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The DiSC ASSAY

A Cost-effective Guide to Treatment for Chronic Lymphocytic Leukemia?

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Abstract

The differential staining cytotoxicity (DiSC) assay involves in vitro drug panel testing against patient tumor cells to identify optimal therapy. This observational study investigated whether DiSC assay guided treatment could improve outcome in patients with chronic lymphocytic leukemia. A cohort of 178 patients were categorized either as sensitive to drugs in vitro and receiving a sensitive drug in vivo, sensitive in vitro but not treated with a sensitive drug, or having disease resistant to all drugs tested in vitro. Response and survival for these patient categories were compared using multivariate regression techniques. Patients receiving a sensitive drug, compared with those who though having sensitivity did not, had a higher remission rate (odds ratio, 6.5; 95% CI, 2.91–14.53) and reduced death rate (hazard ratio, 0.29; 95% CI, 0.16–0.53). Having adjusted for all known confounding factors, the results suggest that in vitro drug sensitivity is an important independent prognostic variable to include in future trials, and that the DiSC assay may be a cost-effective use of health resources: the estimated incremental cost-effectiveness was £1,470 per life-year gained. A randomized controlled trial is required to confirm the benefit and estimate reliably the potential impact of assay-guided choice of therapy.

Keywords: Cost-Benefit Analysis; Drug Screening Assays, Antitumor; Leukemia, Lymphocytic, Chronic; Survival Analysis.

Chronic lymphocytic leukemia (CLL) is a hematological malignancy occurring mainly in older people. It represents about 25% of cases of leukemia in the western hemisphere (17) and is the most common leukemia in Europe and the United States (14). Medical Research Council (MRC) trials of treatments for CLL patients

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indicated that the most important prognostic factors governing survival after treatment are stage of disease, age, gender, and remission (9;10). In the United Kingdom, most patients are treated initially with chlorambucil (about 70% of these cancers respond) and empirically on relapse with a range of chemotherapies (10–50% respond) (12).

Sensitivity to different chemotherapies can vary markedly between individuals, and it has been shown that remission is strongly correlated with receiving a drug that effectively destroys tumor cells (5). The differential staining cytotoxicity (DiSC) assay is an in vitro drug sensitivity test performed on white cells isolated from patient blood samples using a panel of drugs. The DiSC assay is one of a number of similar tests (6). This paper reports a multivariate analysis of therapeutic response and survival in patients whose in vitro drug sensitivity is assessed using the DiSC assay. Its objectives are to explore the potential effectiveness (increased survival) and cost-effectiveness (cost per life-year gained) of using the DiSC assay to guide the treatment of patients with CLL.

METHODS

Patients with a primary diagnosis of CLL, assayed between 1988 and 1994 by Bath Cancer Research and treated within 6 months of their assay were included in a prospective cohort study. The 178 patients identified were a mixed cohort, predominantly from two groups of patients: those being entered into the MRC CLL III Clinical Trial and those patients from whom samples were sent to Bath Cancer Research for testing during routine care. Prognostic variables and treatment given were recorded. Stage of disease was assessed in accordance with the system proposed by Binet et al. (3).

DiSC assay assessment involves a standardized test that finds the lowest concentration of drug at which 90% of tumor cells are eradicated in vitro (LC_{90}) (7). Main drugs tested (with threshold LC_{90} sensitivity applied, in μg/ml) were chlorambucil (12.8), cyclophosphamide (mafosfamide in vitro, (1.6), doxorubicin (0.32), epirubicin (0.32), fludarabine (2), cladribine (0.64), pentostatin (250), methylprednisolone (10), prednisolone (5), and vincristine (1), all of which have been shown in trials to be effective alone or in combination. Useful sensitivity to a particular drug is indicated when a patient's LC_{90} for that drug is less than or equal to the reference threshold (which was defined on the basis of previous comparisons of test results with subsequent patient response). DiSC assay assessment meant that, for each patient, in vitro sensitivity to the treatment given and to other potential treatments was known. This means that each patient can be categorized overall in terms of in vitro drug sensitivity and subsequent treatment thus:

$$\text{Ex vivo sensitivity and treatment} \quad [= \text{Sens}] = \begin{bmatrix} 0\text{: Not sensitive to any drug(s) given or tested, i.e., resistant} \\ 1\text{: Sensitive to some drug(s) tested but not to drug(s) given, i.e., unexploited sensitivity} \\ 2\text{: Sensitive to drug(s) given, i.e., exploited sensitivity} \end{bmatrix} \quad (\mathbf{1})$$

Analysis using this categorization can distinguish the value of having a pathology sensitive to drugs (Sens = 0 versus Sens = 1, 2), and the advantage of exploiting such a pathology (Sens = 1 versus Sens = 2). Those found to be sensitive to the drugs given (Sens = 2) are referred to as those with exploited sensitivity; patients categorized as Sens = 1 are referred to as those with unexploited sensitivity.

The outcomes recorded were remission (after a minimum of two monthly courses of therapy) and survival time from the date of the assay. Response was categorized as remission (complete or partial response to therapy) and no remission according to standard MRC criteria (14).

The association of drug sensitivity and response was assessed by logistic regression analysis. Univariate analysis was performed followed by multivariate analysis in order to adjust for the effects of potential confounding variables: age, sex, stage of disease, previous treatment, trial membership, the influence of feedback of DiSC assay findings to clinicians, and interactions between variables. The adjusted odds ratios for various categories of drug and treatment sensitivity were estimated.

Analysis using Cox's proportional hazards model assessed the relationship of drug sensitivity and treatment with survival. Survival probability S at time t is expressed in general as:

$$S(t) = \exp[-H_0(t) \times \exp(PI)]; \qquad PI = b_1X_1 + b_2X_2 + ... + b_nX_n \qquad (2)$$

where H_0 is the underlying cumulative hazard function and PI (the prognostic index) is the set of independent variables influencing survival $X_{1..n}$ and their regression coefficients $b_{1..n}$ (1). Hazard ratios for patients in the various categories were estimated, adjusting for potential confounding variables and interactions and testing for constant proportionality over time.

Survival curves were generated, and gains in life expectancy were estimated, from the baseline cumulative hazard function and prognostic index. Since several variables in the prognostic index influenced survival, confidence intervals for the estimates of survival were generated by a stochastic simulation (11). This involved generating a large number of estimates of each coefficient in the prognostic index of the hazard function, where each estimate was drawn from a normal distribution using the estimated mean and standard error of the coefficient. In this manner a mean and standard error were obtained for the prognostic index in total for each patient subgroup. Ten thousand randomly determined sets of coefficients were generated.

All logistic and survival estimations were carried out using EGRET and replicated on SPSS for Windows. Stochastic simulations were performed using SPSS for Windows.

Major costs were identified and the potential effect of the introduction of DiSC assay assessment upon treatment choices was explored.

RESULTS

Assays were conducted for 178 CLL patients: 94 as they entered into the MRC CLL III Trial; 37 as they entered into other trials; 47 at the commencement of nontrial treatment. The mean age at the start of treatment was 65 years: this did not vary significantly by stage of disease or patient gender. Maximum follow-up from the time of commencing treatment was 5.9 years with a median of 1.3 years. Overall, 70% of patients were male (typical of CLL patients in general), although the proportion of female patients with stage A disease was higher than for the other stages. The median treatment duration was 4.9 months and continued beyond 12 months for only 2% of patients. Nearly 40% of patients had previously received chemotherapy, and 17% had received more than one treatment regimen. Seventy percent of patients were sensitive to at least one drug received (exploited sensitivity)

as shown in Table 1. A further 23% were sensitive to one or more drug(s) but not to the drug(s) they were given (unexploited sensitivity). Twelve patients (7%) indicated no sensitivity to any drug tested in vitro. Remission was achieved in 59% of patients, about a quarter of whom experienced a complete response.

Patients with more advanced disease, as indicated by stage, were less likely to have received a drug to which they were found to be sensitive in vitro, less likely to have responded to therapy, and were more likely to have died during the study. Sixty-one patients (34%) had died (any cause) by the end of the study. Four patients died of causes unrelated to CLL (the cause was other cancers; all four were in the Sens = 2 category).

The rate of remission was more than 70% in patients with exploited sensitivity (Sens = 2); but only 30% in patients with unexploited sensitivity (Sens = 1). Only 2 of the 12 patients with no drug sensitivity experienced remission after treatment (Sens = 0). Nearly a quarter of patients who received a drug to which they were sensitive died during the follow-up period, compared with over 90% of those with no drug sensitivity. The assay results were returned to clinicians in 30 cases (17%) and were known to influence treatment in 18 patients (10%): the effect of this was tested for in the models generated and found not to influence results. Assay results were not returned in the case of trial enrollees, since this might have influenced trial results.

Although there were insufficient patient numbers to perform survival analyses by drug, patient categories of drug sensitivity (and subsequent response) were spread fairly evenly over the various regimens (Table 1).

Remission

The result of the univariate logistic regression to estimate the probability of remission is shown in Table 2. This shows the odds ratio of remission relative to the base case of patients with unexploited sensitivity. Thus, patients with exploited sensitivity had a 6.5 times greater odds of remission (95% CI, 2.91–14.53) than those with unexploited sensitivity. The model also suggests that patients with no drug sensitivity had half the odds of remission of the baseline group, but this finding is not statistically significant.

Potential confounding variables, identified in trials as important, were added in an incremental manner starting with age and sex. Adjustment for these variables did not materially alter the estimates of odds ratios for patients in different categories of drug sensitivity.

Survival

The result of the univariate estimation of incidence of death is shown in Table 3; the hazard ratio for each category is expressed relative to the base case of patients with unexploited sensitivity. The rate of dying was reduced to less than a third in patients with exploited sensitivity (95% CI, 0.163–0.525), compared with the base category. Patients with no drug sensitivity experienced a rate of death twice that of base case patients (95% CI, 0.983–4.191), although this is of borderline statistical significance. The corresponding Kaplan-Meier survival curves are shown in Figure 1.

A multivariate regression model, adding age, sex, and stage ($\chi^2[4] = 23.2$, $p < .001$), did not materially alter the hazard ratios associated with drug sensitivity status. Increasing age and stage C disease are associated with a decreased survival rate as expected; female gender is associated with increased survival as expected (9). Other potentially confounding variables were added, but none of these significantly

Table 1. Cross-tabulations on Drug Sensitivity Status

		Sens = 0[a] Treatment resistant		Sens = 1[a] Unexploited sensitivity		Sens = 2[a] Exploited sensitivity		All
Number		12/178	7.0%	41/178	23.0%	125/178	70.2%	178
Age (years, mean ± SD)		69.1	±6.19	62.7	±9.03	65.3	±10.21	65
Sex (male/all)		6/12	50.0%	35/41	85.4%	83/125	66.4%	178
Vital status[b] (alive/all)		1/12	8.3%	21/41	51.2%	95/125	76.0%	117/178
Trial membership		7/12	58.3%	22/41	53.7%	102/125	81.6%	131/178
Stage	A	4/39	10.3%	3/39	7.7%	32/39	82.1%	39
	B	3/54	5.6%	13/54	24.1%	38/54	70.4%	54
	C	5/85	5.9%	25/85	29.4%	55/85	64.7%	85
Regimen								
Chlorambucil (± Prednisolone)		5/63	7.9%	8/63	12.7%	50/63	79.4%	63
Chlorambucil + epirubicin		2/50	4.0%	6/50	12.0%	42/50	84.0%	50
Fludarabine		2/27	7.4%	8/27	29.6%	17/27	63.0%	27
Cladribine		0/10	0.0%	5/10	50.0%	5/10	50.0%	10
Other single/combination therapy		3/28	10.7%	14/28	50.0%	11/28	39.3%	28
Previous therapy	0	6/108	5.6%	16/108	14.8%	86/108	79.6%	108
	1	4/39	10.3%	6/39	15.4%	29/39	74.4%	39
	⩾2	2/31	6.5%	19/31	61.3%	10.31	32.3%	31
Responded to treatment[c]		2/12	16.7%	11/38	28.9%	90/124	72.6%	103/174

[a] See equation 1 for drug sensitivity categories.
[b] Vital status at end of follow-up allowing for mortality by any cause.
[c] Response was unknown for four patients in the cohort.

Table 2. Univariate Logistic Estimation of the Determinants of Remission
Outcome = L (remission)
Dependent variable: Response

Term	Coefficient	Std. error	*p*-Value	Odds ratio[a]
Constant	−.898	.358	.012	.407
Sens = 0	−.712	.853	.404	.491
Sens = 2	1.871	.410	<.001	6.497
Deviance on 171 *df* = 202.2				
Likelihood ratio statistic on 3 *df* = 39.0, $p < .001$				

[a] Odds of remission in other patient groups relative to the group with unexploited drug sensitivity (Sens = 1). See equation 1 for drug sensitivity categories.

improved the fit of the model or materially altered the hazard ratios for the categories of drug sensitivity. The model was simplified by combining stage A and stage B patient categories ($\chi^2[1] = .139$, $p = .709$).

A trend of interaction was found between age and drug sensitivity ($\chi^2[2] = 4.892$, $p = .087$) (Table 4). This means that although patients with exploited drug sensitivity have, on average, one quarter of the incidence of death of the baseline group, the size of benefit may decrease with increasing age.

The assumption of constant proportionality over time for the explanatory variables was tested and accepted, in each model shown, by fitting (logarithmic) time covariates: none of these was statistically significant or substantially altered the hazard ratios for the categories of drug sensitivity.

Years of Life Gained

In order to calculate the potential benefits from using the DiSC assay, it was assumed that the survival experience of a patient with unexploited drug sensitivity, if given a drug to which he or she was sensitive, would improve to match that of an (in all other respects similar) patient with exploited sensitivity. The implications of this assumption are explored in the sensitivity analysis.

Examples of survival curves, generated from the regression model (Table 4), are shown in Figure 2. Survival for each group was calculated by adjusting baseline survival using the regression coefficients and underlying hazard function. Survival gains were estimated for 3.3 years following treatment, since this was the time span over which the underlying hazard function was calculable. No extrapolation of survival gains beyond this is included in the analysis.

The anticipated average gain in life expectancy was calculated to be 0.98 life-years for each male patient, aged 65 with stage A or B disease, currently not

Table 3. Univariate Cox Estimation of Survival Rates for Different Sensitivity Categories
Outcome = hazard of death
Dependent variable = survival from time of treatment
Censoring variable = vital status at analysis

Term	Coefficient	Std. error	*p*-Value	Hazard ratio[a]
Sens = 0	.695	.376	.065	2.004
Sens = 2	−1.229	.299	<.001	.293

[a] Hazard rate in other patient groups relative to the group with unexploited drug sensitivity (Sens = 1). See equation 1 for drug sensitivity categories.

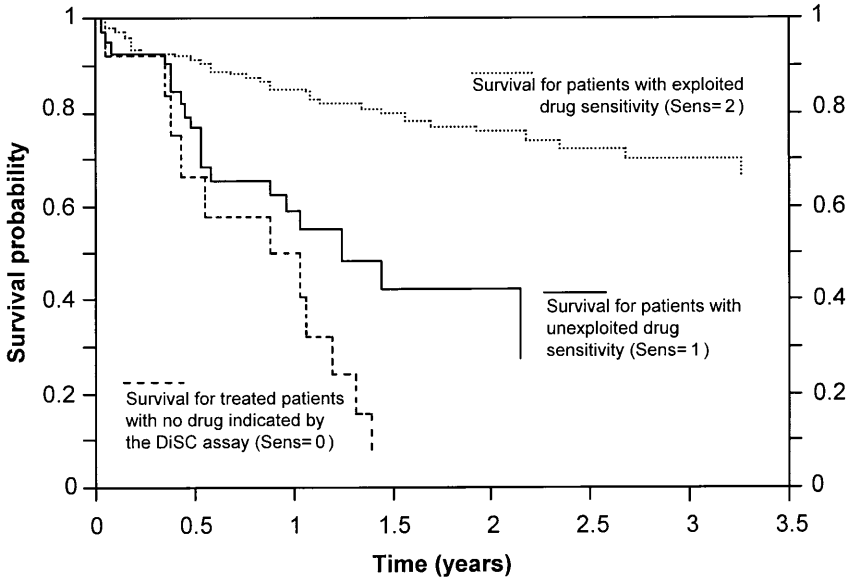

Figure 1. Patient survival (Kaplan-Meier) stratified by sensitivity to drugs. These survival curves are not adjusted for differences in prognostic variables between groups.

receiving a drug to which his cancer is sensitive (Figure 2). For a similar female patient, the average gain was 0.64 life-years. In this cohort, 35 of 124 male patients had unexploited drug sensitivity, and so the implied benefit is 0.28 life-years gained per DiSC assay for men (35/124 × 0.98]. Similarly, 6 of 54 women patients would be predicted to benefit, leading to 0.07 life-years gained per DiSC assay for women (6/54 × 0.64).

Survival gains implied by changing treatment using DiSC assay results were estimated for various patient age and disease categories (Table 5). Female patients derived less of an advantage than males because of their relatively more favorable baseline prognosis. Conversely, stage C patients benefit more than stage A or B patients of the same age because of greater scope for improvement in survival. The survival gains for all groups decrease with age.

Table 4. Multivariate Cox Estimation of Factors Influencing Survival Rate
Outcome = hazard of death
Dependent variable = survival from time of treatment
Censoring variable = vital status at analysis

Term	Coefficient	Std. error	*p*-Value	Hazard ratio	95% CI
Age[a]	0.013	0.024	.581	1.013	0.967–1.061
Gender = female	−0.656	0.337	.052	.519	0.268–1.005
Stage = C	0.541	0.276	.050	1.718	1.000–2.950
Sens = 0	0.785	0.453	.083	2.193	0.903–5.323
Sens = 2	−1.403	0.342	<.001	.246	0.126–0.481
Age65T.Sens = 0	0.057	0.051	.266	1.058	0.958–1.169
Age65T.Sens = 2	0.074	0.033	.027	1.077	1.008–1.150

Deviance = 521.2
Likelihood ratio statistic on 7 *df* = 58.0, $p < .001$

[a] Age = Age at start of treatment − 65.

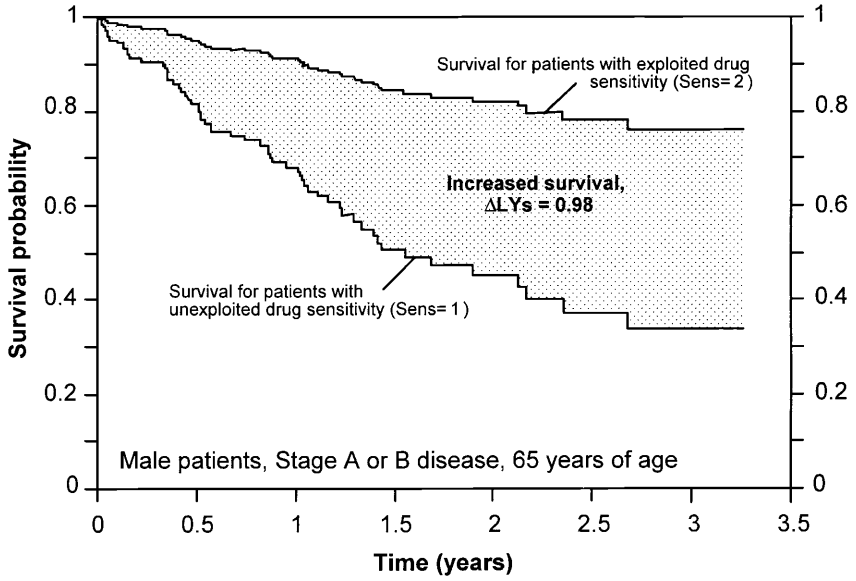

Figure 2. Survival for baseline male patients (from the proportional hazards regression model) showing improvement due to treatment with a sensitive drug. These survival curves, estimated from multivariate survival analysis, adjust for differences in stage and other known prognostic variables between groups.

Cost Analysis

The cost of a DiSC assay is currently £380 (1998 prices). Costs of administering various chemotherapies vary by more than a factor of 10 (2); however, no systematic relationship between cost and efficacy has been reported. Patients with unexploited drug sensitivity would, by definition, have a different therapy recommended as a result of the assay than the one given previously. It is not possible to estimate reliably in what combination a clinician would give this therapy to the patient, and so the assumption was made that the cost of treatment before and after the assay result would not change. This may be a conservative assumption since, for all patients with in vitro sensitivity, there will be instances where two drugs offer equivalent in vitro responses, but one is many times cheaper.

The survival expectation of patients without any in vitro drug sensitivity is very poor, even with treatment. It may be shown from future trials, using the DiSC assay, that such patients should not receive CLL-specific therapy. This would constitute a resource saving if the level of palliation remains unchanged.

Patients for whom therapy fails may proceed to another therapy. However, the therapies are immunologically harmful and induce resistance to other drugs (4;8). Failure to select a sensitive drug the first time around is likely to involve unnecessary treatment costs and may adversely influence outcomes. In addition, optimal therapy may also be expected to reduce the need for blood transfusions and other supportive treatment due to comorbidity.

Consideration of the probable changes in treatment costs suggests that the cost of the assay alone is a conservative estimate of the total change in costs. Although no adequate data are available to estimate savings in blood transfusions or optimization of therapy, the value of these could considerably offset the cost of the DiSC

Table 5. Estimates of Survival Gains and Cost-effectiveness for DiSC Assay Guided Treatment of CLL, Stratified by Gender and Stage of Disease

Sex	Stage	Age	Life-years (LYs) gained per benefiting patient (95% CI)		LYs gained per DiSC assay	C/LY gained per DiSC assay, r = 0	C/LY gained per DiSC assay, r = 0.05 (95% CI)	
M	A, B	50	1.286	(0.949–1.399)	0.363	1,050	1,150	(1,050–1,550)
M	A, B	70	0.798	(0.263–1.117)	0.225	1,690	1,850	(1,320–5,580)
M	C	50	1.703	(1.097–1.901)	0.481	790	860	(770–1,340)
M	C	70	0.962	(0.093–1.517)	0.272	1,400	1,520	(970–15,700)
F	A, B	50	0.809	(0.570–0.874)	0.090	4,230	4,640	(4,300–6,580)
F	A, B	70	0.533	(0.023–0.755)	0.059	6,410	7,040	(4,970–165,000)
F	C	50	1.196	(0.756–1.309)	0.133	2,860	3,140	(2,870–4,960)
F	C	70	0.752	(−0.177–1.137)	0.084	4,550	4,980	(3,300–∞)

Abbreviations: C/LY = Cost per life-year gained (£/LY), based on the cost of a DiSC assay of £380 (April 1998), and assuming no net change in other costs; r = discount rate applied to future benefits, 0% and 5% per annum shown.

assay. Finally, as the uptake of newer, more expensive drugs becomes routine, so the potential cost savings from careful selection of therapy could increase.

Cost per Life-year Gained

Estimates of cost-effectiveness ratios for DiSC assay assessment for men and women are shown in Table 5; these include confidence intervals derived from the survival estimates shown. The cost per life-year gained (C/LY) with DiSC assay guided treatment ranges from £790 for male patients aged 50 with stage C disease to £6,410 female patients aged 70 with stage A or B disease. The influence of discounting future benefits at 5% per annum is predictably small, since survival is truncated to 3.3 years; the range becomes £860 to £7,040 per life-year gained. The range of estimates for men and women are similar to, or below, many currently funded health service activities. Weighted by the study cohort's particular mix of age, sex, and stage of disease, the estimated average incremental cost-effectiveness of DiSC assay assessment was £1,470 per life-year gained (undiscounted).

Sensitivity Analysis

The estimates of cost-effectiveness presented are subject to uncertainty. With follow-up limited to only a few years, estimates of survival gains have been truncated, reflecting the estimated hazard function. This makes estimates of benefits conservative and, if the emerging survival pattern was extrapolated, then the cost-effectiveness ratios would become more attractive, assuming benefits were sustained, particularly in younger patients. For example, if it is assumed that the survival curves converge after 3.3 years at the rate at which they diverged, this would double the survival gains and potentially halve the undiscounted cost-effectiveness estimates.

The analysis assumes that intervention (tailoring therapy using the DiSC assay) will improve survival for those with unexploited sensitivity to the level achieved by those with exploited sensitivity. The analysis has controlled for important prognostic variables indicated in trials, but it is possible that there are other unmeasured systematic differences between these two groups. It may be, in fact, that only a proportion rather than all of the improvement in survival is achieved. Consequently, the reported cost-effectiveness ratios would rise accordingly.

The patient sample reflects the male, older age–oriented nature of CLL. However, the patient sample may not be representative of all patients with CLL: levels of remission and general drug sensitivity are higher than expected, particularly so in stage C patients. If other patient cohorts have, on average, a more limited response to therapy, then the choice of drug will become more critical and a higher proportion of patients may benefit from the DiSC assay, resulting in a proportionate decrease in the cost-effectiveness ratios generated. Similarly, if the net cost of DiSC assay assessment is less than the cost of the assay (due to reduced costs of drugs, management, and care), then the cost-effectiveness estimates will improve.

DISCUSSION

Analysis shows that the odds of remission among CLL patients is increased by about six times for patients with exploited drug sensitivity indicated by the DiSC assay, compared with those with unexploited sensitivity ($p \leqslant .001$). Two important inferences emerge from the survival analysis. First, patients whose drug sensitivity is exploited by receiving treatment with a drug indicated by the assay results have markedly better survival than those whose drug sensitivity is not exploited ($p \leqslant$

.001). Second, there is a notably poorer survival for those patients with no sensitivity to any drugs tested ($p = .044$).

This implies that it may be useful to perform DiSC assays to tailor treatment to ensure that patient drug sensitivity is exploited. In addition, when interpreting CLL patient survival data, it is important to be able to differentiate between patients with and without in vitro drug sensitivity, since these groups have different prognoses. This promotes interest in Schrek's hypothesis that there are essentially different kinds of CLL that require different treatment approaches (15;16).

The analysis did not find strong evidence to differentiate between patients with stage A and B disease. This may be partially due to the unexpected older age of stage A patients, because of patient selection (many stage A patients are not treated and hence could not be included in the analysis) and the length of available follow-up.

An attempt was made to control for the effects of known confounding factors by statistical adjustment, though in all observational studies some bias may remain due to undetected patient differences (13). However, the large odds ratios found are unlikely to be wholly explained by the effects of residual confounders. Based on this observational study, in vitro drug sensitivity appears to be an important explanatory variable relating to patient remission and survival. It is recommended that future CLL treatment trials include DiSC assay assessment as a prognostic variable and that oncologists consider the applicability of the findings of this study to other related disease areas. The available evidence suggests that the DiSC assay may be a cost-effective technology for improving patient outcomes and should be more widely evaluated. The data justify the investment in a well-designed randomized controlled trial to establish more reliably and precisely the benefits and costs of using the DiSC assay to tailor drug treatment for CLL.

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