Myeloma during a decade: Clinical experience in a single centre


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Summary

One hundred and fifty-six patients with multiple myeloma were treated over a period of 12 years at St. Bartholomew's Hospital. The progress of the disease was affected in 96/156 patients (61%). Response was defined as achieving a plateau of M component. A partial or complete response was seen in 68/120 patients treated conventionally (56.5%), and in 28/36 patients treated with high-dose therapy (77.7%). The median survival of the group as a whole was 20 months, with a 2-year survival of just over 40%. In the 36 patients treated with high-dose therapy, median survival was 6 years, and in a small group who have had maintenance Interferon therapy, the median has not yet been reached. In a univariate analysis, age, intensity of therapy, haemoglobin and creatinine levels were significant, but multivariate analysis showed that only age and intensity of therapy were independent predictors for survival. The outlook for relapsed patients who showed progression of disease remains poor, but palliation was best achieved by steroid and Interferon in combination. Patients who achieve complete responses and are maintained on Interferon appear to be doing better both in terms of freedom from symptoms and in survival, and methods to enable an elderly population to tolerate this form of therapy need to be explored.

Key words: intensive chemotherapy, maintenance and relapse therapy, myeloma, survival

Introduction

The last decade has seen major changes in the principles underlying treatment in myeloma. The mainstay of therapy has always been Melphalan and Prednisolone. A large number of multidrug combinations have been employed, but a review of randomised trials came to the overall conclusion that these had added little to response rate or survival in this disease [1]. The disease continues to be regarded as incurable. Following the introduction of high-dose Melphalan [2] a considerable improvement in the response rate occurred, and it was possible to define for the first time a complete response (CR) as denoting absence of all demonstrable disease [3]. These improved responses were not translated into cures, and patients continued to relapse at about 18–24 months following high-dose therapy, although there are some long-term survivors [4, 5]. This Unit, in the second half of the eighties, adopted a policy of using cytoreduction with Vincristine, Adriamycin infusion, and Methyl Prednisolone (VAMP) [6], followed by high-dose Melphalan and, later, maintenance with Interferon, as part of a randomised trial [7]. A number of regimens for relapsed or refractory disease were also explored, and these are discussed in the overall experience of the unit from 1980 to 1992. Our results are reviewed in the context of the experience of others during the same period.

Methods

Patient population

One hundred and fifty-six consecutive patients with myeloma presenting to St. Bartholomew's Hospital from 1980 to 1992 form the subject of this analysis. Diagnosis was confirmed in all patients on the basis of two or more of the following features: a biopsy showing a mass of plasma cells; the presence of monoclonal protein in the serum; monoclonal light chain in the urine; bone marrow infiltration of >30% with abnormal plasma cells; lytic lesions on skeletal survey. Patients with monoclonal gamopathy of undetermined significance (MGUS), indolent or smouldering myeloma, multiple plasmacytomas, or plasma cell leukaemia were excluded. Patient characteristics are given in Table 1. All patients were staged according to Durie and Salmon [8], with the exception of eight patients who either declined further investigation or were too ill.

Treatment

Treatment with chemotherapy was chosen on the basis of stage, age and renal function. The treatment programmes were modified during the decade. At the beginning of the decade (Table 2), all patients with adequate renal function who were not pancytopenic were treated with Melphalan and Prednisolone, or Melphalan alone. In those with persistent impairment of renal function, Cyclophosphamide or a non-Melphalan-containing regimen was used. These treatments were given until a maximum response or a 'plateau' of the 'M' component in the serum was achieved. 'Plateau' is defined as the relief of symptoms due to myeloma for a period of more than 3 months, absence of dependence on transfusion of blood products, and either no paraprotein in the blood or urine, or (what is more usual) a stable level of paraprotein over a similar period of 3 months.
Treatment with VAMP was used to reduce the bone marrow plasma manipulation to remove plasma cells. Both these programmes were cell infiltration to <30%, but the marrow was not subjected to any of Melphalan, with ABMT.

In the mid-eighties, treatment was intensive treatment with Melphalan 140 mg/m\(^2\) without autologous bone marrow support (ABMT). In the mid-eighties, treatment was intensified with the use of up to 220 mg/m\(^2\) of Melphalan, with ABMT. Treatment with VAMP was used to reduce the bone marrow plasma cell infiltration to <30%, but the marrow was not subjected to any manipulation to remove plasma cells. Both these programmes were carried out in conjunction with the Royal Marsden Hospital, and are the subject of separate reports [4, 5]. Patients with renal impairment, with an EDTA clearance of <30%, were treated with high-dose Busulphan.

From 1989, patients under the age of 65 who were previously untreated were offered cyto-reduction with C-VAMP or VAMP; then Melphalan 220 mg/m\(^2\) supported by ABMT, and on recovery of the blood count, were started on maintenance or continuation therapy using Interferon-\(\alpha\)2\(\beta\) 3 megaunits/m\(^2\) 3 times a week subcutaneously. Other patients did not receive Interferon maintenance, and are the subject of a separate report of a joint study with the Royal Marsden Hospital [7]. A few patients with severe persistent renal failure were given high-dose therapy with Busulphan 4 mg/kg 4 times a day for 4 days supported by ABMT.

The criteria for inclusion in the high-dose therapy programme were: no patient should have a past history of ischaemic heart disease; cardiac function should show a normal left ventricular ejection fraction; there should be no evidence of recurrent chest infections such as pneumonia, acute or chronic bronchitis; all patients should have normal lung function. Contraindications were other haematological conditions (e.g. polycythaemia rubra vera) or other known complications of myeloma that make treatment hazardous (e.g. amyloidosis). Chronic renal failure was not a contraindication, and on occasions physically fit patients over the age of 65 were given high-dose therapy, but a maximum age of 70 was strictly observed.

All other patients continued to be treated with either Melphalan or Prednisolone, Melphalan, or Cyclophosphamide. This group largely consisted of patients over the age of 65, and those who were excluded from intensive therapy.

Patients who relapsed and progressed following conventional high-dose therapy were considered for either further alkylating agents, for VAMP, Etoposide and Vincristine, or (more recently) high-dose Methyl Prednisolone and Interferon-\(\alpha\)2\(\beta\).

Radiotherapy was used with palliative intent to treat bone pain or to control neurological complications such as incipient cord compression, with the exception of one patient, who wished to be treated with hemibody irradiation.

### Statistical methods

Survival time was defined as the time from diagnosis to death from any cause. The cut-off date for follow-up was June 1993. Graphs of survival were drawn using the Kaplan-Meier method and comparisons of survival times between different levels of a variable were made using the log rank test [10]. The variables found to be significant at $p<0.1$ were put into a stepwise Cox regression model to find out which were independently prognostic [11].
Results

Conventional therapy

The survival for the whole group of 156 patients is shown in Fig. 1. With a median follow-up of 5.3 years, median survival was 20 months, and the two-year survival was just over 40%. There is an inexorable attrition with no patient surviving beyond 10 years.

One hundred and twenty patients were treated with conventional therapy as defined in Table 2. As seen in other series, just over 56% showed some response, the majority being partial responders. Another 18% proved refractory to all therapy (Table 3). The median survival of 120 patients is shown in Fig. 2. There was no difference in survival between the groups treated with Melphalan and Prednisolone, Melphalan or Cyclophosphamide.

Table 3. Response to chemotherapy in 156 patients.

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>High-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Complete response</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>Partial response</td>
<td>27</td>
<td>22.5</td>
</tr>
<tr>
<td>Stable disease</td>
<td>39</td>
<td>32.5</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>22</td>
<td>18.3</td>
</tr>
<tr>
<td>Early death/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>not assessable</td>
<td>30</td>
<td>25.0</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>100</td>
</tr>
</tbody>
</table>

High-dose therapy

Thirty-six patients were treated with high-dose therapy, of whom 11 went on to receive Interferon maintenance (discussed separately). Table 4 gives the type of high-dose therapy used. All patients who were eligible for high-dose therapy and who received VAMP treatment went on to be treated by high-dose Melphalan or Busulphan supported by ABMT.

Table 4. High-dose therapy.

<table>
<thead>
<tr>
<th>High-dose treatment</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan 140 mg/m² without ABMT</td>
<td>14</td>
</tr>
<tr>
<td>Bulsulphan 4 mg/kg q.d.s. × 4 with ABMT</td>
<td>4*</td>
</tr>
<tr>
<td>Melphalan 220 mg/m² with ABMT</td>
<td>17b</td>
</tr>
<tr>
<td>Methyl prednisolone 1 g/5 days</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3 shows the markedly increased numbers of patients achieving CR in the high-dose therapy group – 55% at the end of all chemotherapy – and over three-quarters of the patients treated showed either a complete or partial response. One patient died with an infective complication during transplantation, and a further six died at home, either from complications of disease, or possibly from infection (although post mortem examination was not obtained).

It must be emphasised that this experience with high-dose therapy was not randomised against conventional therapy. Randomised studies addressing this question are only just beginning. Any comparisons made will attract the usual criticisms which apply to all historical comparisons, such as selection of patients, improvements that have occurred in supportive care during the period of study, the immaturity of the more recent therapeutic results. A further difficulty is that prognostic variables which have been recently established (e.g. β₂-microglobulin, IL-6 and C-reactive protein (CRP)) are either not available on earlier patients, or numbers are so small as to make comparison impossible.

In reviewing the selection of eligible patients from 1989 to 1992, there were a total of 21 patients under the age of 65 with myeloma who had stage IIIA or B disease. Twelve were treated with high-dose therapy during that period. Nine were excluded on the basis of...
a variety of medical complications including atrial fibrillation, ischaemic heart disease, recurrent pulmonary infections, amyloidosis, polycythaemia rubra vera, myelodysplasia etc. No eligible patient refused the offered high-dose therapy for personal reasons.

Patient survival following high-dose therapy for stage III disease is shown in Fig. 3. This shows a median survival of just under 6 years compared with the 20 months for conventional therapy. It is evident that the remissions obtained with high-dose therapy are not durable, and late relapses are still occurring. So far there appear to be no long-term survivors. However, median survival has trebled, and the quality of life for these patients is excellent.

When the whole group of 156 patients is subject to a univariate analysis of a number of clinical and biochemical features, treatment modality stood out as one of the most significant factors, together with age, creatinine and haemoglobin (Table 5).

When the four variables were put in a stepwise Cox regression model, age and treatment were independently predictive. For a 10-year difference in age, the relative risk of death was 1.3 (95% confidence interval (1.0, 1.6), p<0.05) and the relative risk of death for conventional treatment versus high dose was 2.6 (95% confidence interval (1.4, 4.7), p<0.002).

**High-dose therapy and Interferon maintenance**

Eleven patients were treated with VAMP or C-VAMP followed by either high-dose Melphalan or Busulphan supported by ABMT.

All patients were aged 65 or under, and 9/11 were at an advanced stage of disease, with 3 in renal failure. One patient has relapsed and has started to excrete large quantities of light chain (13.2 g/24 hr) some 15 months after achieving remission. He is currently without symptoms.

![Overall survival myeloma high dose therapy patients](image)

**Table 5. Prognostic factors – univariate analysis.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>( \chi^2 )</th>
<th>( p )</th>
<th>Degree of freedom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I vs. II vs. III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 1.2</td>
<td>1.7</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>4.20</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>4.13</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.84</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>0.99</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>0.87</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>'M' band reduction</td>
<td>1.3</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>High dose vs. conventional chemotherapy</td>
<td>19.72</td>
<td>&lt;0.01</td>
<td>1</td>
</tr>
</tbody>
</table>

NS = not significant.

**Treatment of patients with relapsed and progressing disease**

Once patients relapse with myeloma it is notoriously difficult to regain control of the disease. This has been the experience using various chemotherapeutic programmes. In this population, only 5/42 (11%) second responses were seen in patients previously treated with Melphalan and Prednisolone, when Melphalan was given for relapse. Five heavily treated patients in progressive relapse were treated with VAMP, but only one achieved stable disease. Experimental programmes using Vincristine 2 mg i.v. and Etoposide 200 mg daily for 4 days orally were used in 15 patients [12]. A minimal response was seen in two patients, which were transient.

Much more successful in terms of symptom relief and improved performance status was the use of high-dose Methyl Prednisolone 1 g daily for 5 days with Interferon-a2B 3 x 10^6 units/m^2 three times weekly. Of 11 patients who had relapsed and showed progression, four responded, and a further two achieved a minimal response and stabilisation of disease. Every patient became symptom-free [13].

**Discussion**

This report reflects the changing approach to treatment of multiple myeloma (MM) at St. Bartholomew's Hospital over the last decade, and suggests that selected patients have benefited from the more recent series of intensive treatments supported by autologous bone marrow transplantation. Increasing numbers of complete responses have been translated into an increased duration of good quality survival, and this has been very apparent in those who were randomised to receive Interferon-a2B as maintenance in the co-operative trial with the Royal Marsden Hospital [7]. The patients were, of course, highly selected, and a definitive answer
must come from the prospective randomized trials now starting in the United States, France and the United Kingdom.

Over 2000 deaths occur annually from MM in England and Wales [14]. With an increasingly aged population, MM accounts for an increasing proportion of haematological malignancy in the elderly. In this study, the patients were very similar in type and Salmon & Durie stage to those reported by Kyle [15, 17] and the Italian co-operative group [16] (Table 6). These crude comparisons show that our patient population was very similar to that seen in the United States and Europe, with a median age of 62 and the usual distribution of paraprotein type.

At the beginning of the decade, the standard therapy was Melphalan and Prednisolone, which had been established for many years [18]. Melphalan and Prednisolone produced responses in 40% of patients, with a reduction of 75% in paraprotein levels, a reduction of 95% in the excretion of Bence Jones protein in the urine, and a reduction to less than 5% plasma cell infiltration of the bone marrow. Median duration of remission was two years, and median survival was three years. Fewer than 10% of patients, however, survived for more than 10 years. There appeared to be no subgroup who were cured. The 120 patients treated at St. Bartholomew's Hospital with Melphalan and Prednisolone show these features, with a response rate of just under 50% and a median survival of 20 months, no patient having lived for more than 10 years.

These disappointing results have led to a constant review of treatment options. Although it has not been the Unit's policy to employ multidrug regimens on their own, it is necessary to discuss the rationale for using these, as a large number of trials have been conducted since the early '70s, employing agents in addition to Melphalan and Prednisolone. There has been no question as to the activity of Melphalan and Cyclophosphamide, and later Carmustine (BCNU), nor the benefit produced by steroids. Quite early on it was shown that cycle-specific agents such as Methotrexate, Mercaptopurine, Thioguanine, Fluorouracil and Cytosine arabinoside were ineffective [19–21].

Although the vinca alkaloids have been extensively used in combinations, Vincristine (for example) has relatively little activity when used alone in MM. In the single phase II trial of Vincristine [22], only a minimal response occurred in 2/21 refractory patients. An MRC trial in which Vincristine was added in a randomised fashion found no improvement in response or survival in patients receiving the Vincristine/Melphalan/Prednisolone combination [23].

Doxorubicin has also had a poor record as a single agent, with two studies showing a response rate of less than 10%; even when combined with Bleomycin there was no improvement [24–26]. Even so, it has been added to widely-used regimens such as VAD and VAMP. It has been difficult to dissect out the contribution to high-dose steroids to these combinations, but

<table>
<thead>
<tr>
<th>Protein</th>
<th>SBH (%)</th>
<th>MAYO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>57</td>
<td>50</td>
</tr>
<tr>
<td>IgA</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>LCO</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>IgD</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Biclonal</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Non-secretor</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

LCO = light chain only.

Alexanian [27] has estimated that Dexamethasone contributed most of the activity of the Vincristine/Abramycin/Dexamethasone (VAD) combination.

It was evident quite early on that cross-resistance was not a feature of the alkylating agents, and that these could be combined with steroids. In a randomised study the National Cancer Institute of Canada could show no benefit from administering the alkylating agents Melphalan, Cyclophosphamide and Carmustine (BCNU) concurrently rather than sequentially, using a control group consisting of patients treated with Melphalan alone [28].

Despite the poor results with single agents other than alkylating agents, outlined above, many studies have been undertaken comparing these drugs with Melphalan and Prednisolone. It was no surprise that in an overview of 18 published trials [1] giving the cumulative responses in nearly 4000 patients, no advantage could be discerned for combinations over Melphalan and Prednisolone in terms of survival. A study by Peest et al. [29] showed an advantage for Melphalan and Prednisolone compared to VCMP, and more recently an MRC trial of ABCM against Melphalan alone suggested an advantage for ABCM [30]. The reason for these two opposite and anomalous results is unclear. Nevertheless, the advantage in survival is small, and the conclusion must be that with the drugs currently available further exploration of multidrug therapy in conventional doses is unlikely to prove helpful.

In 1983, McElwain and Powles [2] reported the response of MM patients to high-dose Melphalan at a dose of 140 mg/m². Since a dose-response relationship was evident for Melphalan, and as the limiting toxicity was bone marrow suppression, our unit found this approach more attractive, and a series of joint studies with the Royal Marsden Hospital had begun in 1982. The dose of Melphalan was elevated from 140 to 200 mg/m², supported with ABMT for the latter patients. Although biochemical relapse with return of serum paraprotein was seen after 18–24 months in a number of patients, long-term overall survival has been remarkable. Sixty-three patients treated with 140 mg/m² from 1982–1985 have shown a survival of 35% at nine years [4]. This is two or three times the long-term survival recorded for conventional multidrug chemotherapy.

The next step was to attempt cytoreduction safely without allowing resistance to Melphalan to develop. In
53 patients treated with VAMP or C-VAMP therapy followed by 200 mg/m² of Melphalan supported by ABMT, the median survival has not yet been reached at 64 months, with the possibility of survival being 63% [5]. There was only one treatment-related death, and the quality of life following completion of consolidation is excellent. For the first time it is evident that long-term survival of high quality may be possible, and the importance of achieving complete response, in which all symptoms of myeloma are abolished and paraprotein, light chain and plasma cell infiltration eliminated, now appears to correlate with survival.

Subsequent studies by Jagannath [31] explored the use of moderate-dose Melphalan 140 mg/m² or Thiotepa combined with total body irradiation in a mixed population of primary resistant or relapsed MM patients. They showed that patients with resistant relapses did badly, but responsive patients who were at high risk did well with a 4-year projected survival of over 70%, a result much superior to their historical controls. In this elderly population the use of total body irradiation would appear to provide a considerable additional hazard. It was their conclusion that escalating the dose of Melphalan was the best option, and they are now exploring the use of sequential treatments with high-dose Melphalan.

All the patients in the St. Bartholomew's study were previously untreated or had had cyto reduction with VAMP or C-VAMP. Only two patients (1.5%) of the 120 receiving conventional chemotherapy achieved a CR, compared with 20/36 (55.5%) who received myeloablative therapy (Table 3). In these patients the good response was translated into improved survival (Fig. 3), and even when no further maintenance therapy was given, median survival of 6 years has been achieved.

It is still probably that all of these patients will eventually relapse, either because of the survival of a malignant clone (which may still happen even with more precise definition of CR proposed by Gore et al. [3]), or because viable malignant plasma cells are rein fused with autologous marrow. In view of this, the use of a relatively non-toxic form of suppressive therapy is attractive, and has been the reason for the exploration of the use of Interferon (IFN). Three randomised studies have been completed and published, where IFN has been shown to prolong either remission duration or both remission and survival, when patients treated with IFN are compared with controls [7, 32, 33]. In the latest study [33] of 85 Canadian patients with MM treated with 2 megaunits IFN/m² three times a week, compared with 92 controls, overall median survival was 39 months in the IFN-treated group compared to 34 months for the controls — a highly significant improvement (p = 0.007).

Eleven of the St. Bartholomew's patients received Interferon-α2β in a dose of three megaunits/m² subcutaneously three times a week, in the course of a randomised trial [7]. Ten achieved CR before being randomised to IFN. Six achieved CR after VAMP or C-VAMP, so that the high-dose therapy could be considered as consolidation in these patients. Two patients, both with light chain MM, were unable to tolerate IFN for long, and in one of these a biochemical relapse, with light chain reappearing in the urine, has occurred. All these patients are alive and asymptomatic up to 3½ years.

Proponents of high-dose therapy with maintenance are faced with the fact that in this generally elderly population secondary pathology is often a problem. As our results show, 9/21 patients who were eligible on the basis of age and stage had a variety of other medical problems which proved to be contra-indicative for high-dose therapy. No patient in this group refused transplantation. Even so, 43% were ineligible. Since 65 is close to the median age, this means that only about a quarter of patients who present would be eligible for high-dose therapy. There is now a need to explore the myeloablative regimen, and investigate the role of peripheral blood stem cell support in order to make this procedure more acceptable to elderly patients.

**Relapsed and refractory patients**

Management of relapsed or refractory MM remains a challenge since approximately half the patients presenting with the disease will not respond to conventional therapy, and most patients will eventually relapse. Buzaid and Durie [34], reviewing programmes for this situation, concluded that some form of high-dose steroid therapy was best for truly resistant patients, and that Vindristine, Adriamycin and Dexamethasone (VAD) was one of the most effective salvage therapies. Multidrug regimens containing alkylating agents have been singularly unsuccessful, with unpleasant side-effects, and even when success has been claimed for such regimens as Etoposide, Doxorubicin, Cyclophosphamide and Beta-methasone [35], the authors concluded that the steroid was the single most important component. When used without high-dose steroid, our regimen of Vincristine and Etoposide was singularly unsatisfactory, with only two minor responses in 15 patients [12].

Interferon has been reported to be an effective agent in refractory or resistant MM, and with an overall response rate of 20%, is at the top of the list of effective agents [36]. Its use with Dexamethasone has been reported as successful in relapsed patients [37, 38], but other studies in previously untreated patients have suggested that Dexamethasone alone is as successful as Dexamethasone and IFN [39]. Ganjoo et al. [13], in a study of refractory and relapsed patients at St. Bartholomew's Hospital, found that a combination of Methylprednisolone and Interferon was well tolerated and provided major benefit in terms of relief of pain and improvement of performance status, which in a palliative care setting was highly satisfactory. Unlike
the experience with Etoposide and Vincristine, a worthwhile duration of response was seen, a median survival of six months being achieved in a very poor prognostic group.

Second malignancies

The increased incidence of acute leukaemia in myeloma is well established, with an actuarial risk of developing the disease of 14% at 60 months or 25% at 10 years [40]. These patients are at an age when solid tumours are common, and in this series two patients have developed acute myelogenous leukaemia, one patient a carcinoma of the cervix, and another a carcinoma of the bronchus. These patients had both been treated with alkylating agents. Until June 1993, no patient treated on the high-dose therapy programme developed a second malignancy, although the numbers and the time elapsed were small, and it is probable that this group will also be susceptible.

Conclusion

It would seem, from the experience of this unit that intensification of therapy (in those who can tolerate it) is the only way to produce an improvement in the duration and quality of survival. Interferon maintenance, in our experience, increases the durability of these responses in those patients who have achieved a complete response to chemotherapy.

Acknowledgements

The authors would like to acknowledge the role of the late Professor Tim McElwain in inspiring these studies, and the contribution made by the medical and nursing staff at St. Bartholomew's Hospital to the care of these patients. We are grateful to Mrs J. Barton for her help with the preparation of this manuscript.

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