.L., Lasagna, L., Owens, A.H., Jr & Miller, S.P. (1966) A controlled trial of urethane treatment in multiple myeloma. *Blood*, **27,** 328–342.

Joshua, D.E., Penny, R., Matthews, J.P., Laidlaw, C.R., Gibson, J., Bradstock, K., Wolf, M. & Goldstein, D. for the Australian Leukaemia Study Group (1997) Australian Leukaemia Study Group Myeloma II: a randomized trial of intensive combination chemotherapy with or without interferon in patients with myeloma. *British Journal of Haematology*, **97,** 38–45.

Joshua, D.E., Snowdon, L., Gibson, H., Iland, H., Brown, R., Warburton, P., Kulkarni, A., Vincent, P., Young, G., Gatenby, P., Bassten, A. & Kronenburg, H. (1991) Multiple myeloma: plateau phase revisited. *Hematology Reviews*, **5,** 59–66.

Korst, D.R., Clifford, G.O., Fowler, W.M., Louis, J., Will, J. & Wilson, H.E. (1964) Multiple myeloma. II. Analysis of cyclophosphamide therapy In 165 patients. *Journal of the American Medical Association*, **189,** 156–161.

Kyle, R.A. & Greipp, P.R. (1980) Smoldering multiple myeloma. *New England Journal of Medicine*, **302,** 1347–1349.

MacLennan, I.C.M., Chapman, C., Dunn, J. & Kelly, K. (1992) Combined chemotherapy with ABCM versus melphalan for treatment of myelomatosis. *Lancet*, **339,** 200–205.

MacLennan, I.C.M., Drayson, M. & Dunn, J. (1994) Multiple myeloma. *British Medical Journal*, **308,** 1033–1036.

Malpas, J.S. (1998) Clinical presentation and diagnosis. *Myeloma: Biology and Management* (ed. by J. S. Malpas, D. E. Bergsagel, R. A. Kyle and K. C. Anderson), pp. 187–209. Oxford University Press.

Marmont, F., Levis, A., Falda, M. & Resegotti, L. (1991) Lack of correlation between objective response and death rate in multiple myeloma patients treated with oral melphalan and prednisone. *Annals of Oncology*, **2,** 191–195.

McLaughlin, P. & Alexanian, R. (1982) Myeloma protein kinetics following chemotherapy. *Blood*, **60,** 851–855.

Oivanen, T.M., for the Finnish Leukaemia Group (1996) Plateau phase in myeloma: an analysis of long-term follow-up of 432 patients. *British Journal of Haematology*, **92,** 834–839.

Palmer, M., Belch, A., Hanson, J. & Brox, L. (1989) Reassessment of the relationship between M-protein decrement and survival in multiple myeloma. *British Journal of Cancer*, **59,** 110–112.

Samson, D., Gaminara, E., Newland, A., van de Pette, J., Kearney, J., McCarthy, D., Joyner, M., Aston, L., Mitchell, T., Hamon, M., Barrett, A.J. & Evans, M. (1989) Infusion of vincristine and doxorubicin with oral dexamethasone as first-line therapy for multiple myeloma. *Lancet*, **ii,** 882–885.

Schiller, G., Vescio, R., Freytes, C., Spitzer, G., Lee, M., Wu, C.H., Cao, J., Lee, J.C., Lichtenstein, A., Lill, M., Berenson, R. & Berenson, J. (1998) Autologous CD34-selected blood progenitor cell transplants for patients with advanced multiple myeloma. *Bone Marrow Transplantation*, **21,** 141–145.

Selby, P.J., MacElwain, T.J., Nandi, A.C., Perren, J.J., Powles, R.L., Tillyer, C.R., Osborne, R.J., Slevin, M.L. & Malpas, J.S. (1987) Multiple myeloma treated with high-dose intravenous melphalan. *British Journal of Haematology*, **66,** 55–62.

Vesole, D.H., Tricot, G., Jagannath, S., Desikan, K.R., Siegel, D., Bracy, D., Miller, L., Cheson, B., Crowley, J. & Barlogie, B. (1996) Autotransplants in myeloma: what have we learned? *Blood*, **88,** 838–847.

Keywords: multiple myeloma, high-dose therapy, transplant, response, progression.