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WORKING GROUP ON ACUTE PURCHASING

The Use of Alpha Interferon in the Management of Chronic Myeloid Leukaemia

July 1997

GUIDANCE NOTE FOR PURCHASERS 97/06
Series Editor: Nick Payne

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authority and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise, and includes non-clinically qualified scientists and lay members. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of appropriate evidence, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meetings on 21 October 1997 and 20 January 1998 at which this Guidance Note for Purchasers (in a draft form) was considered.

THE USE OF ALPHA INTERFERON IN THE MANAGEMENT OF CHRONIC MYELOID LEUKAEMIA

AUTHORS: Richards RG and McCabe CJ. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 1997. Guidance Note for Purchasers: 97/06.

EXPERT ADVISOR TO TRENT DEC: Dr R G Richards, Public Health Consultant, North Nottinghamshire Health Authority.

DECISION: The Committee considered that alpha interferon had not been shown to be a cost-effective treatment in the management of chronic myeloid leukaemia.

July 1997

THE USE OF ALPHA INTERFERON IN THE MANAGEMENT OF CHRONIC MYELOID LEUKAEMIA

RG Richards
CJ McCabe

Series Editor: Nick Payne

Trent Institute for Health Services Research
Universities of Leicester, Nottingham and Sheffield

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Conflict of Interest None of the authors of this document has any financial interests in the drug or product being evaluated here.

ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Institute:

- provides advice and support to NHS staff on undertaking Health Services Research (HSR);

- provides a consultancy service to NHS bodies on service problems;

- provides training in HSR for career researchers and for health service professionals;

- provides educational support to NHS staff in the application of the results of research;

- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Professor C E D Chilvers (Nottingham); and
Professor M Clarke (Leicester).

Professor Akehurst currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within the University of Sheffield in conjunction with the School of Health and Related Research (ScHARR).

FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Purchasing Authorities Chief Executives (PACE) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterDEC, with units in other regions. These are: The Wessex Institute for Health Research and Development, The Scottish Health Purchasing Information Centre (SHPIC) and The University of Birmingham Department of Public Health and Epidemiology.

Professor R L Akehurst,
Chairman, Trent Working Group on Acute Purchasing.

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EXECUTIVE SUMMARY

This Guidance Note for Purchasers examines the evidence for the effectiveness and cost-effectiveness of alpha interferon in the treatment of chronic myeloid leukaemia (CML).

Chronic Myeloid Leukaemia

CML is a haematological malignancy with peak incidence rate in the late 8th decade of life, though typically for cancers, incidence rates rise steadily with increasing age. Prior to the use of alpha interferon, no treatment had been shown to alter significantly the course of the disease.

Alpha Interferon

Alpha interferon is one of a family of drugs produced by genetic recombinant technology, manufacture being by fermentation methods. This technology is intrinsically expensive because of the possibility of batch contamination resulting from gene mutation. As a result, such drugs are likely to remain expensive even once the research and development costs are recouped and the drugs come off patent.

Evidence of Effectiveness

There is very strong evidence of effectiveness in terms of extension of survival, with three independent randomised controlled trials (RCTs) showing similar benefit over conventional chemotherapy. None of these studies has followed a trial cohort through to death, but ended typically after six years. The degree of benefit is more contentious therefore, depending on the method used to calculate it; each method having different sources of error.

Cost-effectiveness

The high cost of the drug and need for continuing treatment (as opposed to a course or courses of treatment) means that the cost-effectiveness could never be better than £10,000 per Quality Adjusted Life Year (QALY). Using the data presented from the MRC trial,[1] up to six years the cost-effectiveness is £75,000/life year gained (LYG) or £84,750/QALY.

If treatment is restricted to those patients who demonstrate a haematological response by six months of treatment, then the cost-effectiveness improves to £53,820/LYG or £60,800/QALY.

Implications for the Average Health Authority

Treatment prevalence for a typical district of 500,000 population would be 16 patients, costing £160,000 per annum; 11 patients costing £115,000 per annum for the selective model treating only haematological responders; 3 patients costing £60,000 per annum for the selective model treating only cytogenetic responders.

Conclusions

This is a treatment of proven effectiveness but at very high cost compared to other health care activity. Therefore, it must be considered to be a low priority for funding. Options are limited, with no practical opportunity to target treatment at a small group with larger benefits.

1. INTRODUCTION

1.1 Chronic Myeloid Leukaemia : Incidence and Pathology

The registration rate for England and Wales in 1989 was 1.4/100,000, whilst the average annual registration rate in the Trent region for the period 1979 to 1994 was 1.5/100,000. In Trent, 64% of registrations were aged <75, (in England and Wales the figure was 55%) giving an under 75 average annual incidence for Trent of about 1/100,000 total population.

1.2 Prognosis and Mortality

The disease follows a pattern of a prolonged insidious chronic phase (lasting 3-4 years, though the natural history is confused by late presentation), followed by a rapidly progressive accelerated phase leading to death within a few months. Survival curves from Trent Cancer Registry data are presented in Figure 1.

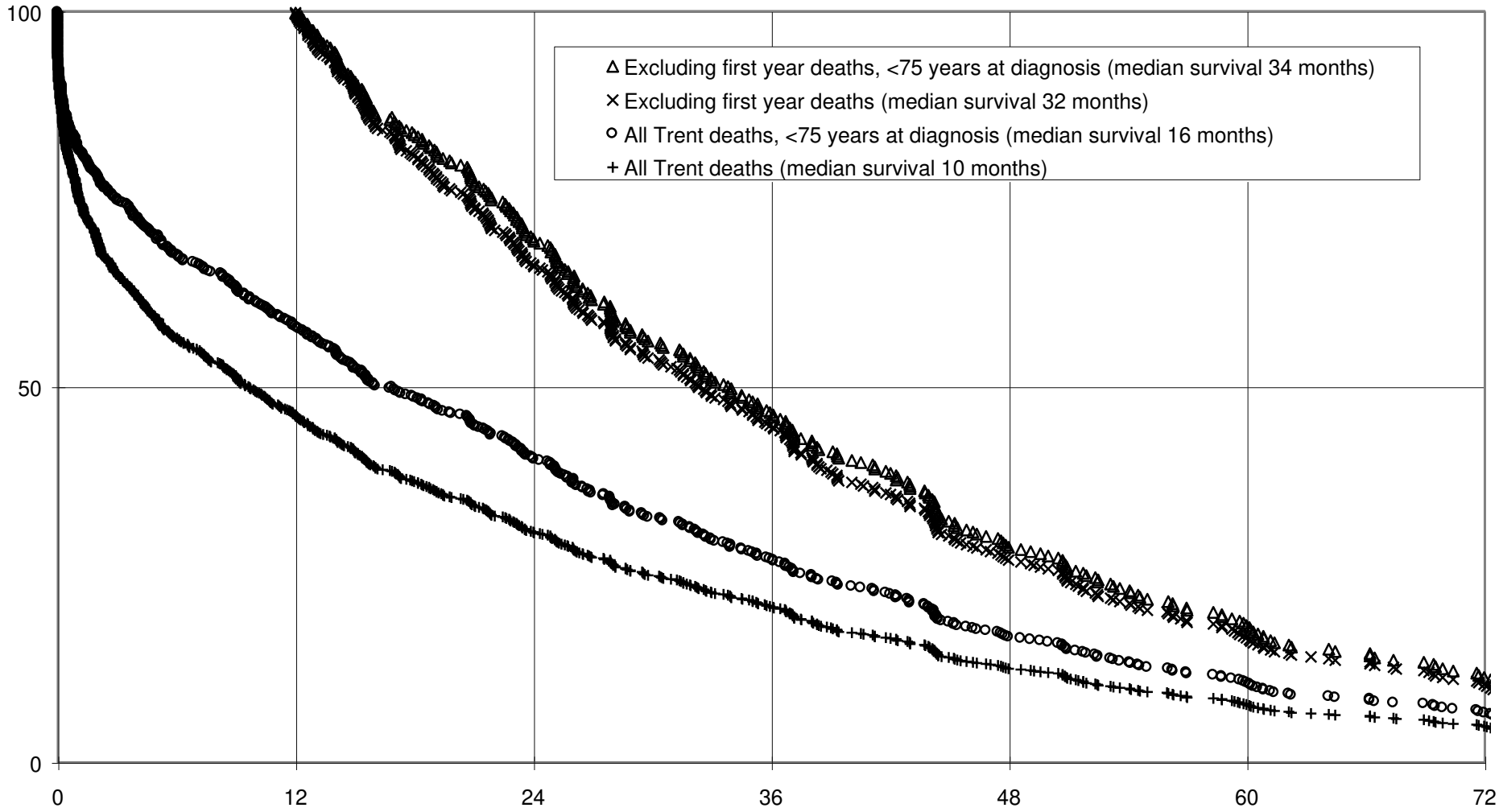
Only data from 1979 to 1994 have been used, as prior to 1979 the data appear suspect and only subsequently stabilise, whilst after 1994 the data are incomplete.

The entry criteria for the MRC study were: “under 75 years ... and ... in first chronic phase. Patients over 75 were excluded because of the risk of neurotoxicity from IFN-α therapy”.[1] Curves for all patients are given, as well as for those under 75 years of age (the MRC study population). Data for those surviving more than one year are also given as the group most likely to have presented with chronic myeloid leukaemia (CML) in the chronic phase (cf. MRC patients) rather than in the accelerated, terminal phase.

1.3 Scale of the Problem in a ‘Typical District’

The age structure of patients in the MRC trial does not match that of the Trent cancer registration data (Table 1), and it would appear that there was a substantial exclusion of patients aged 60-74.

Figure 1: CML (ICD9:205.1) Deaths in Trent 1979-1994: Length of Survival



Source: Trent Cancer Registry

Table 1: Age Structures of Chronic Myeloid Leukaemia Populations

AGE BAND IN YEARS	**<40**	**40 to 49**	**50 to 59**	**60 to 74**	***<75***	**75+**
% BY EACH AGE BAND						
Trent 1979-94	9.7	9.0	12.2	33.3	64.2	35.8
England and Wales 1989	10.3	6.8	9.8	28.4	55.3	44.7
% BY EACH AGE BAND FOR AGES <75 YEARS						
Trent 1979-94	15.1	14.0	19.0	51.9		
England and Wales 1989	18.7	12.4	17.7	51.3		
MRC trial	24.9	20.8	27.8	26.6		
% BY EACH AGE BAND FOR AGES <60 YEARS						
Trent 1979-94	31.5	29.1	39.5			
England and Wales 1989	38.3	25.4	36.3			
MRC trial	33.9	28.3	37.8			

Adjustments to match the MRC structure and thus predict likely treatment use would suggest annual incidence at 0.63/100,000 and, with a median survival at five years, a treatment prevalence of 3.2/100,000 or 16 patients for the average district of 500,000 population.

2. USE OF ALPHA INTERFERON IN THE MANAGEMENT OF CHRONIC MYELOID LEUKAEMIA : SUMMARY OF EVIDENCE OF EFFECTIVENESS

The treatment to be considered is alpha interferon, a protein produced naturally by the body, which acts as an inter-cellular messenger affecting cell function in the immune system.

Alpha interferon is one of a family of drugs produced by genetic recombinant technology, manufacture being by fermentation methods. This technology is intrinsically expensive because of batch contamination resulting from gene mutation. As a result, such drugs are likely to remain expensive even once the R&D costs are recouped and the drugs come off patent.

Three products are currently licensed for the treatment of CML: Intron A (Schering-Plough); Roferon-A (Roche); Wellferon (Wellcome). Treatment protocols recommended in each data sheet are quite different.

Treatment was continuous in the trials and there are, as yet, no recommendations on duration of treatment.

2.1 Conclusion on Direction of Evidence and its Quality

There were three randomised controlled trials (RCTs)[1,2,3] of alpha interferon reported in the literature in 1994 and 1995; the results of studies started in the 1980s. A fourth RCT (alpha interferon vs busulphan) was published in 1995[4] but the data are curtailed much earlier than the other three studies (median follow-up just 50 months) and survival is given as predicted five year survival rates, rather than median survival time. The outcome comfirms those in the other trials but the data are not presented in such a way as to allow detailed comparison.

Comparisons of the three studies

A tool for the assessment of severity at presentation, the Sokal risk score, has been developed, and the data presented in the three studies allow comparison of the casemix at entrance to the three studies; however, the dose of alpha interferon given in these trials differed (Table 2).

Table 2: Casemix and Dosage in Trials

	ITALIAN STUDY[2]	GERMAN STUDY[3]	MRC STUDY[1]
Proportion of Patients in High Sokal Risk Group	24%	36%	42%
Average Dose of Alpha Interferon	7 MIU	3.5 MIU	3.2 MIU

Each study used standard chemotherapy treatment, hydroxyurea or busulphan, for the control group, and the proportion of patients in each Sokal risk group was essentially similar in the alpha interferon arm and control arm within each of three trials, but not between them. All three studies were well-conducted RCTs showing statistically significant benefit for patients receiving alpha interferon regimens, with the exception of the interferon vs hydroxyurea arm of the German trial. The marginal benefit of alpha interferon over standard chemotherapy, as measured by median survival, was 20 months in the MRC and Italian trials and in the busulphan controlled part of the German trial (combined data from the two arms were not presented in the paper; only the busulphan arm is considered in this Guidance Note, the hydroxyurea arm failing to demonstrate significant differences). The severity of the disease as measured by the Sokal risk score was shown to be a strong predictor of survival in the chemotherapy groups and alpha interferon groups (Figure 2), which, in itself, might explain the longer survival in both arms of the Italian study in which the percentage of patients in the high Sokal group was half that of the MRC study.

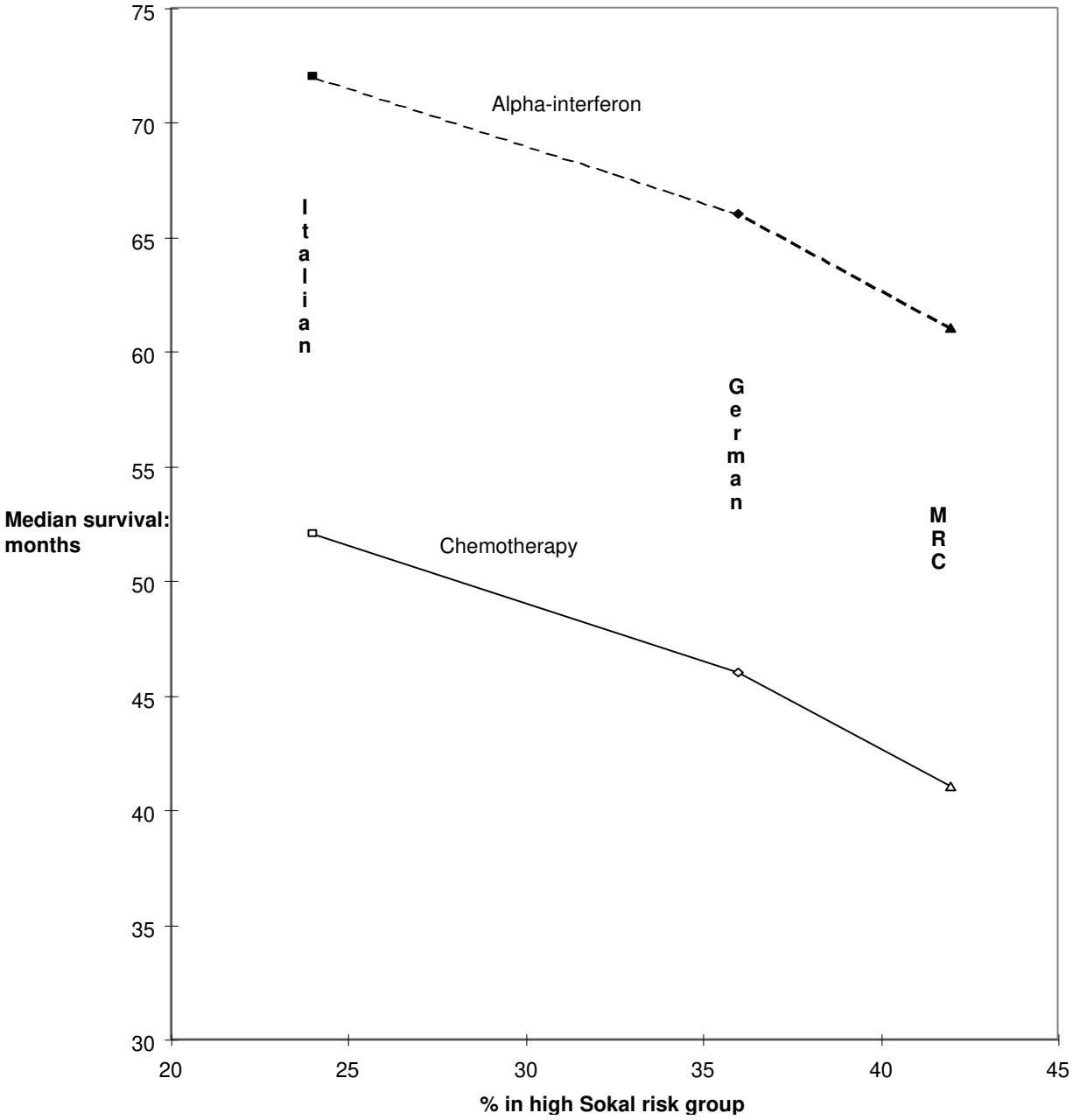
When a crude survival graph is generated from the data in the 1924 JAMA paper,[5] the curve follows closely the chemotherapy curve for the MRC trial up until the third year, but is very different from the Italian chemotherapy curve. Again, this may be explained by differences in the casemix of severity in the various groups studied. Survival curves are shown in Figure 3.

2.2 Evidence Concerning the Use of Smaller Doses

A very small US study[6] on 41 patients used doses averaging half the weekly dose of the MRC trial, but there is no information in the paper on casemix in the form of a Sokal score; therefore, comparisons are not possible and the claim that the outcome was equivalent to higher doses cannot be supported. On the other hand, a review points to the trend for higher rates of cytogenetic response with higher doses.[7]

Two MRC dose ranging trials are currently under way (CML IV and V). These trials started in 1996 and 1995 respectively, therefore, the results cannot be expected for some time.

Figure 2: Differences Between the Three Studies in Sokal Risks and Survival Rates



3. COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

3.1 Trent Analysis

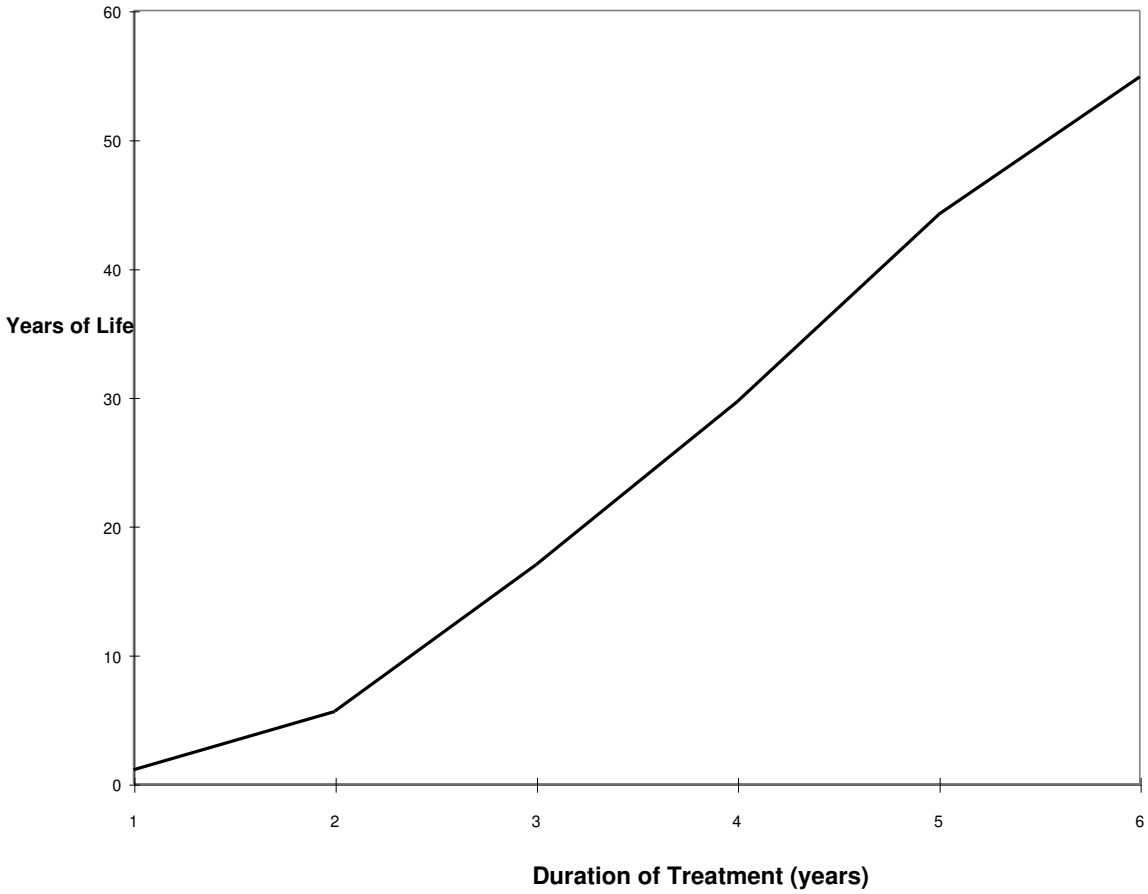
3.1.1 Survival Benefit

Marginal survival advantage has been calculated as the area between the survival curves for the alpha interferon and control groups. The MRC trial data have been used as they give the UK experience and also appear to have the most favourable outcome. A theoretical cohort of 100 patients in each arm of the trial was used to generate the survival curves and marginal survival advantage.

Although this is technically the most accurate method to calculate total survival for the cohorts, it is not without problems. The data are curtailed at six years and the tails may be important, especially if any patients are cured. A Cox regression model could be used to simulate a tail, generating survival curves based on survival ratios averaged across the six years, thus avoiding the problems of random variations in any arbitrary single point measure. However, this assumes some constancy of survival ratios, whilst the reality may be one of systematic changes in survival ratios. Such situations are typically seen in trials with the survival curves of cases and controls first diverging then converging again, if only because of deaths from other diseases, especially in the elderly.

Cumulative survival advantage for an alpha interferon treatment cohort is presented in Figure 4.

Figure 4: Cumulative Survival Advantage for Alpha Interferon Cohort of 100

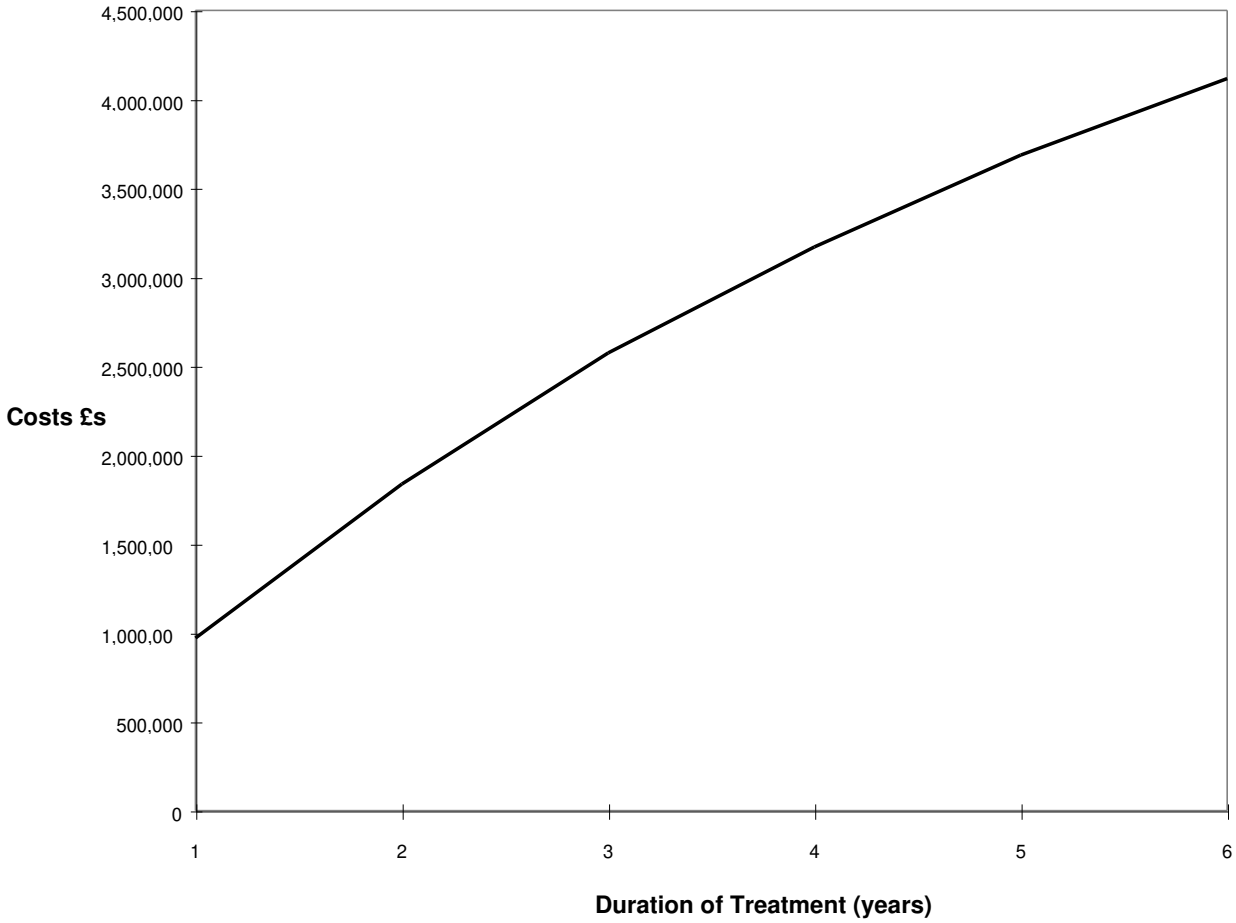


3.1.2 Costs

The major part of the cost of treatment is that of alpha inteferon, whilst the standard chemotherapy costs are very small at between £100 and £200 and have been ignored for this analysis. Using the MRC dosages, theoretical costs of alpha interferon would be £6,666; one Trust has reported actual costs to average about £10,000 per annum, which is an ongoing annual cost. This actual figure of £10,000 per annum has been used in the analysis presented in this Guidance Note.

Again, the survival curve for alpha interferon has been used to generate cumulative treatment costs; this gives the actual costs allowing for the reducing size of the cohort being treated with time. Cumulative costs are presented in Figure 5.

Figure 5: Cumulative Costs of Alpha Interferon for Cohort of 100

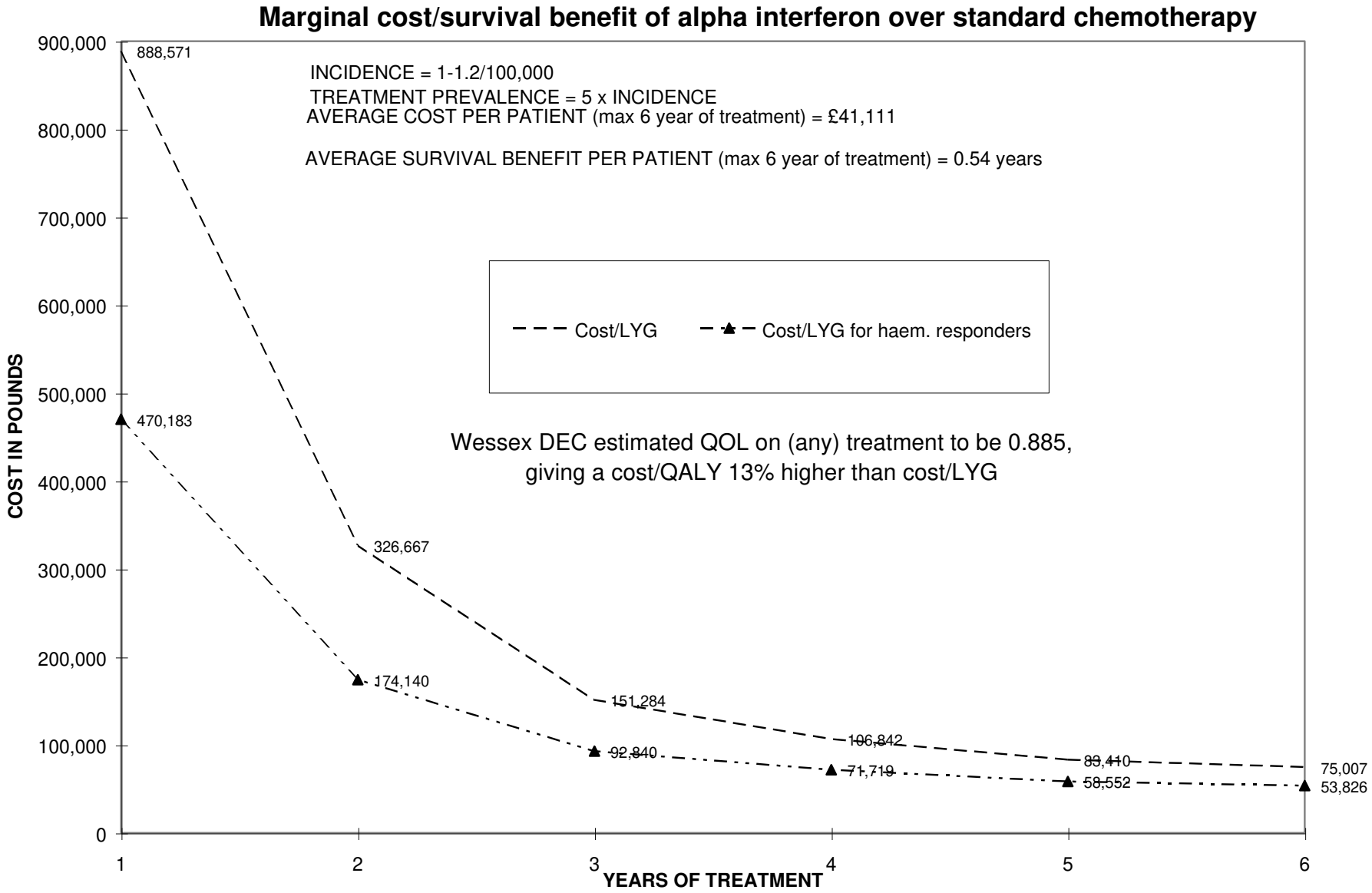


3.1.3 Cost-effectiveness

Cost-effectiveness has been calculated as marginal costs per life year gained (LYG) (Figure 6). The Wessex DEC report[8] assumed a quality of life rating of 0.885 on alpha interferon (similar to the 0.9 used in other economic analyses[9]) or standard treatment which would give a cost per Quality Adjusted Life Year (QALY) 13% higher than the cost per LYG.

This analysis shows that the cost-effectiveness is £75,000 per life year gained or £84,750 per QALY.

Figure 6: Economic Analysis of Alpha Interferon in the Treatment of Chronic Myeloid Leukaemia Assuming Annual Treatment Cost of £10,000



3.1.4 Treatment Sub-groups

The MRC trial identified a large sub-group of patients with a slightly better outcome. Those patients with an 'A type' haematological response within the first six months of treatment with alpha interferon, about 70% of the cohort, had a better relative prognosis. A cost-benefit analysis of this sub-group is also presented, based on treatment for all to six months, then selecting responders only for long-term treatment.

Despite the claims that the Sokal score may predict marginal benefit on alpha interferon,[7] with high risk patients fairing poorly, there is no evidence in these trials to support that claim. The MRC trial has the largest proportion of high risk patients, yet the marginal benefit is at least as good as, if not better than, the Italian and German trials.

It has been suggested that complete cytogenetic responders, that is, those patients showing bcr/abl negativity on qualitative polymerase chain reaction (PCR)[a] or Southern blot test, may have had their Philadelphia chromosome anomalies eradicated and, thus, actually be cured,[7] but more intensive quantitative examination showed residual disease still to be present in such patients.[10] Furthermore, the number of such cytogenetic responders increases with duration of treatment, with major and complete response taking the longest.[3] A proposed protocol[7] suggests that only patients showing any cytogenetic response at six months, or Philadelphia chromosome count < 50% at 12 months, should continue treatment. With a median time to mild cytogenetic response in the MRC trial[3] at 32 weeks (range 4 - 108) and only 22% of patients showing any cytogenetic response during the trial, this would certainly limit the numbers on treatment. However, it is not clear from the available literature whether this selected group would include or exclude those with the best cytogenetic response (major or complete response, 11%), i.e. the group of patients showing the best survival. The data presented in the papers do not permit a cytogenetic responder sub-group health economic analysis; although the data do point to a better cost-effectiveness profile, it cannot be quantified. The best that could be achieved would be £10,000 per QALY for those thus selected, but adjusted to £20,000 - £30,000 per QALY to allow for those on trial of treatment achieving no health gain.

[a] A test on the cellular DNA that detects defects.

3.1.5 Sensitivity Analysis

There are a number of variables which could have an impact on the cost-effectiveness calculations:

a the accuracy of the method of estimating true survival benefit;

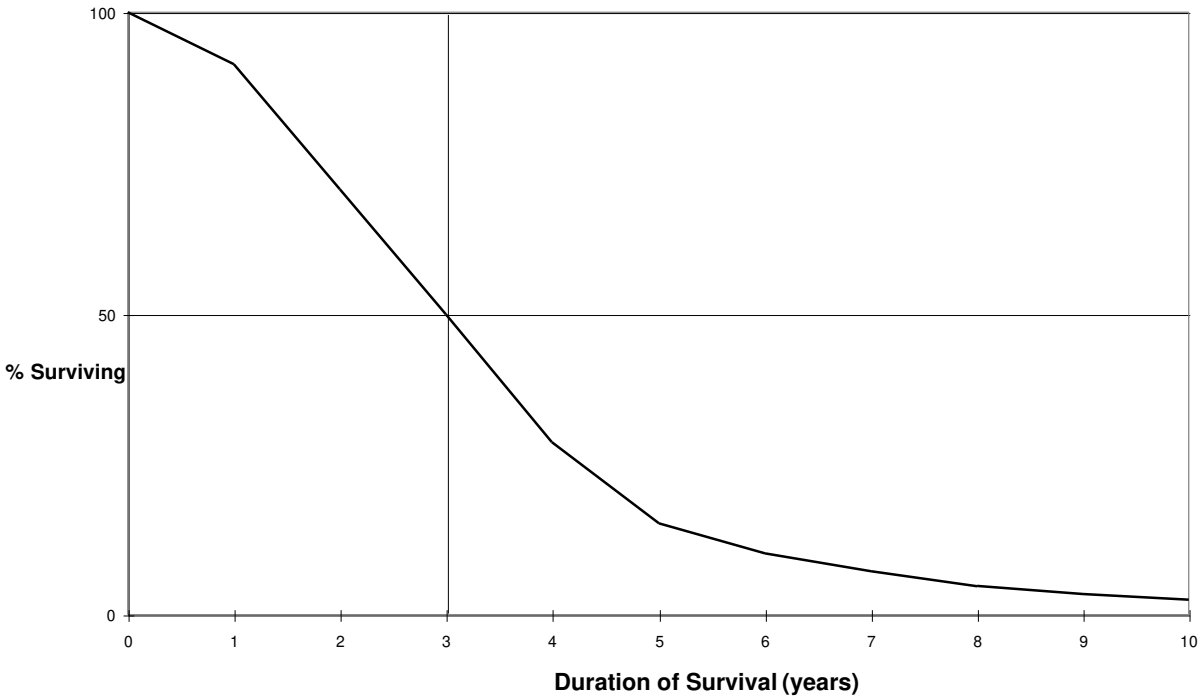
b the dose of alpha interferon (see 2.2 above);

c wasted doses of alpha interferon;

d quality of life estimates.

Using the best possible outcome (increase in *median* survival of 20 months), theoretical drug usage rather than actual, and a quality of life on alpha interferon of 1.0, then the most favourable cost-effectiveness estimate is £20,170 per QALY (see Table 3 below).

Figure 7: Survival Curve for all 130 Patients in 1924 JAMA paper



3.2 Wessex DEC Analysis[8]

3.2.1 Survival Benefits

The Wessex team has chosen to create an historical control group for the purposes of analysing benefits for alpha interferon and standard chemotherapy (the latter despite assertions that standard chemotherapy does not alter disease progression). This generates survival benefits for alpha interferon of 36 and 21 months for the Italian and MRC trials respectively. The use of historical controls is well known to be fraught with problems. In this case, a major problem can be clearly illustrated. The source of the historical data is a 1920s trial of radiotherapy published in the JAMA.[5] The patients are clearly a selected group when compared to those on the Trent Cancer Registry, with survival curves being markedly different. Only when Trent's first year deaths are excluded, does the Trent median survival of 33 months approach the JAMA figure of 36 months (Figure 7).

As has been shown earlier, the Sokal risk score is a potent predictor of survival. The proportion of high risk patients varies between the three trials with concomitant variation in survival. As the Sokal profile of the historical controls is unknown, comparisons between outcomes in any of the three trials and the historical controls is inappropriate.

At the end of the Wessex paper, passing reference is made to marginal benefit over conventional chemotherapy but, again, comparisons within trials are not made and there is no presentation of marginal cost-utility analysis. Marginal benefits within trials are very similar; for each trial there is a 20 months improvement in median survival: MRC 61 vs 41; Italian 72 vs 52; German 66 vs 46 (busulphan arm).

The use of median survival as the outcome measure for comparison is also open to question. Median survival is an arbitrary uni-dimensional measure, established by convention (as is five year survival). It is a measure of the average which may differ considerably from the mean. It would be an accurate measure if survival 'curves' were straight lines, but it is an inappropriate measure for a complex curve. In particular, in assessing the difference between survival of two cohorts, it fails to take into account the possibility (indeed probability) that the curves eventually reconverge.

3.2.2 Costs

There are two additional sources of error, although they counter each other. Firstly, Wessex uses theoretical costs based on average dose to give £6,613 per annum for the MRC trial as opposed to the reported actual cost of £10,000 per annum used here. The Wessex DEC does note this however: "The cost/utility ..... does not take account of the cost of unused interferon in the opened vial".

The second results from the use again of median survival, this time for the calculation of lifetime costs. If a cost of £10,000 per annum is applied to the Wessex data then lifetime costs become £50,833, whereas using the survival curve gives costs (up to six years) of £41,163.

3.2.3 Cost-effectiveness Analysis

The Wessex analysis of cost-utility gives a cost per QALY of £26,020 and £12,080 for the Italian and MRC trials respectively. If marginal benefits within trials and adjusted costs at £10,000 per annum are used, then the cost-utility calculations using marginal median survivals from the MRC trial are much closer to those presented above (Section 3.1.3).

3.3 Annals of Internal Medicine Analysis[9]

This analysis is based on complex modelling techniques using decision trees and probabilities to generate both costs and benefits for a 50 year old and appears to be based on USA practice, which is much more aggressive (using intensive in-patient treatment) during the accelerated phase and blast crises than is practice in the UK.

3.3.1 Survival Benefits

The model generates median survivals of 69 months on alpha interferon and 58 months on hydroxyurea, but life expectancies (mean survival) of 91 and 73 months respectively; the difference reported being due to the long survival tails seen in CML. The median survival benefit is less than the 20 months actually seen in the three RCTs (though, of course, the German hydroxyurea arm showed no significant benefit), whilst life expectancy benefit is closer at 18 months. The analysis uses mean survival as its benefit which is equivalent to using the area under the survival curve. It is not possible to generate true mean survivals from the MRC and Italian data as they are curtailed at six years, but figures up to six years are presented in Table 4.

The data from the Trent Cancer Registry (Figure 1) for those under 75 years of age and surviving longer than one year (i.e. an approximation to the study group) do not give the large difference between median and mean seen in the Annals of Internal Medicine model.

Patients on alpha interferon were ascribed a Quality of Life (QOL) score of 0.9 as against 1.0 for those on hydroxyurea. Wessex used 0.885 for both treatment groups, the figure also used to adjust the years of life in the Trent analysis presented in this Guidance Note.

3.3.2 Costs

Costs on the other hand have been generated in a highly sophisticated way more closely resembling the survival curve method. However, whilst the lifetime cost for the alpha interferon arm does not seem greatly different from the UK cost at $118,000 (about £74,000), the hydroxyurea arm was prodigiously costly at $93,000 (about £58,000), reflecting the use of in-patient treatments.

3.3.3 Cost-effectiveness Analysis

The (discounted) marginal cost-effectiveness for the 50 year old was $26,500 (about £16,600) per LYG, and cost/utility $34,800 (about £21,700) per QALY. These figures are sensitive to the cost of alpha interferon, the age of the patient and quality of life measures; however, in terms of comparison with the other two analyses above, it is the reported cost of hydroxyurea $93,000 (about £58,000) that is a key feature. If that cost better reflected the costs of hydroxyurea suggested in the UK, the marginal costs and, thus, the cost-effectiveness, would be four times higher and, therefore, greater than our Trent estimate.

Table 3: Comparisons Between Wessex, Trent and Best Outcome Analyses

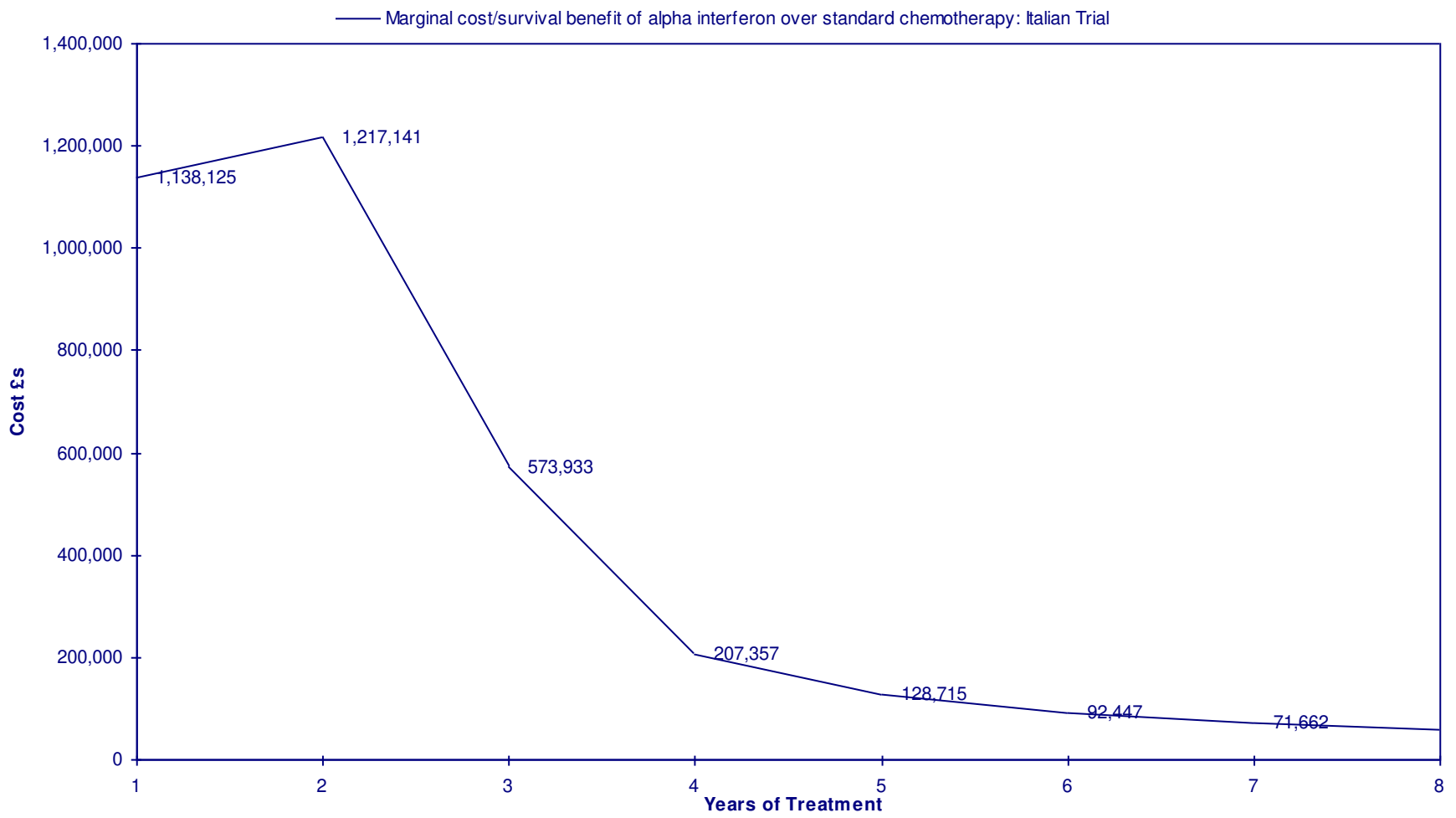
Analysis	Annual Costs £ £	Lifetime Costs £ (Not Discounted)	Benefit Over Historical Controls: Survived Months	Benefit Over Italian Hydroxyurea Controls: Survived Months	In-Trial Marginal Benefit: Survived Months	QOL Adjusted Benefit: Years	Cost/QALY £
Wessex MRC	6,613	33,616	25			2.5	13,450
Wessex MRC	6,613	33,616		9		0.7	48,020
Wessex MRC	10,000	50,833			20	1.48	34,460
Trent MRC	10,000	41,163			6.6	0.49	84,750
Trent MRC	6,613	33,616			6.6	0.49	69,210
Most favourable	6,613	33,616			20	1.67	20,170

Table 4: Comparisons Between Median and Mean Survivals

Data Source	Median Survival: Months	Mean Survival: Months	Difference Between Mean and Median: Months
Annals of Internal Medicine Analysis: Alpha Interferon	69	91	22
Annals of Internal Medicine Analysis: Hydroxyurea	58	73	15
Trent Region: all	10	20	10
Trent Region: aged <75	16	25	9
Trent Region: all surviving > 1 year	32	39	7
Trent Region: aged <75 surviving >1 year	34	41	7
Trent Region: aged <75 surviving >1 year curtailed at 6 years	30	34	4
MRC Trial to 6 years: Alpha Interferon	61	49*	-12
MRC Trial to 6 Years: Chemotherapy	41	43*	2
Italian Trial to 6 years: Alpha Interferon	72	56*	-16
Italian Trial to 6 Years: Chemotherapy	52	50*	-2

* calculated from area under survival curve.

Figure 8: Economic Analysis of Alpha Interferon in the Treatment of Chronic Myeloid Leukaemia Assuming Annual Treatment Cost of £10,000



3.4 Conclusions

The shape of the survival curve is crucial in determining the relationship between the median and the mean. The median survival, a point measure, is suspect as a measure of the true average survival of a cohort that would permit an accurate estimate of benefit. The mean is dependent on the nature of the tail occurring after the end of the trial. The shape of that tail is dependent on both the effectiveness of the drug (a large effect would increase the mean with time) and the age of the cohort (an elderly cohort would see large numbers of non-CML deaths in the tail, reducing the mean with time). The Italian trial shows the most favourable survival curves, still diverging in year six, but in year six the number necessary to treat is three (four in the MRC trial), giving a cost-effectiveness for that year of £30,000. It is unlikely, therefore, that even a favourable tail would have much impact on the overall cost-effectiveness profile. Figure 6 gives an impression of the changes in cost-effectiveness with time for the MRC study, illustrating the tendency for the curve to flatten out; Figure 8 shows the same analysis for the Italian data, projected to year eight.

However, the mean at six years as calculated in the Trent analysis, is the most accurate calculation of average survival using the data available, rather than attempting extrapolations (a process that is not recommended).[10]

4. OPTIONS FOR PURCHASERS AND PROVIDERS

Option 1 Do not fund from mainstream NHS funds as it is not a cost-effective treatment. Await further evidence from MRC dose ranging trials.

Option 2 Fund on the basis of selection of haematology responders by six months. Supported by the research; clinically appropriate targeting of scarce resource. Total costs are less and cost-effectiveness improved, though still very poor.

Option 3 Treat only cytological responders (any at six months or Ph chromosome count <50% at 12 months). This is likely to be the most cost-effective option; though unquantifiable, figures are unlikely to fall below £20,000/QALY because of the large numbers of patients initially on trial of treatment for whom there will be no health gain.

5. DISCUSSION AND CONCLUSIONS

5.1 Technical Issues

Questions can be raised about methodologies, especially as they have such large effects on the analyses. However, it is considered that the survival curve method offers the most accurate estimate of average survival, though sensitive to the post trial 'tail'. It was also agreed that in-trial, *marginal* benefit must be used as the benefit outcome to be measured.

5.2 Lower Dose Alternatives

A USA study indicates that much smaller doses of alpha interferon can be used without reducing benefits. These data are mentioned in paragraph 3.3 above. The MRC dose ranging studies will confirm or refute the preliminary results of that trial.

5.3 Possibility of Cure

It can be suggested that a small sub-group of patients has cytogenetic responses indicative of cure, a claim mirrored in the literature.[7] However, this is apparently refuted by more detailed analysis.[11]

5.4 Meta-analysis

A meta-analysis of the three trials should improve the quality of the information and possibly identify sub-groups which might derive greater benefit. In particular, the effect of Sokal scores on outcomes of treatment as well as the prognostic significance of the haematological and/or cytogenetic responses needs to be addressed given the conflicting information in the literature.

A comparative analysis of the Italian and German trials has been published in the form of a letter.[12] It seeks to compare the data for the two trials by retrospectively applying uniform entry criteria. It is not, however, a meta-analysis and does not answer any of the questions raised here.

5.5 Paradoxical Response to Quality Research

There appears to be a paradox in that good quality research, which generates data of sufficient detail to permit health economic analysis, would be penalised by revealing the true costs, whilst poor quality research, or none at all, might deny that analysis and permit poor medicine to become normal practice. Nevertheless, this in itself is not a reason to accept new cost-ineffective treatments, nor to cease quality research. The role of research is to test treatments not prove them.

This is of particular concern for haematologists, as almost uniquely in medical practice, the vast majority of their cancer related work is driven by such high quality research.

5.6 Responsibilities of the MRC

Alpha interferon is already used routinely by a number of providers. This is partly the result of communications from the MRC informing collaborators of early results, the curtailment of the study, and a statement to the effect that it would be unethical to continue the trial and deny patients alpha interferon. Clinicians felt that they would be held negligent if they subsequently denied alpha interferon to their patients.

In terms of the ethics of the clinical trial as established, the MRC response is sound. In a resource constrained environment the ethics are not so clear cut, as alpha interferon therapy must be set against other calls on limited resources. In this environment, great care is required by those making statements with regard to the ethics around provision of any specific treatment.

Broader issues are also raised about the end-points of trials and the questions to be answered. Trials designed to answer simple effectiveness questions may fail to provide sufficient data necessary for the difficult and complex process of priority setting.

5.7 Comparison with Bone Marrow Transplantation

Bone Marrow Transplantation is also high cost and used in the treatment of CML. A comparative cost-effectiveness analysis of these alteratives would be of value. However, it is beyond the scope of this report and the need for a RCT to compare these alternatives is highlighted elsewhere.[9]

6. USE OF ALPHA INTERFERON IN THE MANAGEMENT OF CHRONIC MYELOID LEUKAEMIA : SUMMARY MATRIX

PATIENT GROUP	**PATIENT CRITERIA (GUIDELINES NOT PROTOCOLS)**	**ESTIMATED FUTURE ACTIVITY** (treatment prevalence)	**OPPORTUNITY FOR COST SAVING**	**AUDIT POINTS**	**EFFECTS THAT COULD BE EXPECTED IN RELATION TO STARTING POINT**	**COST-EFFECTIVENESS** *(after up to 6 years of treatment)*
CML patients under 75 years.	As per MRC trial entry criteria.	16 per annum (3.2/100,000)	NONE	Treatment criteria as for MRC trial. Side-effects and drop out rates.	Average improvement in survival of 6.6 months (49 vs 43).	£75,000/YoL £84,750/QALY.
CML patients under 75 years: haematological responders.	As per MRC trial entry criteria: continued treatment only of those with haematological response by 6 months.	11 per annum (2.2/100,000)	NONE	Treatment criteria as for MRC trial plus response status. Side-effects and drop out rates.	Average improvement in survival of 10.4 months (53 vs 43).	£53,820/YoL £60,800/QALY.
CML patients under 75 years showing cytogenetic response by 12 months.	As per MRC trial entry criteria: continued treatment only of those with any cytogenetic response by 6 months or Ph count <50% by 12 months.	Approx 3* per annum plus 3** patients per annum on trial of treatment (0.6/100,000 plus 0.6/100,00).	NONE	Treatment criteria as for MRC trial plus cytogenetic response status. Side-effects and drop out rates.	UNKNOWN but better than either of above.	UNKNOWN but better than either of above.

Numbers are for an average District of 500,000 population

* assumes a median survival much greater at 8 years and 12.5% of patients showing cytogenetic response

** MRC equivalent entry criteria giving annual incidence of 0.63/100,000 (see 1.3 above)

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