RESEARCH COMMUNICATION

Myeloid Leukaemia Treatment and Survival - the South Australian experience, 1977 to 2002

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Abstract

Objective: To evaluate trends in survival and treatment for myeloid leukaemia in South Australia during 1977-2002, using population-based survival data plus data on survival and treatment of patients at three teaching hospitals. Methods: Population data were analysed using relative survival methods and hospital registry data using disease-specific survival. Univariate and multivariable analyses were undertaken. Multiple logistic regression analysis was used to investigate factors associated with first-line chemotherapy. Results: South Australia recorded 1,572 new cases of acute myeloid leukaemia (AML) in 1977-2002, together with 536 cases of chronic myeloid leukaemia (CML). Of these cases, 42.6% were recorded in teaching hospital registries. The five-year survival for AML at the teaching hospitals of 14.5% was similar to the corresponding 12.0% for South Australia as a whole. The five-year survival for CML at these hospitals was higher, however, at 48.1% compared with 37.5% for all South Australian cases. Younger patients had higher survivals, both for AML and CML. An increase in survival was evident for more recently diagnosed cases for both leukaemia types, after adjusting for age. This increase in survival was accompanied by an increase over time in the proportion of patients at teaching hospitals having a primary course of chemotherapy. Cytarabine in combination with other agents was the most common induction therapy for AML. While hydroxyurea was the most common first-line treatment of CML, there were changes in clinical policies towards higher-dose treatments, plus trials of new agents and combination therapies. Conclusions: Secular gains in survival have occurred from AML and CML in association with an increased use of chemotherapy.

Key Words: Myeloid leukaemia - survival - treatment - secular trends

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Introduction

Ionising radiation, alkylating agents, viruses, genetic factors, benzene and possibly other solvents may be causes of leukaemia, but these factors would account for only a small fraction of cases (Linet et al., 1996; Petridou et al., 2002; TCCSA, 2003). Because most cases occur for no apparent reason, treatment is the only line of defence.

Leading treatment centres generally have data systems to monitor practice and survival, with the aim of optimising quality of care and outcomes. In South Australia, the Royal Adelaide Hospital, Flinders Medical Centre, and Queen Elizabeth Hospital, which are the main teaching hospitals for adult cancer management, have hospital-based cancer registries for this purpose (SACR, 1994; SACR, 1995; SACR, 1996; SACR, 1997). These registries have access to data on their patients from the State's population-based registry, including socio-demographic descriptors and data on cancer site, histology, date of diagnosis, and where relevant, date and cause of death. They also obtain data on stage, other prognostic indicators, treatment and treatment outcomes from case notes, and where necessary from individual clinicians (SACR, 1997).

The Epidemiology Branch of the State Department of Health combines the data from these registries at four-yearly intervals (SACR, 2000). Combined data show the collective experience of hospitals served by these registries, which provides a frame of reference for individual hospitals to use when interpreting their own data. The hospitals covered by these registries are tertiary referral centres, where patients

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often present with advanced cancers and substantial co-morbidity (SACR, 2000). During 1977-1998, over 40% of myeloid leukaemia cases in South Australia were treated as inpatients of these hospitals (SACR, 2000).

South Australian five-year survivals for all leukaemia types collectively were 48% for males and 47% for females in 1987-1998, which were similar to the 49% for males and 46% for females reported by USA SEER centres for the 1992-1994 diagnostic period (SACR, 2000; Ries et al., 2002). These survivals were higher than the corresponding 39% for males and 38% for females reported by European registries for 1990-1994 (Coleman et al., 2003).

Population-based data point to increased survivals for leukaemia in the 1980s and 1990s in some countries, with USA SEER data showing gains in five-year survival from 39% in the 1980-82 diagnostic period to 48% in 1992-94 (Ries et al., 2002). Similar increases have been reported in Europe and Australia (Coleman et al., 2003; Berrino et al., 1995; SACR, 2000).

We investigate survival trends in this study for the more hazardous myeloid category. Relative survival trends are described for all South Australian cases diagnosed in 1977-2002. In addition, trends in survival and treatment are presented for patients recorded on teaching-hospital registries.

Subjects and Methods

The operations of State and hospital-based registries have been described previously (SACR, 1997; SACR, 2000). Hospital-based registries were established with approval of hospital ethics committees and operate with legislative authorisation and protection (SACR, 1994).

Data items included ICD-9 topographical codes during this study period, which excluded pre-leukaemic conditions subsequently interpreted as malignant in the ICD-0-3 classification system (WHO, 1977; Fritz et al., 2000). Other items included SNOMED histology codes, dates of diagnosis, dates and causes of death, and treatments provided during the primary course of care (SACR, 1996; SACR, 2000). These items were classified according to conventional international coding systems and the American Commission on Cancer Registry Operations and Data Standards (SACR, 2000; Hahn et al., 1998). The term chemotherapy refers in this study to all systemic treatments with chemotherapy agents, including agents like interferon and imatinib.

Where available, the French American British (FAB) staging system was used for acute leukaemia (DeVita et al., 2001) (Tobias et al., 1991). White cell and platelet counts, and haemoglobin levels also were available from some clinics. These measures were transformed into binary variables for this study, according to whether they were above or below the median.

In addition, the SEIFA index was derived from census data for postcodes of residence to indicate socio-economic status (ABS, 1998). Index scores were based on income levels, educational status, proportions of residents in skilled occupations, and related characteristics. They were derived by principal component analysis and grouped into four ordinal categories. In addition, place of residence was defined as metropolitan (the State capital of Adelaide) or a country region (SACR, 2000).

The State registry was linked electronically to State death records for data retrieval, whereas information on deaths occurring outside South Australia was obtained from interstate registries and the National Death Index at the Australian Institute of Health and Welfare (SACR, 2000). The extent of loss to follow-up in the first five years from diagnosis has been checked through active tracing and found to be small and to have little effect on calculated survival (Bonett et al., 1988). There is also prima facie evidence from comparisons with North American SEER data that post-diagnostic follow-up is close to complete beyond 10 years (SACR, 2000; Ries et al., 2002).

Relative survival methodology was employed to analyse population-based survival, using data from the State registry, with a date of censoring of live cases of December 31st, 2002 (Voutilainen et al., 2002; Hakulinen et al., 1985; Hakulinen et al., 1987; SAS, 2003). For hospital-based registry data, disease-specific survivals from leukaemia were calculated using Kaplan-Meier product-limit estimation, with the same censoring date (StataCorp, 2005). This method has been shown to give similar survival estimates to the relative-survival method in South Australian population-based studies. For example, the five-year survival from all cancers diagnosed in 1987-95 was estimated to be 55%, irrespective of whether the Kaplan-Meier or relative-survival method was used, with an approximate 1% difference in estimated survival applying between these methods for leukaemia (SACR, 1997). The Kaplan-Meier method is generally preferred for clinical studies, however, where patients' risks of death from competing causes are unlikely to equate with population norms.

Multiple proportional hazards regression was used to show differences in case fatality from AML and CML by person and tumour characteristic, and to indicate levels of statistical significance. Population-based analyses were of excess mortality (the multivariable counterpart of relative survival), whereas hospital analyses were of disease-specific mortality (the multivariable counterpart of the Kaplan-Meier method) (Hakulinen et al., 1985) (SAS, 1997) (StataCorp, 2005). In both instances, all variables were entered into the multivariable analyses, with backwards elimination when this did not reduce model fit ($p>0.050$). Assumptions underlying these tests, such as proportionality and an absence of co-linearity, were tested and found to have been satisfied.

In addition, exposure to a primary course of chemotherapy was compared by patient and tumour characteristic, using the Pearson chi-square or Mann-Whitney U test for univariate analyses, depending on whether characteristics were distributed on a binary or nominal scale, or in an ordinal manner (StataCorp, 2005). Logistic regression was used for multivariable analyses of associations of socio-demographic and tumour variables with

provision of a primary course of chemotherapy as the outcome variable (y/n), again using backwards elimination (StataCorp, 2005).

Because the data came from different hospitals, the presence of confounding and effect modification by hospital was investigated in the regression analyses. In addition, the presence of clustering was investigated using the robust variance estimator (StataCorp, 2005). Because no evidence of these effects presented, the models in this report are based on conventional (un-clustered) analyses that exclude interaction terms.

Results

Survival from acute myeloid leukaemia – population-based data

The State registry recorded 1,572 cases of AML for South Australia in the 1977-2002 diagnostic period. The percentage of patients surviving was 12.0% at five years from diagnosis, 10.3% at 10 years, and 9.4% at 15 years (Table 1). Age at diagnosis was predictive of survival (p<0.001), with five-year survivals reducing with age from 31.6% for patients less than 50 years of age to 3.2% for patients aged 80 years or more.

Diagnostic period also was predictive of outcome (p=0.058), with the five-year survival increasing from 7.0% for 1977-1986 to 11.0% for 1987-1994 and 17.5% for 1995-2002. A secular increase was particularly evident for patients under 50 years of age (p=0.002), where the five-year survival increased from 17.2% for 1977-1986 to 27.4% for 1987-1994 and 49.1% for 1995-2002. Sex was not a significant predictor of survival, nor was socio-economic status or place of residence at time of diagnosis in a metropolitan or country region (p>0.150).

Multiple proportional hazards regression confirmed that survival was higher for more recently diagnosed patients after adjusting for age (Table 2). Compared with 1977-1986, the relative risk (95% confidence limits) of case fatality decreased to 0.84 (0.72, 0.97) for 1987-1994 and 0.72 (0.62, 0.83) for the 1995-2002. In addition, age was predictive of outcome. Compared with patients less than 50 years of age, the relative risk increased with age to 3.50 (2.83, 4.33) for those aged 80 years or more. As in the univariate analyses, sex, socio-economic status, and place of residence in a metropolitan or country region were not predictive of outcome when retained in the multivariable model (p>0.150).

Survival from acute myeloid leukaemia – hospital-based data

Hospital registries recorded 670 AML cases in 1977-2002, comprising 42.6% of all South Australian cases. The five-year survival from AML was 14.5%, with survival reducing to 11.9% at 10 and 15 years (Table 1). Age at diagnosis was predictive of survival (p<0.001), with five-

Table 1. Case survival (+/- s.e.) by Age at Diagnosis and Diagnostic Year for Myeloid Leukaemia in South Australia*

	Period from diagnosis (years)							
Category	1	2	3	4	5	10	15	P value
Acute myeloid leukaemia								
Total SA (n=1572)	30.5%±1.2	19.0%±1.1	15.2%±1.0	12.7%±0.9	12.0%±0.9	10.3%±1.0	9.4%±1.1	
Hospital registries (n=670)	37.7%±1.9	22.8%±1.7	18.9%±1.6	15.7%±1.5	14.5%±1.5	11.9%±1.4	11.9%±1.4	
By age (years):								
Under 50 (n=168)	65.3%±3.7	45.3%±3.9	42.6%±3.9	34.2%±3.8	32.8%±3.8	29.0%±3.8	29.0%±3.8	
50-59 (n=99)	47.5%±5.1	33.4%±4.9	21.4%±4.4	20.0%±4.3	18.7%±4.2	13.0%±4.1	13.0%±4.1	
60-69 (n=183)	32.3%±3.6	12.8%±2.6	10.2%±2.4	9.0%±2.3	6.9%±2.0	6.2%±1.9	6.2%±1.9	p<0.001
70-79 (n=152)	16.3%±3.2	7.6%±2.4	6.6%±2.3	4.0%±2.0	4.0%±2.0	1.3%±1.3	__	
80+ (n=68)	10.0%±3.9	5.0%±2.8	1.7%±1.7	1.7%±1.7	1.7%±1.7	__	__	
By diagnostic period:								
1977-1986 (n=94)	31.9%±5.3	16.0%±4.2	14.7%±4.1	10.7%±3.6	9.4%±3.3	8.0%±3.1	8.0%±3.1	
1987-1994 (n=336)	37.2%±2.7	22.5%±2.4	17.9%±2.2	14.3%±2.0	13.3%±1.9	10.6%±1.8	10.6%±1.8	p=0.032
1995-2002 (n=240)	40.6%±3.2	25.4%±2.9	22.0%±2.9	20.1%±2.8	18.7%±2.8	__	__	
Chronic myeloid leukaemia								
Total SA (n=536)	76.3%±2.0	61.0%±2.3	52.0%±2.4	44.3%±2.5	37.5%±2.5	15.1%±2.3	10.7%±2.4	
Hospital registries (n=227)	88.6%±2.2	72.5%±3.1	62.1%±3.4	55.2%±3.5	48.1%±3.6	25.8%±3.6	20.2%±3.8	
By age (years.):								
Under 50 (n=83)	95.2%±2.4	78.1%±4.6	70.7%±5.0	68.0%±5.2	54.8%±5.8	32.9%±6.2	29.6%±6.4	
50-59 (n=56)	92.7%±3.5	83.6%±5.0	70.6%±6.2	59.2%±6.7	53.1%±6.9	26.3%±6.8	21.9%±6.9	
60-69 (n=33)	84.9%±6.2	63.6%±8.4	60.1%±8.6	53.0%±8.9	53.0%±8.9	24.8%±8.6	__	p<0.001
70-79 (n=37)	78.9%±7.1	55.3%±9.1	40.2%±9.2	34.4%±9.5	34.4%±9.5	11.5%±9.9	__	
80+ (n=18)	67.8%±12.0	58.1%±13.7	29.0%±13.7	__	__	__	__	
By diagnostic period:								
1977-1986 (n=51)	85.3%±5.1	69.8%±6.8	58.1%±7.4	53.5%±7.5	44.2%±7.5	15.7%±5.6	11.8%±5.4	
1987-1994 (n=98)	92.6%±2.7	71.1%±4.7	60.3%±5.1	52.5%±5.2	46.8%±5.2	27.0%±4.7	21.5%±4.7	p=0.039
1995-2002 (n=78)	85.6%±4.0	76.1%±4.9	67.2%±5.5	59.9%±6.0	53.1%±6.5	__	__	

* South Australian data analysed using relative survival and hospital-registry data using Kaplan-Meier product-limit estimation (see text). Date of censoring of live cases: December 31st 2002

Table 2. Relative Risk of Case fatality (95% CI) for Myeloid Leukaemia in South Australia*

	Acute myeloid leukaemia				Chronic myeloid leukaemia			
	No	South Australia	No	Hospital registries	No	South Australia	No	Hospital registries
Age at diagnosis (years):								
Under 50 (ref)	312	1.00	168	1.00	136	1.00	83	1.00
50-59	183	1.47 (1.19, 1.82)	99	1.49 (1.11, 1.99)	99	1.05 (0.71, 1.55)	56	1.29 (0.83, 2.01)
60-69	326	2.31 (1.92, 2.77)	183	2.33 (1.82, 2.98)	96	1.96 (1.39, 2.75)	33	1.54 (0.93, 2.54)
70-79	448	3.38 (2.83, 4.04)	152	3.72 (2.86, 4.83)	108	2.93 (2.11, 4.07)	37	2.74 (1.61, 4.66)
80+	303	3.50 (2.83, 4.33)	68	5.02 (3.64, 6.93)	97	2.29 (1.44, 3.66)	18	4.91 (2.47, 9.75)
Period of diagnosis (years):								
1977-86 (ref)	402	1.00	94	1.00	201	1.00	51	1.00
1987-94	491	0.84 (0.72, 0.97)	336	0.85 (0.65, 1.10)	150	0.62 (0.47, 0.83)	98	0.76 (0.50, 1.14)
1995-2002	679	0.72 (0.62, 0.83)	240	0.75 (0.57, 0.98)	185	0.45 (0.34, 0.62)	78	0.59 (0.37, 0.96)

* Proportional hazards regression analyses (see text). Date of censoring of live cases: December 31st 2002.

year survivals decreasing from 32.8% for patients less than 50 years to 1.7% for those aged 80 years or more.

Meanwhile, there was a secular increase in survival (p=0.032), with five-year survivals increasing from 9.4% for 1977-86 to 13.3% for 1987-94 and 18.7% for 1995-2002. While females were found to have a five-year case survival of 17.9%, which was higher than the 11.9% for males, the difference was not statistically significant (p=0.079). Similarly, there was no significant difference in survival by socio-economic status or place of residence in a metropolitan or country region (p>0.320).

For the subset of cases where FAB classification was recorded (n=399), this characteristic was predictive of survival (p=0.001), with M1 cases having a five-year survival of 2.7%, compared with 18.7% for M2, 50.1% for M3, 25.4% for M4, 20.8% for M6, and with no cases classified as M5 or M7 surviving to five years. Notably, no M0 cases (i.e., undifferentiated) survived beyond one year.

Multivariable proportional hazards regression analysis confirmed that older age was predictive of increased case fatality from AML (Table 2). Compared with patients less than 50 years of age, the relative risk increased with age to 5.02 (3.64, 6.93) for those aged 80 years or more. The model also showed secular improvements, in that compared with the 1977-1986 diagnostic period, the relative risk decreased progressively to 0.75 (0.57, 0.98) for 1995-2002.

Proportional hazards regression for the subset of cases where blood-test results were available (n=311) indicated that a higher than median white cell count was associated with an elevated relative risk (RR 1.78, p<0.001), whereas a higher than median platelet count was associated with a lower relative risk (RR 0.77, p=0.045). Meanwhile, older age remained predictive of poorer outcomes (p<0.001). After adjusting for white cell and platelet counts, and age at diagnosis, diagnostic period remained predictive of outcome, with a relative risk for 1995-2002 compared with earlier years of 0.74 (p=0.032). When FAB status was retained in this model with M0 as the reference category, M1, M2, M3, M4 and M6 were predictive of higher survival, whereas M7 was predictive of poorer survival. The respective relative risks were 0.60 for M1 (p=0.011), 0.46 for M2 (p<0.001), 0.26 for M3 (p=0.001), 0.39 for M4 (p<0.001), 0.45 for M6 (p=0.042), and 2.64 for M7 (p=0.045). The case-fatality risk for M5 was lower than for the M0 reference category, although not to a statistically significant extent (RR 0.79, p=0.478).

Table 3. Percentage of Myeloid Leukaemia Cases Receiving Chemotherapy as Primary Treatment*

	Acute		Chronic	
	No.	Chemotherapy	No.	Chemotherapy
All	670	74.2%	227	89.4%
Age at diagnosis:				
<50	168	92.3%	83	95.2%
50-59	99	90.9%	56	94.6%
60-69	183	78.1%	33	90.9%
70-79	152	58.6%	37	83.8%
80+	68	29.4%	18	55.6%
p value		<0.001		<0.001
Diagnostic period:				
1977-86	94	57.5%	51	78.4%
1987-94	336	70.5%	98	89.8%
1995-02	240	85.8%	78	96.2%
p value		<0.001		0.006

*Data source: South Australian Hospital Registries

Survival from chronic myeloid leukaemia – population-based data

The State registry recorded 536 CML cases for South Australia in 1977-2002. The five-year relative survival was 37.5%, compared with 15.1% at 10 years and 10.7% at 15 years (Table 1). Age at diagnosis was predictive of outcome (p<0.001), with the five-year survival decreasing with age from 48.4% for patients less than 50 years to 21.0% for 70-79 year olds and 21.5% for those aged 80 years or more.

Diagnostic period was also predictive (p=0.006), with five-year survivals increasing from 30.1% for 1977-1986 to 38.1% for 1987-1994 and 48.0% for 1995-2002. Gains were particularly evident among 70-79 year olds (p=0.014), where the five-year survival increased from 14.0% for 1977-1986 and 13.7% for 1987-1994 to 48.0% for 1995-2002. By comparison, sex was not a significant predictor of survival,

nor was socio-economic status or place of residence in a metropolitan or country region (p>0.400).

Multivariable proportional hazards regression confirmed the association of age at diagnosis and diagnostic period with outcomes (Table 2). Compared with patients less than 50 years of age, the relative risk of case fatality increased with age to 2.93 (2.11, 4.07) for 70-79 year olds, and 2.29 (1.44, 3.66) for those aged 80 years or more. Also, compared with 1977-1986, the relative risk decreased to 0.62 (0.47, 0.83) for 1987-1994 and 0.45 (0.34, 0.62) for 1995-2002. By comparison, neither sex, place of residence in a metropolitan or country region, or socio-economic status was predictive of outcome (p>0.400).

Survival from chronic myeloid leukaemia - hospital-based data

Hospital registries recorded 227 CML cases for 1977-2002, comprising 42.4% of all CML cases in South Australia. The five-year survival was 48.1%, compared with 25.8% at 10 years and 20.2% at 15 years (Table 1). Age at diagnosis was predictive of outcome (p<0.001), with the five-year survival decreasing with age from 54.8% for patients less than 50 years to 34.4% for 70-79 years, and with lower survivals indicated for cases aged 80 years or more.

Secular increases in survival took place (p=0.039), with the five-year survival increasing from 44.2% for 1977-86 to 53.1% for 1995-2002. While five-year survival was higher at 52.0% for males than the corresponding 43.2% for females, the difference was not statistically significant (p>0.200). Similarly, there was not a significant difference by socio-economic status or place of residence in a metropolitan or country region (p>0.900).

Multivariable proportional hazards regression analysis confirmed that age at diagnosis and diagnostic period were predictive of outcome (Table 2). Compared with cases less than 70 years, the relative risk of case fatality was 2.74 (1.61, 4.66) for 70-79 year olds, and 4.91 (2.47, 9.75) for older patients. After adjusting for age, case fatality was lower for 1995-2002 than for 1977-86, with a relative risk of 0.59 (0.37, 0.96). For the sub-set of cases where haemoglobin levels were recorded (n=97), the regression model indicated that a higher than median haemoglobin level was predictive of a lower case fatality (RR=0.42, p=0.008), when adjusting for age and period of diagnosis. By comparison, white cell and platelet counts were not predictive of outcome (p>0.200).

Table 4. Relative Odds (95% CI) of Receiving Chemotherapy as Primary Treatment for Myeloid Leukaemia*

	No.	Acute cases	No.	Chronic cases
Age at diagnosis:				
Under 50 yrs	168	1.00	83	1.00
50-59 yrs	99	0.90 (0.36-2.23)	56	0.70 (0.14-3.38)
60-69 yrs	183	0.33 (0.17-0.65)	33	0.49 (0.10-2.39)
70-79 yrs	152	0.11 (0.05-0.21)	37	0.25 (0.07-0.99)
80+ yrs	68	0.03 (0.01-0.07)	18	0.04 (0.01-0.19)
Diagnostic period:				
1977-1986	94	1.00	51	1.00
1987-1994	336	2.05 (1.19-3.53)	98	2.08 (0.73-5.96)
1995-2002	240	6.48 (3.43-12.24)	78	9.63 (2.16-42.96)

*Data source: South Australian Hospital Registries

Primary Treatment of Myeloid Leukaemia – Hospital-based data

Acute Cases

Of AML cases, 74.2% had a primary course of chemotherapy and 4.2% had radiotherapy (Table 3). The proportion receiving chemotherapy reduced with age (p<0.001) from 92.3% for patients less than 50 years to 29.4% for those aged 80 years or more. In addition, there was a secular increase in proportion receiving chemotherapy from 57.5% in 1977-1986 to 70.5% for 1987-1994 and 85.8% for 1995-2002 (p<0.001). By comparison, there was no significant difference by sex, socio-economic status, or place of residence in a metropolitan or country region (p>0.050).

Multiple logistic regression analysis confirmed that likelihood of chemotherapy reduced with age at diagnosis and was higher for more recent diagnostic periods (Table 4). No other variables were found to be predictive of this treatment when retained in the model (p>0.200). Cytarabine was the most common initial treatment, applying to 80.0% of all chemotherapy patients. There was a secular increase in dose and in frequency of use of this drug in combination with other agents.

Chronic Cases

Of CML cases, 89.4% had a primary course of chemotherapy and 4.0% had radiotherapy (Table 3). Exposure to chemotherapy was more common in younger patients (p<0.001), with the proportion so treated being 95.2% among patients under 50 years, reducing to 55.6% for those aged 80 years or more.

Meanwhile, there was a secular increase in the proportion receiving chemotherapy from 78.4% in 1977-1986 to 89.8% for 1987-1994 and 96.2% for 1995-2002 (p=0.006). By comparison, differences in exposure to chemotherapy were not observed by sex, socio-economic status, or residence in a metropolitan or country region (p>0.150).

Multiple logistic regression analysis confirmed that likelihood of chemotherapy reduced with age at diagnosis and was higher for the more recent diagnostic periods (Table 4). No other variables were predictive of this treatment. The most common chemotherapy drug of choice was hydroxyurea, which was administered to more than half of chemotherapy patients during this period. Oral hydroxyurea remains the most common initial therapy of recent cases, with interferon and imatinib being used selectively and in follow-up treatments.

Discussion

The incidence of leukaemia is relatively high in South

Australia by international standards, with 3.4% of all notified cancers falling into this category in 1977-2002 (SACR, 2005). Age-standardised incidence rates show no evidence of a decline since the State cancer registry commenced operations in 1977 (TCCSA, 2003). It is particularly important in this regard that treatment is of a high standard and outcomes are optimised. In general, survival outcomes for leukaemia have been similar in South Australia to those for USA SEER centres (Ries et al., 2002).

The population-based five-year survival for South Australian AML patients was 12.0% during 1977-2002, which was similar to the 14.5% for patients at teaching hospitals. Meanwhile the corresponding population-based survival was 37.5% for CML, compared with a higher figure of 48.1% for patients at teaching hospitals.

More recently diagnosed patients showed higher survivals, both for AML and CML. Secular gains persisted after adjusting for age. Regression analysis revealed an increased exposure to primary courses of chemotherapy after adjusting for age, which may have contributed to these gains. In addition, a policy shift towards higher doses and more common use of combination agents was evident.

A combination of cytarabine and daunorubicin, in association with 6-thioguanine or etoposide, was the most common chemotherapy for AML. More recently, idarubicin has been used instead of daunorubicin, possibly because it is considered to produce more sustained remissions (DeVita et al., 2001). Numerous trials are underway to assess the efficacy of alternative regimens, including the concurrent use of mitoxantrone and cytarabine (De Vita et al., 2001). Oral hydroxyurea remains the most common initial therapy for CML, with interferon alpha and imatinib being used at particular stages and in subsequent treatments. The increased use of high-dose chemotherapy in the initial treatment of myeloid leukaemia has been associated with increasing and more successful implementation of bone-marrow transplantation (De Vita et al., 2001).

Case survivals from AML and CML were observed to decrease with age, both at a population level and for cases treated at the teaching hospitals. This trend is consistent with findings for other cancers in South Australia (SACR, 2000). Older patients are more likely to have significant co-morbidity, which may compromise the doses of chemotherapy provided. Our data indicated that older patients were less likely than younger patients to have received chemotherapy, both for AML and CML.

Age has been construed as a progressive loss of stress tolerance, due to a decline in functional reserve of multiple organ systems, a high prevalence of co-morbid conditions, limited socio-economic support, and a higher prevalence of psychological problems (Balducci et al., 2000). Effects of aging are highly individualised, however, and actual age may not reflect the functional reserve available to tolerate cytotoxic therapies. Each case should therefore be assessed on an individual basis.

Changes associated with aging include decreased renal function, and increased susceptibility to mucositis, cardio toxicity and neurotoxicity. Such changes require that chemotherapy regimens be optimally tailored to impact on the leukaemia, while minimising undesirable consequences such as neutropenia, thrombocytopenia, anaemia, enterocolitis, cardio depression, peripheral neuropathy and brain dysfunction (Balducci et al., 2000). Comparative studies show that chemotherapy-related toxicity is similar in older and younger patients, with the exception of increased cardio toxicity and possibly haematological toxicity in the elderly (Kimmick et al., 1997).

The absences of differences in survival by socio-economic status, or by place of residence in a metropolitan or country region, are interpreted as a favourable finding of this study, suggesting an equitable access to treatment services in South Australia.

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References

Australian Bureau of Statistics (ABS) (1998). 1996 census of population and housing. Socio-economic indexes for areas. Canberra: Australian Bureau of Statistics.

Balducci L, Extermann M (2000). Management of cancer in the older person: a practical approach. *The Oncologist*, **5**, 224-37.

Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T, Esteve J (eds) (1995). Survival of cancer patients in Europe. The Eurocare Study. IARC Scientific Publications No. 132. Lyon: International Agency for Research on Cancer.

Bonett A, Roder D, Esterman A (1988). Cancer case survival rates for South Australia: a comparison with US rates and a preliminary investigation of time trends. *Med J Aust*, **148**, 556-9.

Coleman MP, Gatta G, Verdecchia A, Esteve J, Sant M, Storm H, Allemani C, Ciccolallo L, Santaquilani M, Berrino F, EUROCARE Working Group (2003). EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. *Annals Oncol*, **14**, 128-49.

DeVita VT, Hellman S, Rosenburg SA (eds) (2001). Cancer: principles and practice of oncology. 6th Edition. Philadelphia: Lippincott, Williams and Wilkins.

Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S (eds) (2000). International Classification of Diseases for Oncology. 3rd Edition. Geneva: World Health Organization.

Hahn Johnson C, Richards L (eds) (1998). Standards of the Commission on Cancer. Volume 2. Registry operations and data standards (ROADS). Chicago: Commission on Cancer.

Hakulinen T, Abeywickrama KH (1985). A computer program for relative survival analysis. *Comp Progr Biomed*, **19**, 197-207.

Hakulinen T, Tenkanen L (1987). Regression analysis of relative survival rates. *Appl Statist*, **36**, 309-17.

Kimmick CG, Flemming R, Muss HB, Balducci L (1997). Cancer chemotherapy in older adults. A tolerability perspective. *Drugs Aging*, **10**, 34-49.

Linet MS, Cartwright RA. The leukemias. In: Schottenfeld D, Fraumeni JF (eds) (1996). Cancer Epidemiology and Prevention. Second edition. New York: Oxford University Press, pp 841-92.

Petridou E, Trichopoulos D. Leukemias. In: Adami H-O, Hunter D, Trichopoulos D (eds) (2002). Textbook of Cancer Epidemiology. Oxford: Oxford University Press, pages 556-72.

Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Mariotto A, Feuer EJ, Edwards BK (eds) (2002). SEER Cancer Statistics Review, 1973-1999. Bethesda, MD: National Cancer Institute.

SAS Institute Inc. (2003). SAS-STAT Software: Changes and releases through Release 9.1. Cary, NC: SAS Institute.

South Australian Cancer Registry (SACR) (1995). Epidemiology of cancer in South Australia. Incidence, mortality and survival, 1977 to 1994. Incidence and mortality, 1994. Adelaide: Lutheran Press.

South Australian Cancer Registry (SACR) (1996). Epidemiology of cancer in South Australia. Incidence, mortality and survival, 1977 to 1995. Incidence and mortality, 1995. Adelaide: Lutheran Press.

South Australian Cancer Registry (SACR) (1997). Epidemiology of cancer in South Australia. Incidence, mortality and survival, 1977 to 1996. Incidence and mortality 1996. Adelaide: Openbook Publishers.

South Australian Cancer Registry (SACR) (2000). Epidemiology of cancer in South Australia. Incidence, mortality and survival, 1977 to 1999. Incidence and mortality, 1999. Adelaide: Openbook Publishers.

South Australian Cancer Registry (SACR) (2005). Cancer in South Australia 2002 with projections to 2005. Adelaide: Department of Health.

South Australian Cancer Registry (SACR) (1994). South Australian hospital-based cancer registry network. Adelaide: South Australian Health Commission.

StataCorp (2005). Stata Statistical Software: Release 9.0. College Station, Texas: StataCorp.

The Cancer Council South Australia (TCCSA), Centre for Cancer Control Research (2003). Lymphomas, myelomas and leukaemias. Monograph No. 5. Adelaide: TCCSA, pp 15-9.

Tobias JS, Williams CJ (1991). Cancer: a color atlas. Philidelphia: Lippincott, pages 170-84.

Voutilainen ET, Dickman PW, Hakulinen T (2002). SURV-3: Relative Survival Analysis Program, version 3.01. Helsinki: Finnish Cancer Registry.

World Health Organization (WHO) (1977). Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death (based on recommendations of the Ninth Revision Conference, 1975). Geneva: World Health Organization.