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Statistics

Criteria for the validity of clinical trials of treatments of cohorts of cancer patients based on the Hardin Jones principle

(vitamin C/ascorbic acid)

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ABSTRACT **With the assumption of the validity of the Hardin Jones principle that the death rate of members of a homogeneous cohort of cancer patients is constant, three criteria for the validity of clinical trials of cancer treatments are formulated. These criteria are satisfied by most published clinical trials, but one trial was found to violate all three, rendering the validity of its reported results uncertain.**

The Hardin Jones Principle

In 1956 Hardin Jones (1) pointed out that the death rate is constant for a presumably homogenous cohort of cancer patients, such as those with breast cancer with generalized advanced metastasis and classed inoperable when originally observed. For such a homogeneous cohort the fraction surviving, S, at time t is given by Eq. 1, in which α is the death rate:

$$S = e^{-\alpha t}. \quad [1]$$

A plot of ln S against t is then a straight line, with negative slope equal to α. An example, from Burch (2), is shown in Fig. 1, and another example, from Cameron and Pauling (3), in Fig. 2. Sometimes, as has been pointed out in a recent discussion (4), resolution of the survival curve into the sum of two or more Hardin Jones exponentials, with death rates α_i and coefficients f_i, can be made:

$$S = \sum_i f_i e^{-\alpha_i t}. \quad [2]$$

An example is given in Fig. 3.

Some uses of the Hardin Jones principle, such as the identification and characterization of a long-lived subcohort in a heterogeneous cohort, have been discussed in earlier papers. Another use is in formulating criteria for the reliability of reported clinical trials of treatments of cancer patients, as discussed below.

The First Criterion of the Validity of a Trial of the Effectiveness of a Treatment of a Cohort of Cancer Patients

In order to increase the significance of the study, the cohort should be reasonably homogeneous, so that Eq. 1 or Eq. 2 can be applied in the analysis of the data. Moreover, the treatment of all the members of the cohort should be the same, and it should be continuous and unchanged from the time $t = 0$ when the patient enters the trial until the time t when the patient dies or t^+ when, without dying, is withdrawn from the set of survivors at risk. Any patient who stops the treatment or changes the treatment at any t^+ should be removed from the study and included in the analysis by the Kaplan–Meier renormalization procedure (5) or the alternative procedure developed in ref. 4. If the trial is to test the later response of a patient to a short-term course of treatment (with or without a following continuous treatment), the time $t = 0$ is to be taken as the time at which the short-term course was completed, with only those patients who survived the course included in the cohort.

The Second Criterion

For more than 200 studies of survival of cohorts of cancer patients examined by us, we have found that the Hardin Jones straight line passes through the 100% axis at time $t = 0$. No statistically significant lag period during which no deaths occur is observed. A trial producing a set of survival times with a significant lag period, during which the value of α would lead to the expectation that several deaths would occur, can be considered to be faulty.

The Third Criterion

If the cohort is heterogeneous and the study is properly carried out, with conditions constant during the period of the study, the semilogarithmic survival curve must bend away from the Hardin Jones initial straight line only in the direction of increased survival times for the longer-term survivors, as shown in Fig. 3. This is, of course, to be expected, since the subcohort of patients with shorter life expectancy is depleted, leaving the subcohort with longer life expectancy. The observation of a deviation of the curve in the opposite direction indicates faulty design or execution of the trial. For example, after the death of many or most of the patients in the subcohort with high death rate, some of the survivors might have had their treatment changed in such a way as to increase their death rate. Under our first criterion, they should at that time have been removed from the study.

An Example of a Study that Fails to Meet These Criteria

We have found a reported clinical trial that fails on each of the three criteria for validity discussed in the preceding sections (6).

This study, described as a randomized double-blind comparison of vitamin C (10 g per day) and a lactose placebo in 100 patients with advanced adenomatous colorectal cancer, gave survival times published only in a Kaplan–Meier figure. We have measured the published curves and produced the semilogarithmic plot shown as Fig. 4.

Each of the 51 vitamin-C patients received vitamin C for some time (median stated to be 2.5 months). The vitamin C was stopped for 19 patients with clearly measurable areas of malignant disease when there was a 50% increase in the product of the perpendicular diameters of any of these areas and for the other 32 when there was some other evidence of progression of the disease. Each of the 51 patients then entered a period of no treatment, during which some of them

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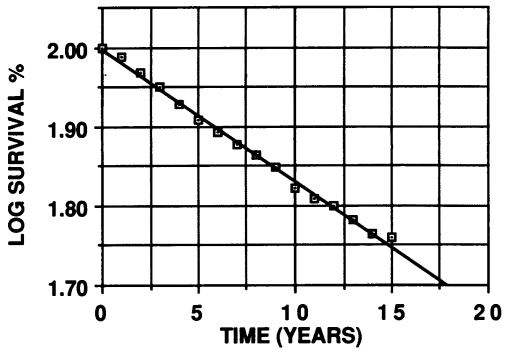

FIG. 1. Logarithm of percent survival of 5159 California women of all ages with localized breast cancer (after ref. 2); $t_{1/2}$ = 18.0 years.

died. Then 30 of them entered a third period, after, the authors say, they had "discontinued participation in this study." This was the period during which they received chemotherapy, mostly with fluorouracil, either alone or in combination with other agents. There were accordingly, by our first criterion, four separate periods for the patients: the period of regular intake of vitamin C, the following period of no treatment (with some possible aftereffects of the earlier vitamin C), the period of the chemotherapy treatment, and the period after the end of the course of chemotherapy.

The authors treat the data, however, as though it were a single clinical trial. This violates the first criterion of validity.

As shown in Fig. 4, the second criterion is also violated. The Hardin Jones straight line has an unexplained intercept.

The third criterion is also violated, in that after 350 days the death rate increases significantly.

All three criteria are also violated by the study of the 49 patients who began taking a placebo, then stopped it and entered the period of no treatment, then (28 of them) received chemotherapy, and then entered into the fourth period, with no treatment.

We are not able to explain the lag period of 70 days (Fig. 4), during which only one patient died, rather than about 25 expected from the Hardin Jones principle. Also, we are not able to make a good biostatistical analysis of the death rates under the four separate conditions (vitamin C or placebo being taken, no treatment, chemotherapy being given, then no treatment), because we could not obtain information about the times during which the individual patients were in each of these four periods. One conclusion, however, is certain: this study provides no information about the value of a continued intake of 10 g per day of vitamin C in extending survival time, because none of the patients died while taking the vitamin.

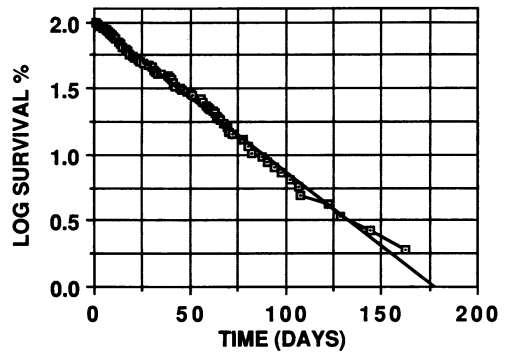

FIG. 2. Logarithm of percent survival of 130 Scottish patients with untreatable cancer of the colon (after ref. 3), compared with Eq. 1 (straight line) with average rate constant $\alpha = 2.58 \times 10^{-2}$ d^{-1} ($t_{1/2}$ = 26.9 d).

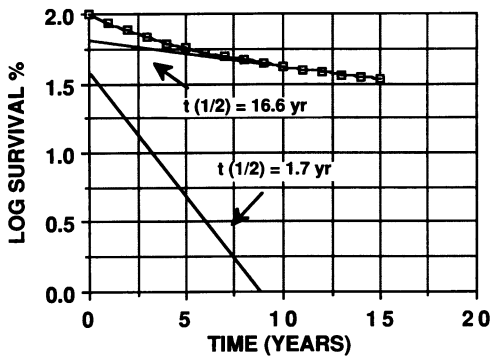

FIG. 3. Logarithm of percent survival of 13,392 California women of all ages and with breast cancer of all degrees of severity, roughly resolved into two negative exponential functions, one with $t_{1/2}$ = 1.7 years and one with $t_{1/2}$ = 16.6 years (after ref. 2).

Another conclusion can also be reached from the violation of the third criterion. It is that the life expectancy of these patients was decreased somewhat by chemotherapy.

It has been pointed out (ref. 7, page 117) that the sudden stopping of high doses of vitamin C leads to a rebound effect that may be dangerous for cancer patients. During the period from 70 to 120 days 10 vitamin-C patients died and only 4 placebo patients. Also, the reported death rate during this period for the vitamin-C patients was significantly greater than during the following 300 days. The fact that this increased death rate occurred immediately after the median withdrawal date of the vitamin C, 75 days, suggests that it may have been caused by the rebound effect.

The administration of chemotherapy to 58 patients who had withdrawn from the study had begun by 250 days, when 58 were still alive (Fig. 4). At about 350 days the death rate increased. It is certain, from the Hardin Jones principle, that something had changed in the treatment or environment of the patients, and the conclusion that this change was the administration of chemotherapy seems to be justified.

Conclusion

Three biostatistical criteria have been formulated for the validity of clinical trials of treatments of cancer patients. The first criterion is that the regimen of a patient in the cohort should not be changed during the period of the trial; if it is

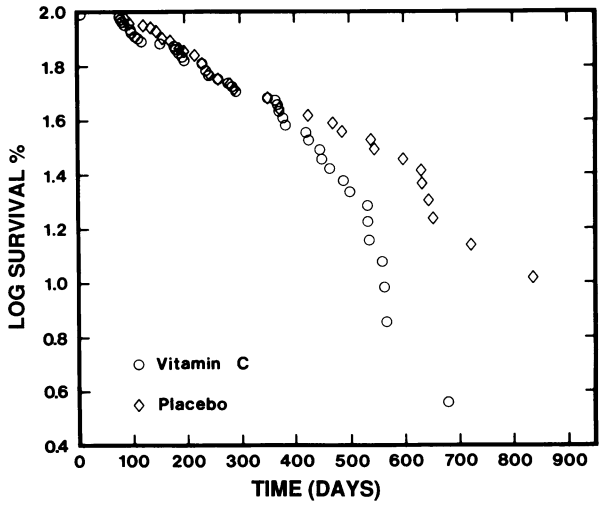

FIG. 4. Logarithm of the Kaplan–Meier survival percentage S for advanced colorectal cancer patients for two cohorts (vitamin C and placebo) as a function of the time t from onset of treatment (data from ref. 6).

changed, the patient should be withdrawn from the trial. The second criterion is that the Hardin Jones line on a semilogarithmic plot of the fraction surviving at time t should go to 100% at time 0; deviation by a significant amount indicates some sort of error in reporting the time at which patients entered the study. The third criterion is that the semilogarithmic curve should not deviate from the initial Hardin Jones straight line in the direction of increased mortality at later times. Such a deviation shows that the regimen has been changed for some members of the cohort, who should then have been removed from the study.

We have found that most of the reported results of clinical trials of cohorts of cancer patients satisfy these criteria of validity. One study, however, fails by all three. The conclusion reached in that study, that ascorbic acid has no more value than lactose in extending the survival of patients with advanced colorectal cancer, is not justified.

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