行政院國家科學委員會補助專題研究計畫成果報告

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成人急性骨髓性白血病長期存活患者之「調整品質後存活時間」分析

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Introduction

Quality of life (QOL) has been increasingly recognized as an important endpoint in the evaluation of efficacy of cancer therapy. It is especially informative when alternative treatment options are available and when a trade-off between survival benefit and treatment-related toxicity needs to be considered. Incorporation of QOL assessment into clinical decision making will thus take into accounts both the quality and quantity of survival.

We have developed a novel approach to quantifying the impact of QOL by direct integration of the patient cohort's survival function with the QOL function, the latter can be estimated by a cross-sectional survey of the surviving patients in the cohort.[1] Since most QOL questionnaires have a multi-dimensional construct, the integration of the psychometric scores from different dimensions with the survival function will generate a survival-weighted 'health profile' of the patient cohort. Furthermore, the calculation of the survival-weighted psychometric scores (SWPS) can be extrapolated beyond the follow-up limit of the patient cohort to produce life-long estimation of QOL changes.[2]

The Survival-weighted Health Profile for Long-term Survivors of Acute Myelogenous Leukemia (AML)

High-dose chemotherapy plus allogeneic bone marrow transplantation (BMT) has an established role in the treatment of AML. For AML patients who have achieved complete remission after induction chemotherapy, BMT is often recommended as consolidation treatment for young patients who have a human leukocyte antigen-compatible sibling donor because BMT will produce a lower rate of disease relapse and longer disease-free survival.[3,4] However, many studies indicated that BMT patients may suffer from prolonged physical as well as psychosocial problems. Therefore, the choice between different treatment strategies will depend on both the potential survival benefit and the patients' long-term subjective QOL assessment.

In the first part of this study we sought to construct a 'health profile' for long-term survivors of AML by using the survival-weighted psychometric scores (SWPS). The study cohort included all patients who had been diagnosed and treated in National Taiwan University Hospital from 1985 to 1999 and achieved complete remission after standard chemotherapy (n=259). At the time of this study, 134 patients had died during follow-up. One hundred and four of the 125 surviving patients agreed to be interviewed to estimate the QOL function of the cohort. Forty-one patients underwent BMT as consolidation or salvage therapy; 63 received chemotherapy alone. Two QOL questionnaires were used: the European Organization for the Research and Treatment of Cancer (EORTC)-QLQ-C30 questionnaire and the brief form of World Health Organization quality of life questionnaire (WHOQOL-BREF). The clinical characteristics of the interviewed patients were summarized in Table 1.

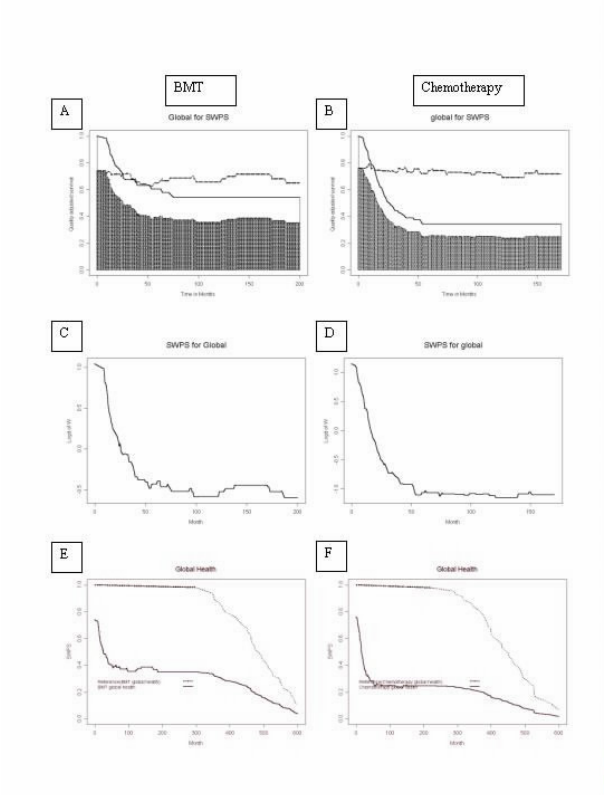
Table 1. Clinical characteristics of the AML patients

	BMT group (n= 41)	Chemotherapy group (n= 63)	
		Age ≤ 50 years (n=45)	All patients (n=63)
Male/female	22/19	18/27	28/35
Age at diagnosis (years)(median/range)	28.8/ 15.1-42.1*	33.3/ 16.9-49.8*	41.1 / 16.9- 65.9
Age at interview (years)(median/range)	34.3 / 20- 51.4**	39.2/ 19.8-58.4**	45.9 / 19.8- 69.6
Disease status at interview			
First CR	29	31	42
Second/third CR	12	12	19
Second relapse	0	2	2
Time from last chemotherapy to interview			
≤ 2 year	11	18	25
> 2 years	30	27	38
Education			
Elementary School	1	1	8
High school	11	22	30
College/university and up	29	22	25
Employment at the time of interview			
Paying job/ self-employed/ studying	33	32	38
Working at home/ unemployed	8	13	25
Personal income (NT dollar #/month)			
< 10,000	11	13	25
10000- 29999	10	9	12
30000-59999	11	16	19
≥ 60000	9	7	7

The mean scores of EORTC-QLQ-C30 and WHOQOL-BREF did not differ significantly between patients who received BMT or those who received chemotherapy only (p>0.01). SWPS for every functioning domain and symptom item was obtained by direct integration of the mean QOL function with the survival function of the cohort:

$$\mathrm{E(SWPS)} = \int_0^{\infty} E[q(t)]\, S(t)\, dt$$

A Monte Carlo method was used to extrapolate the life-long SWPS beyond the follow-up limit. In the following figures the estimation and extrapolation of SWPS were shown, using QOL results from the global health domain of EORTC-QLQ-C30 in the calculation.



(A) and (B) represent the survival function curve (solid lines) and the quality-of-life function curve (dashed lines) for patients who received BMT or chemotherapy alone. The hatched area under the curves represents the cumulated SWPS. (C) and (D) represent the logit of W curve over time for the two groups of patients. W represents the ratio of SWPS between the study cohort and the reference population (W= $SWPS_{\mathrm{study}}(t)$ / $SWPS_{\mathrm{ref}}(t)$) . (E) and (F)represent extrapolation of SWPS curves beyond the follow-up limit. The upper curves in the two graphs represent SWPS curves of the reference population, which equal to the overall survival curve because the QOL value was set to be 1 (normal health). The lower curves represent the SWPS curves of the study cohort.

The mean SWPS and the life-long extrapolation of SWPS were summarized in Table 2.

Table 2. Mean and extrapolated SWPS for AML patients

	Mean SWPS (mean± SE)			Projected Life-long SWPS (mean±SE)		
	BMT	Chemo-therapy*	p value	BMT	Chemo-therapy*	p value
EORTC-QLQ-C30						
Global health	83.1 ± 9.8	52.0 ± 6.4	0.005	183.2 ± 28.7	121.2 ± 18.9	0.04
Functional scales						
Physical	103.9 ± 10.2	60.4 ± 6.4	< 0.001	237.3 ± 30.0	147.3 ± 19.1	0.006
Emotional	96.3 ± 10.6	55.4 ± 4.9	< 0.001	213.8 ± 30.4	125.4 ± 13.9	0.004
Cognitive	89.7 ± 8.7	55.4 ± 6.4	< 0.001	191.9 ± 24.4	127.6 ± 18.4	0.02
Role	105.9 ± 10.6	62.7 ± 7	< 0.001	248.1 ± 30.5	156.4 ± 21.1	0.007
Social	102.1 ± 10.6	53.0 ± 5.9	< 0.001	238.6 ± 30.0	132.1 ± 18.2	0.002
Symptom scales						
Fatigue	86.7 ± 9.1	49.1 ± 5.4	< 0.001	197.3 ± 27.2	113.7 ± 17.3	0.003
Pain	105.2 ± 10.3	59.1 ± 5.9	< 0.001	241.3 ± 27.9	141.3 ± 18.0	0.002
Nausea/ vomiting	114.4 ± 12.1	64.8 ± 7.1	< 0.001	261.8 ± 32.4	155.8 ± 21.1	0.002
Symptom items						
Appetite loss	104.6 ± 12.5	60.7 ± 7.0	0.001	246.7 ± 35.8	147.3 ± 20.8	0.01
Constipation	113.3 ± 11.5	63.7 ± 7.4	< 0.001	261.1 ± 32.6	154.0 ± 21.7	0.002
Diarrhea	96.3 ± 11.1	60.8 ± 6.6	0.003	221.2 ± 29.6	151.1 ± 20.0	0.02
Dyspnea	99.9 ± 11.0	63.2 ± 6.1	0.002	224.7 ± 30.6	152.8 ± 18.0	0.02
Financial difficulty	106.5 ± 10.8	54.3 ± 6.6	< 0.001	242.7 ± 32.4	134.2 ± 18.6	0.003
Insomnia	89.5 ± 9.1	50.1 ± 5.7	< 0.001	208.6 ± 26.9	121.0 ± 19.6	0.002
WHOQOL-BREF						
Domain 1 (physical)	80.5 ± 8.9	46.4 ± 4.6	< 0.001	185.7 ± 26.0	111.1 ± 13.7	0.007
Domain 2 (psychological)	77.9 ± 9.0	44.8 ± 4.0	< 0.001	171.8 ± 28.3	103.2 ± 11.5	0.01
Domain 3 (social)	74.2 ± 7.8	47.5 ± 4.7	0.002	164.2 ± 24.3	119.1 ± 13.9	0.06
Domain 4 (environmental)	80.5 ± 9.2	46.5 ± 5.4	< 0.001	176.4 ± 26.4	112.5 ± 15.4	0.02

Patients who received BMT had significantly (p<0.01) better SWPS in all of the functioning domains and symptom items

of EORTC-QLQ-C30 and all four domains of WHOQOL-BREF. However, when the life-long extrapolation of SWPS was made, these differences diminished in global health and several symptom items of EORTC-QLQ-C30 as well as in the social and environmental domains of WHOQOL-BREF. Patients' perspective on QOL may be domain-specific and may evolve over time.

The above results indicate that SWPS may be useful to evaluate the efficacy of different treatment strategies for AML. Confirmation of the relative merit of bone marrow transplantation vs. chemotherapy alone from prospective studies is needed. *(Accepted for publication in Quality of Life Research)*

The Survival-weighted Health Profile for Patients with Hematological Malignancies: Comparison Between Patients who Underwent BMT vs. Peripheral Blood Stem Cell Transplantation (PBSCT)

The relative merits of BMT vs. PBSCT in patients with hematological malignancies remain undetermined.[5] The advantages of PBSCT include faster engraftment after transplantation, lower hospital stay and medical cost, and convenience for the donors.[6,7] On the other hand, the larger number of donor lymphocytes in peripheral blood stem cells seems to be a two-edge sword. It may induce greater graft-versus-leukemia effect and result in lower relapse rate and longer survival.[8,9] It may also increase the risk of graft-versus-host disease (GVHD) and thus increase the long-term morbidity of the patients.[10,11] A meta-analysis of 16 studies comparing BMT and PBSCT indicates that PBSCT is associated with higher incidence of both acute and chronic GVHD. The relapse rate may be lower for PBSCT but the long-term overall survival appears similar.[12] Therefore, to determine the relative merits of BMT vs. PBSCT, the long-term treatment-related morbidity and the patients' quality of life (QOL) must be taken into account.

In the second part of this study we use the SWPS approach to compare the long-term QOL between patients with hematological malignancies who underwent BMT or PBSCT. The study cohort consisted of 120 patients with hematological malignancies and underwent hematopoietic stem cell transplantation in National Taiwan University Hospital (74 BMT, 46 PBSCT). The 85 surviving patients agreed to be interviewed by using EORTC-QLQ-C30 and WHOQOL-BREF questionnaires to estimate the QOL function. SWPS for every functioning domain and symptom item was calculated by direct integration of the mean QOL function with the survival function of the cohort. Estimation of SWPS was extrapolated by 5 years beyond the follow-up limit by a Monte Carlo method as described above. The clinical characteristics of the interviewed patients were summarized in Table 3.

Table 3. Clinical characteristics of the interviewed patients

	BMT group (n= 52)	PBSCT group (n= 33)	P value
Male/female	24/28	21/12	0.12
Age at diagnosis (years)(median/range)	29.8/ 12.6-44.5	30.5/ 16.5-52.4	0.15
Age at transplantation (years)(median/range)	30.4/ 13.1-45.1	31.8/ 17.6-53.1	0.15
Age at interview (years)(median/range)	31.4 / 13.3-48.6	32.9/ 17.7-53.4	0.13
Diagnosis of underlying diseases			0.53
AML	20	15	
ALL	9	3	
CML	17	10	
Lymphoma	5	2	
MDS	1	2	
Myeloma	0	1	
Time from last chemotherapy to interview (months)(median/range)	15.0/ 1.2-59.6	25.8/ 1-48.8	0.49
cGVHD at interview*			< 0.001
Absent	28	5	
Present	11	17	
Education			0.29
Elementary School	8	8	
High school	18	14	
College and up	26	11	
Employment at the time of interview			0.59
Paying job/ self-employed/ studying	33	21	
Working at home/ unemployed	19	12	
Personal income (NT dollar #/month)			0.34
< 10,000	29	19	
10000- 29999	10	3	
30000-59999	11	7	
≥ 60000	2	4	

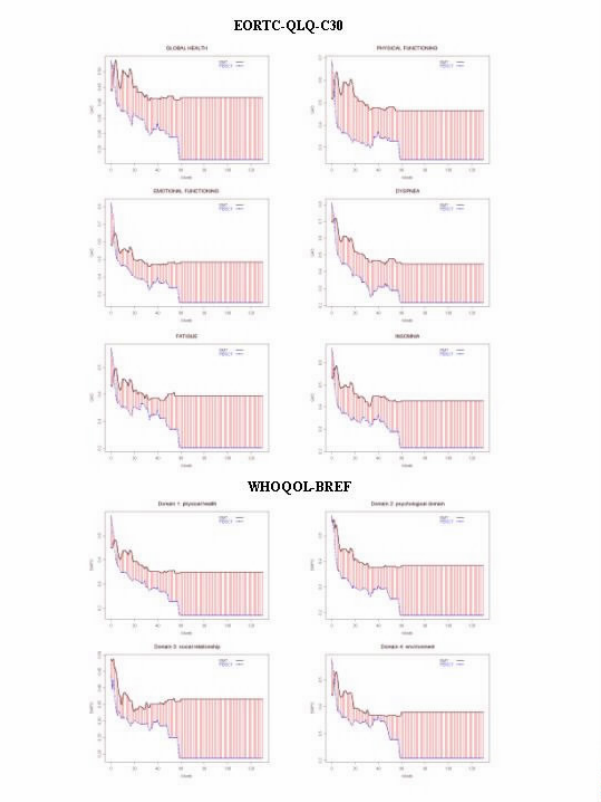
* Only patients surviving more than 100 days after transplantation were included.

The 5-year overall survival rate was similar between patients who received BMT or PBSCT (56.6% vs. 34.7%, p=0.36). The mean and extrapolated SWPS for patients who received BMT or PBSCT were summarized in Table 4. Patients who underwent BMT had significantly better SWPS in global health and most of the functioning domains of EORTC-QLQ-C30 and the psychological domain of WHOQOL-BREF. The differences persisted when estimation of SWPS was extrapolated by 5 years.

Table 4. SWPS between patients who underwent BMT and PBSCT

	Mean SWPS (± SE)			Projected SWPS (± SE)		
	BMT	PBSCT	p value	BMT	PBSCT	p value
EORTC-QLQ-C30						
Global health	30.6 ± 3.2	22.4 ± 3.1	0.02	55.5 ± 7.0	35.4 ± 7.5	0.02
Functional scales						
Physical	35.4 ± 3.2	25.6 ± 3.6	0.02	63.1 ± 6.6	40.2 ± 8.6	0.01
Emotional	35.3 ± 3.3	26.9 ± 3.7	0.04	64.3 ± 6.8	42.1 ± 8.4	0.02
Cognitive	34.3 ± 3.2	27.6 ± 3.7	0.07	62.0 ± 6.6	41.4 ± 8.5	0.03
Role	33.0 ± 3.2	23.2 ± 3.5	0.02	57.2 ±7.5	37.5 ± 8.4	0.05
Social	33.3 ± 3.4	23.5 ± 3.3	0.02	60.5 ± 7.7	38.2 ± 9.2	0.03
Symptom scales						
Fatigue	28.6 ± 3.0	22.1 ± 3.5	0.08	52.3 ± 6.4	34.2 ± 7.3	0.04
Pain	36.0 ± 3.4	27.9 ± 4.0	0.06	65.8 ± 7.8	44.9 ± 8.7	0.03
Nausea/ vomiting	39.7 ± 3.6	29.5 ± 4.4	0.04	71.6 ±7.2	46.9 ± 10.6	0.03
Symptom items						
Appetite loss	34.4 ± 3.4	26.2 ± 4.2	0.07	62.1 ± 7.5	40.9 ± 10.0	0.05
Constipation	41.5 ± 3.6	33.6 ± 4.4	0.10	75.4 ± 7.8	53.6 ± 11.3	0.06
Diarrhea	37.6 ± 3.4	32.2 ± 4.5	0.15	68.5 ± 7.1	49.5 ± 10.5	0.06
Dyspnea	35.8 ± 3.4	24.3 ± 3.8	0.02	62.6 ± 7.5	37.3 ± 8.9	0.01
Financial difficulty	33.3 ± 3.2	25.7 ± 3.4	0.07	60.1 ± 7.2	41.3 ± 8.3	0.04
Insomnia	32.0 ± 3.2	23.0 ± 3.8	0.03	57.7 ± 6.3	36.0 ± 8.4	0.02
WHOQOL-BREF						
Domain 1 (physical)	26.8±2.8	20.0±2.6	0.04	47.4±5.9	30.2±6.7	0.03
Domain 2 (psychological)	28.5±2.5	20.2±3.0	0.01	51.5±5.2	31.6±7.1	0.01
Domain 3 (social)	25.7±2.8	19.4±2.7	0.05	47.6±6.3	30.6±6.8	0.03
Domain 4 (environmental)	27.9±2.7	22.7±3.1	0.11	50.7±5.6	35.2±7.7	0.06

Comparison of extrapolated SWPS in selected EORTC-QLQ-C30 and WHOQOL-BREF items was shown graphically in the following figure. The hatched area denoted the difference of E(SWPS) between patients who underwent BMT or PBSCT.



The above data suggest that for patients with hematological malignancies, those who received PBSCT may have worse QOL than those who received BMT. *(Accepted for presentation in the Annual Meeting of the American Society of Hematology 2002 in Philadelphia)*

Future Research: Problems and Prospects

The SWPS approach has several clinically useful features. First, the QOL data can be obtained by interview with the surviving patients in the study cohort. The estimated QOL function thus reflects what the patients did experience when they received the specific treatment. Second, the QOL function obtained by multi-dimensional questionnaires may detect the change of different QOL facets that may be variably affected by the disease course or treatment-related toxicity. Thus, SWPS assessment may provide a more comprehensive view than a single utility value can. [13, 14] Third, extrapolation of SWPS estimation beyond the follow-up limits may

help predict the long-term outcome of different treatments. The use of a reference population has also been proposed in another cost effectiveness study.[15] In our model, we assume a linear relationship of the logit of quality adjusted survival ratio ($SWPS_{study}(t)$ / $SWPS_{ref}(t)$) between the study cohort and the reference population. Our data fit well with the assumption.

It is arguable to use the psychometric scores from Likert-type questionnaires to represent the QOL values, because these scores are not true interval scores, and thus comparisons among different items may be difficult. Studies by other investigators have shown satisfactory 'scalability' of most of the functioning domains and symptom items of EORTC-QLQ-C30, although improvement in reliability may be needed for domains that relied on the scores of only one to two items. To improve the accuracy of SWPS comparison, future quality of life research may incorporate instruments using true interval scales.

In the study between patients who underwent BMT or PBSCT, comparison of SWPS between patients with or without chronic GVHD did not show significant difference (data not shown), although chronic GVHD is a major factor in the patients' QOL impairment. This may be due to the heterogeneity in manifestation and extent of chronic GVHD. Because of the limited number of patients, further stratification by extent of chronic GVHD or other important disease- or treatment-related factors is not allowed. The limited patient number may also affect the precision of SWPS estimation. Our previous simulation study suggested that a sample size of 100 or more in each group might be needed to reduce the bias of long-term SWPS estimation to less than 5 to 7 percent. Another problem is the sensitivity of QOL instruments.[16] Therefore, more patients are needed to improve the sensitivity and validity of the SWPS as an endpoint for evaluation of clinical efficacy.

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