A Notable Change in Mortality of Aplastic Anemia Observed During the 1970s in Japan

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The age adjusted mortality rate of aplastic anemia in Japan decreased sharply in the mid-1970s; before this time, it had increased only slightly. A report on the survival rate among a substantial number of patients with aplastic anemia showed that patients who sought medical care at the hospital after 1973 had a better survival rate than those who sought care before 1973; the extent of improvement in the survival rate was almost equal to the extent of decrease in the mortality rate. The supply of platelet concentrates was found to increase with the decrease in the age adjusted mortality rate. Although there were several factors that affected the mortality rate from aplastic anemia, the major recognizable factor seemed to be therapeutic improvement, mainly due to the platelet concentrates. Probably neither a decrease in the incidence nor factors related to the data processing of vital statistics played a major role.

DURING THE 1970s in Japan, a noticeable change occured in the mortality rate from aplastic anemia.[1] This prompted a series of epidemiologic studies on the etiology of the disease.[2-5] At that time, one of the main suspected factors was drug use, especially chloramphenicol. Under the assumption that mortality closely reflects incidence, the relationship of time trends between mortality rates and suspected factors were examined. However, no epidemiologic studies succeeded in confirming causal factors by analyzing the mortality trend of aplastic anemia in Japan.

Nationwide surveys on the incidence of aplastic anemia among workers in major industries have suggested that incidence does not change consistently with mortality from aplastic anemia. Instead, the surveys indicated a stable incidence among workers during the 1970s.[6] Interestingly, an additional report showed that the overall survival of registered patients with aplastic anemia had been improving,[1] suggesting that the change in the mortality rate may partly be due to therapeutic improvement.

In conjunction with this theory, this report attempts to give a plausible explanation for the marked change in mortality trend for aplastic anemia, based on the findings accumulated to date through both clinical and epidemiologic studies in Japan. Besides the data derived from the efforts made by the Specific Disease Research Committee on Aplastic Anemia (effective 1972 to 1977) and the Specific Disease Research Committee on Idiopathic Hematopoietic Disorders (effective from 1977 to present), statistics closely related to therapreutic measures were examined.

MATERIALS AND METHODS

Mortality data on aplastic anemia were obtained from Vital Statistics, Japan (International Classification of Diseases [ICD] 292 from 1965 to 1967, and ICD 284 from 1968 to 1985).[7] For calculating the age adjusted rate (adjustment made on 5-year age group basis), the Segi's world population figure was used as a standard population.

Survival experiences were demonstrated using the data from 1,000 patients with aplastic anemia aged ≥15 years who were treated in approximately 40 hospitals with which the members of the Specific Disease Research Committees were affiliated.[8]

As the statistics related to therapeutic measures for aplastic anemia, we also examined the production amount of platelet concentrates provided by the Japanese Red Cross Society,[9] the supplied volume of whole blood units throughout Japan,[10,11] and the dates when antibiotics were offered for sale.

RESULTS

Time trends in age specific mortality rates of aplastic anemia in Japan from 1965 to 1985 are demonstrated in Fig 1 (males) and 2 (females). (Age adjusted mortality rates as a summary statistic are shown in Figure 4.)

In males, the age specific mortality rates of age-groups 0 to 19 and 20 to 39 showed a continuous declining trend from 1965. In the 40 to 59 age-group the declining tendency was similar to that of the younger age groups, but seemed to be remarkable from 1973 to 1979. The 60 to 79 age group had a slowly increasing tendency before 1973, followed by a gradual decreasing tendency until 1978. The oldest age group showed an increasing trend during the whole period from 1965 to 1985.

Figure 2 shows that the trends in females were slightly different from those in males. The more drastic decline in the age specific mortality rates were observed in the mid-1970s, except for the age group of ≥80 years, which increased steadily from 1965 to 1985. However, the beginning of the decline was not exactly the same in terms of calendar year among the age groups.

The largest number of annual deaths from aplastic anemia in males was in 1973 (520 deaths), and in 1974 for females (682 deaths). The number of annual deaths decreased approximately three-fourths among males in the following years (eg, 390 deaths in 1978) and about three-fifths among female (389 deaths in 1977).

The age specific mortality rates of age groups <40 years were lower than those >40 years. The number of deaths of the ≥80 age group was small (eg, 23 cases in 1975, which was 4.8% of the total number of deaths from aplastic anemia).

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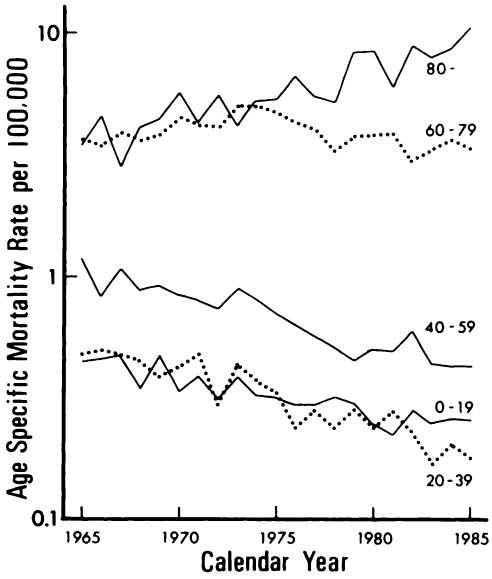

Fig 1. Time trends in the age specific mortality rate of aplastic anemia in Japanese males.

Consequently, those aged 40 to 79 made up the majority of patients with aplastic anemia, when observed in locales of medical practice.

Figure 3 shows the survival curves among the patients aged ≥15 years with aplastic anemia who were treated by hematologists belonging to the Specific Disease Research Committees. Approximately 80% of the patients were <60 years of age. The proportion of the patients aged ≥80 years was <1%. Patients who were classified by the year during their first visit to one of the hospitals, were followed-up for years. The group of patients whose first visit was during the period from 1973 to 1977 and 1978 to 1982 experienced a significantly better survival rate than those during the period

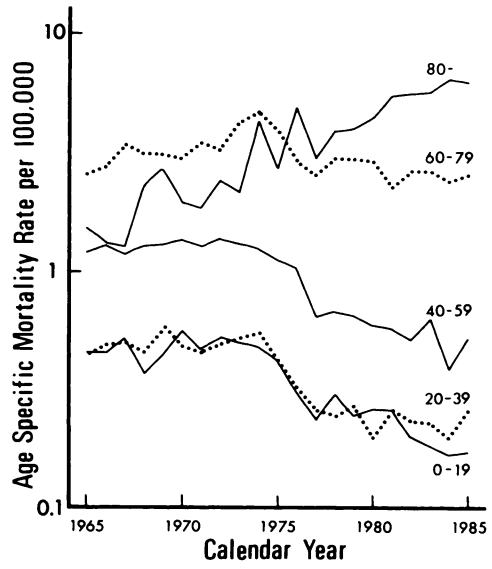

Fig 2. Time trends in the age specific mortality rate of aplastic anemia in Japanese females.

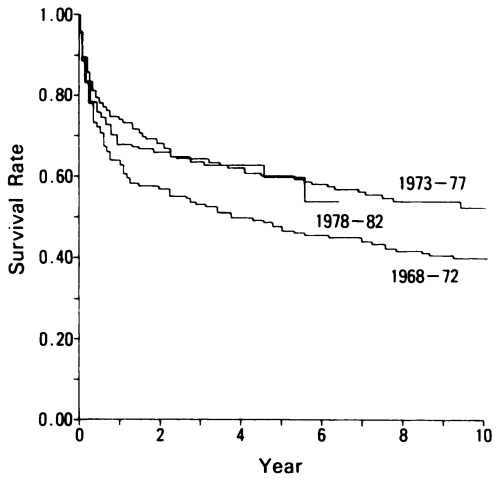

Fig 3. Survival curves of the patients with aplastic anemia, ≥15 years, who were treated at the hospitals with which the members of the Specific Disease Research Committees were affiliated, according to the year of the first visit.

from 1968 to 1972 ($P < .05$). The case fatality rate of the two recent groups was approximately three-fourths of that of the patients who visited the hospital during the period from 1968 to 1972. For example, the 5-year fatality rate was 52.8% for group 1968 to 1972; 39.7% for group 1973 to 1977; and 40.1% for group 1978 to 1982.

Figure 4 shows the production amount of platelet concentrates supplied by the Japanese Red Cross Society, along with the trends in age adjusted mortality rates from aplastic anemia according to sex. It demonstrates a close temporal association between the decline in age adjusted mortality rates and the rise in the production of platelet concentrates.

In contrast, the reported supply of whole blood units in Japan was stable during the 1970s, ie, 462,000 L in 1970; 599,000 L in 1975; and 414,000 L in 1980. Even before 1970, a substantial amount of whole blood units was supplied in Japan (eg, 585,000 L in 1964).

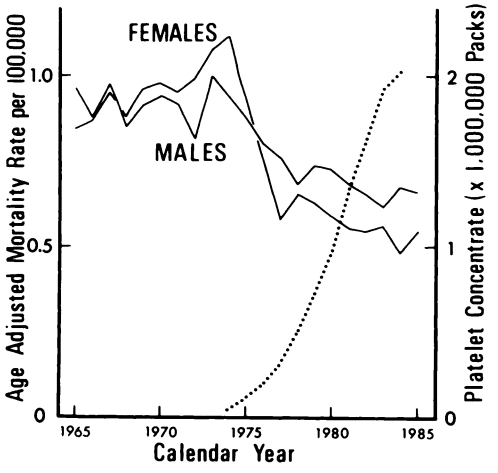

Fig 4. Production amount of platelet concentrates supplied by the Japanese Red Cross Society (dotted line) and trends in age adjusted mortality rate of aplastic anemia by sex (solid lines).

Figure 5 is a list of antibiotics that came into the market from 1965 to 1979 in Japan. There was no major change in the availability of antibiotics in the first half of the 1970s. Among penicillins, for example, benzylpenicillin, phenethicillin, and ampicillin had been available even before 1965; dicloxacillin came into the market in 1968; five penicillins during the period from 1970 to 1974; and another five penicillins from 1975 to 1979. No antibiotics with overwhelmingly high efficacy, seemed to have become available before the mortality change.

DISCUSSION

The demonstrated change in the mortality rate of aplastic anemia during the 1970s was so remarkable that a change in significant factors related to the mortality rate was suspected. Since the time trends in the mortality rate were not similar among age groups, as demonstrated in Figs 1 and 2, the factors may have affected the mortality rate heterogeneously in terms of the age of patients.

An age adjusted rate could not be used as a summary statistic when the rates with a different curve of age specific rate were compared. However, in this specific case, the age adjusted rates in Fig 4 could show comparable expected rates under an almost real situation in Japan. This is because the world population, used as a standard population, has similar proportions of the elderly to those of Japanese males in 1975 (11% *v* 10.5% for those aged ≥60 years; 4% *v* 4.1% for those aged ≥70 years; 1% *v* 0.8% for those aged ≥80 years). In females, the proportions of the elderly were higher than those in males, so the world population was closer to Japanese females around 1960. The real magnitude of the decrease in the mortality rate may possibly be recognized from Fig 4.

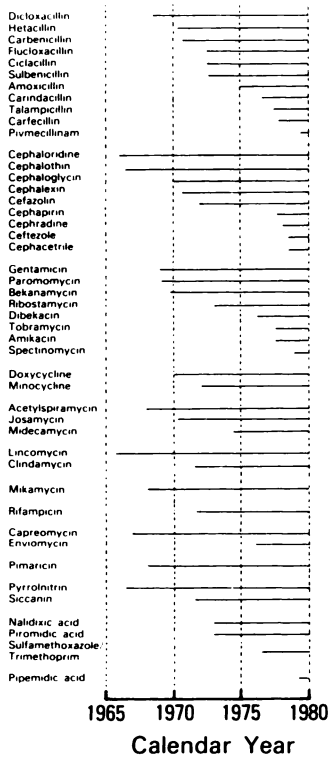

Fig 5. List of antibiotics that were offered for sale from 1965 to 1979 in Japan. The left end of each line shows the date of initial sale.

The factors that affect the mortality rate may be classified into three categories: factors relating to the incidence of the disease; factors resulting in an improved case fatality rate (a better prognosis reduces mortality rate when the incidence is stable); and artificial factors introduced during the process of reporting survey results from local medical practices to the publication of Vital Statistics, such as changes in the conception or definition of the disease due to development in diagnostic techniques, completeness of death certificates, modification of disease classification, etc.

In the case of aplastic anemia in Japan, survival had reportedly improved among the patients treated by the members of the Specific Disease Research Committees, whose hospitals were widely located throughout Japan. Although the decline in the age specific mortality rate among females <80 years of age was larger than that among males, and the timing of the decline was not completely consistent among age groups, the extent of improvement in survival was almost equal to the decline in the mortality. It became very difficult to examine the relationship between the mortality rates and the causal factors of the disease because the mortality rates no longer reflected the incidence rates.

As an example, chloramphenicol, which was well-known suspected causal factor of aplastic anemia, had been intensively examined in Japan by means of descriptive epidemiology. The results did not confirm causal relationship. Although the production amount of chloramphenicol also decreased abruptly in 1975,[3] the relationship between the decrease in chloramphenicol and the decrease in incidence of aplastic anemia has not been documented in Japan. Other suspect drugs, such as phenylbutazone, also decreased in use during the 1970s,[12] but it seems unlikely that these drugs could affect mortality as such. On the contrary, the nationwide survey of workers in major industries indicated that the incidence of aplastic anemia was stable during the 1970s in Japan, although the survey did not cover the older unemployed population.[6] Another reason why such studies by descriptive epidemiology have difficulties in demonstrating a causal relationship is that the attribution of suspected factors (eg, chloramphenicol) to the total number of aplastic anemia patients (ie, etiological fraction) might be too small to be demonstrable. The International Agranulocytosis and Aplastic Anemia Study estimated that the etiological fraction of drug use of butazones, indomethacin, and diclofenac could be several percent for aplastic anemia in the European countries.[13] If the fraction of cases due to chloramphenicol was <10%, for example, during the 1970s in Japan, a causal relationship would not be evident from a descriptive method based on mortality data.

Changes in the concept of the disease may have affected the mortality trend. From 1972 to 1973, a nationwide survey on aplastic anemia was performed by the Specific Disease Research Committee on Aplastic Anemia, which distributed lists of diagnostic criteria for aplastic anemia. A small peak

in the mortality rate from the disease was observed immediately afterward. Since other intractable diseases that were surveyed at the same time also showed a similar increase, the transient peak observed in the mid-1970s might be due to the effect of "education" by nationwide survey. However, it seems unlikely that the nationwide survey could account for a subsequent decrease in aplastic anemia mortality.

The changes in coding of causes of deaths seemed to play little part in the mortality rate change in the 1970s, because Vital Statistics in Japan applied ICD-8 from 1968 to 1978. Recently, refractory anemia has been studied apart from aplastic anemia by the Specific Disease Research Committee on Idiopathic Hematopoietic Disorders. However, enthusiastic studies on refractory anemia began in the 1980s. Other aplastic anemia-like diseases may have been classified more correctly in the 1970s. However, the effect on the aplastic anemia mortality rate seems to be limited. For example, the number of deaths from myelofibrosis was reported in Vital Statistics to be 21 in 1970; 56 in 1975; and 53 in 1978. Considering the number of deaths from aleukemic leukemia misclassified as aplastic anemia, there were no available data directly related. In the 1972/1973 nationwide survey, aplastic anemia patients with hypercellular bone marrow were <10% among the 1,594 reported prevalent cases, including an 8.8% of unexamined cases.[14] In these patients with hypercellular bone marrow, there may be aleukemic leukemia patients who may have been misclassified as aplastic anemia cases unless they became overt leukemia cases. Since aplastic anemia patients with hypercellular bone marrow were unchangeably classified (or misclassified) as having aplastic anemia in the 1970s, this was unlikely to be a major reason for the notable mortality change.

Changes in patients' access to medical facilities may have modified the diagnoses given on death certificates. For example, when undiagnosed aplastic anemia patients die as a result of a cerebral vascular accident or septicemia, a diagnosis of aplastic anemia would never have appeared on the death certificate. In contrast, frequent access to medical facilities may promote earlier diagnosis, and seemingly better prognosis. In Japan, health care insurance succeeded in providing coverage for the entire population in 1961. As a result, physician visits per 100,000 persons per day leveled off at the beginning of the 1970s; they were 3,301 in 1955; 4,805 in 1960; 5,910 in 1965; 6,987 in 1970; 7,049 in 1975; and 6,847 in 1980.

If we accept that most of the change in mortality figures was caused by an improved prognosis, there are two elements to be considered: changes in the distribution of severity among patients with aplastic anemia and improvement of therapy for the disease. According to the analysis of patients aged 15 or over who were treated in the hospitals that the members of the Specific Disease Research Committees belonged to, those classified at diagnosis as severe cases were 43.6% in the 1968-1972 group; 39.8% in the 1973-1977 group and 51.8% in the 1978-1982 group. Mild cases at diagnosis were 17.6%, 13.9%, and 14.2%, respectively. The rest were moderate cases. These figures suggest that there was no substantial shifting in the distribution of severity at the time when those patients were diagnosed. Besides, the survival rate analysis by severity of aplastic anemia patients showed that survival among moderate cases and mild cases was greatly improved during the period.[8] Therefore, it seems likely that the main reason for the decline in the mortality rates was improvement of therapy.

The direct causes of death among patients with aplastic anemia are homorrhages, infections, and transfusional hemosiderosis anemia. Antibiotics for infections and red cell transfusions for anemia had been performed before the 1970s. The availability of antibiotics and red cell transfusions may have improved gradually, and more effective methods of their medication may have become prevalent, but there were no available data on them. No major changes in the used antibiotics and red cell transfusions were recorded during the 1970s. Although corticosteroid hormones and anabolic steroid hormones reportedly improved the prognosis of aplastic anemia patients,[15] they had been in use by most hematologists before the drastic decrease in the mortality rate. Bone marrow transplants for aplastic anemia were very rarely performed during the 1970s (only two cases reported).[16]

On the other hand, there was no effective treatment for hemorrhages before the introduction of platelet concentrate transfusions in the mid-1970s. Platelet concentrates have been almost exclusively supplied by the Japanese Red Cross Society in Japan; Fig 4 represents a vivid picture of the temporal relationship of their use to mortality rates. As supportive evidence, the direct causes of deaths from aplastic anemia were reported to shift from homorrhages to infections.[17]

It is conceivable that several factors have affected the drastic change in the aplastic anemia mortality rate in the 1970s. Each factor must have played some part in this change. Among them, the improvement of therapeutic techniques, especially platelet concentrate transfusions, could be regarded as one of the major factors, based on the data accumulated so far. The factors for the oldest age group, whose age specific mortality rate has been increasing, should be considered separately from the other age groups.

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