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Correlation between postoperative prognosis in gastrointestinal cancer patients and blastformation rate of lymphocytes

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Abstract

Gastrointestinal cancer patients were followed up for up to 30 months postoperatively and their clinical status related to a parameter of nonspecific immunity, the blastformation rate of peripheral blood lymphocytes against phytohemagglutinin. By the fourth postoperative week, the blastformation rate had recovered from the effect of the operation. In patients who had undergone curative resection, the postoperative level rose to exceed the preoperative level, whereas whereas in those in whom resection had not been possible, the blastformation rate failed to show this rise by the fourth week, and continued at the decreased immediate postoperative level. Results for long-term follow-up (30 months postoperatively) showed that the blastformation rate continued at high levels (almost all over 40%) in cases of curative resection without recurrence, but remained low (under 40%) in those in which the tumor could not be removed. The 40% level of the blastformation rate test thus correlated well with the prognosis. The blastformation rate, therefore, proved a very good parameter for following the pre-and post-operative clinical course of gastrointestinal cancer patients.

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CORRELATION BETWEEN POSTOPERATIVE PROGNOSIS IN GASTROINTESTINAL CANCER PATIENTS AND BLASTFORMATION RATE OF LYMPHOCYTES

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Abstract. Gastrointestinal cancer patients were followed up for up to 30 months postoperatively and their clinical status related to a parameter of nonspecific immunity, the blastformation rate of peripheral blood lymphocytes against phytohemagglutinin. By the fourth postoperative week, the blastformation rate had recovered from the effect of the operation. In patients who had undergone curative resection, the postoperative level rose to exceed the preoperative level, whereas in those in whom resection had not been possible, the blastformation rate failed to show this rise by the fourth week, and continued at the decreased immediate postoperative level. Results for long-term follow-up (30 months postoperatively) showed that the blastformation rate continued at high levels (almost all over 40%) in cases of curative resection without recurrence, but remained low (under 40%) in those in which the tumor could not be removed. The 40%level of the blastformation rate test thus correlated well with the prognosis. The blastformation rate, therefore, proved a very good parameter for following the pre- and post-operative clinical course of gastrointestinal cancer patients.

Decreases in specific and non-specific cell-mediated immunity have been demonstrated in gastrointestinal cancer as well as in other types of malignant tumors. A nonspecific cell-mediated immune reaction, the blastformation rate of peripheral blood lymphocytes against phytohemagglutinin (PHA) has been reported to decrease in nonlymphoid malignancies (1) but this is still debated (2). Previously, we reported the use of non-specific tests of cell-mediated immunity in gastrointestinal cancer patients as a preoperative parameter for assessing the extent of cancer progress (3, 4). The blastformation rate of peripheral blood lymphocytes proved effective for such assessment and was useful in deciding whether or not curative resection was possible. The present paper continues this study and relates postoperative changes in the lymphocyte blastformation rate with the clinical condition of gastrointestinal cancer patients. H. MIWA and K. ORITA

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MATERIALS AND METHODS

Subjects. Gastrointestinal cancer patients in whom adequate investigation of the blastformation rate both before and after operation had been possible were grouped into three surgical classes: curative resection, noncurative resection and nonresection. Patients over 70 years of age (in whom cell-mediated immunity is low (5)), recurrent cases, and nonoperated cases were omitted from the present study.

Methods. Blastformation tests were performed with 5 ml of heparinized peripheral blood using the authors' standard technique (6).

RESULTS

Changes in the blastformation rate before and after operation. Figure la shows the results for blastformation rates before, and up to one month after, operation.



operation., curative resection; \blacktriangle \bigstar , noncurative resection; $\leftthreetimes{}$ \bigstar , noncurative resection; $\leftthreetimes{}$ $\leftthreetimes{}$, nonresection

In the curative resection group, the blastformation rates before operation and weekly thereafter (to the fourth postoperation week) were $48.5 \pm 15.8\%$, $38.6 \pm 13.4\%$ ($0.05), <math>38.1 \pm 17.3\%$ ($0.01), <math>39.8 \pm 13.4\%$ ($0.02), and <math>49.2 \pm 14.1\%$ (p > 0.5), respectively. The blastformation rate in most of cases fell during the first three weeks postoperatively, but had recovered by the fourth postoperative week. The blastformation rate by the fourth week had not only regained the pre-operative level, but often exceeded it. In the non-curative resection group, and also in the non-resection group, the postoperative blastformation rate showed no recovery from the preoperative blastformation rate and was still low at the fourth week postoperatively. The proportion of patients having blastformation rates over 40% decreased postoperatively, but had begun to increase by the fourth week postoperatively (Fig. 1b). In conjunc-

tion with the similar pattern of fall and rise of the blastformation rate, this indicates that the direct effects of undergoing surgery had been overcome by the fourth postoperative week.

The two groups of curative resection and nonresection were then compared by taking an arbitrary level of 40% for the blastformation test. There were 91 cases of curative resection. Sixty-one of these had preoperative blastformation rates over 40% and this level was still being maintained in 53 of them (86.9%) one month after operation. Of the remaining 30 cases with preoperative blastformation rates under 40%, 18 (40%) had rates over 40% by one month after operation. Overall, those with blastformation rates over 40% in this group were 67% of cases preoperatively, and 78% by one month postoperatively (Table 1).

%	No. of cases	One month after operatiou	Before operation
58.2	53	+	+
8.8	8	_	+
19.8	18	+	
13.2	12	-	
100. 0	91		

TABLE 1. FLUCTUATIONS OF BLASTFORMATION RATE BEFORE AND AFTER CURATIVE RESECTION IN CANCER PATIENTS

+ : Blastformation rate of over 40%

- : Blastformation rate of under 40%

There were 46 patients in the nonresection group. Of these 76.1% had blastformation rates less than 40% before operation, but the number of those with rates less than 40% had increased to 84.8% by one month after operation (Table 2). This difference in the blastformation rates for curative resection and

 TABLE 2. FLUCTUATIONS OF BLASTFORMATION RATE BEFORE AND AFTER

 OPERATION IN CASES NOT UNDERGOING CANCER EXTIRPATION

Before operation	One month after operation	No. of cases	%
+		3	6.5
+	-	8	17.4
	+	4	8.7
_	-	31	67.4
		46	100.0

+ : Blastformation rate of over 40%

- : Blastformation rate of under 40%

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nonresection was extremely important clinically since the cases of curative resection with blastformation rates over 40% continued to have a favorable clinical course. This was probably due to recovery of following complete tumor extirpation.

Changes in postoperative blastformation rates in the long-term. In both the curative resection and the nonresection groups, the blastformation rate was followed for up to a period of two and a half years postoperatively. Tests were



Fig. 2. Fluctuations of blastformation rat : after curative resection.



Fig. 3. Fluctuations of blastformation rate after nonresectable operation.

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repeated when any sudden fall in the blastformation rate was encountered. In the 91 cases of curative resection, the majority had blastformation rates over 40% a short time after the operation (by the fourth week). A few exceptions occurred who continued to have low blastformation rates (<40%) by the eighth postoperative month not related to recurrence of the cancer. However, the blastformation rates had all risen to over 40% by the end of the first year (Fig. 2).

The 51 patients in whom the tumor was not removed continued to have low blastformation rates (<40%) until their death (Fig. 3).

DISCUSSION

The use of immunological monitoring in various clinical conditions is becoming well-established. At present, such monitoring is based on parameters of cell-mediated immunity. These parameters consist of specific immune tests based on the interaction of the host's lymphocytes with cancer and on nonspecific immune tests which only assess the non-specific immunocapacity of the host. The blastformation rate to PHA is a representative non-specific immune test and has already been reported as giving a good indication of the extent of cancer and the feasibility of curative resection (3, 4). Parameters of both specific and non-specific cell-mediated immunity are also being used for assessing the results of cancer immunotherapy (*e.g.*, BCG) but as yet, there has been non authorative statement as to which type of parameter is most reliable.

To be reliable, the test of cell-mediated immunity should reflect the clinical status of the cancer-bearing patient before and after operation. We investigated whether the blastformation rate satisfies such requirements.

Figure 1 illustrates the effects of operation and anesthesia up to the fourth postoperative week as shown by the blastformation rate. The rate fell from the first week to the third week postoperatively, then recovered by the fourth postoperative week to regain the preoperative level. Similar results have been reported by Riddle and Berenbaum (7).

In the curative resection cases, the fact that blastformation rates after operation were higher than before operation indicates that the host immunity is restored by tumor extirpation. Those not undergoing tumor extirpation had low blastformation rates, a reflection of their loss of immunity. Similar results have been reported using macrophage migration inhibition tests (MIT) (8).

Long-term observation of the patient post-operatively (30 months) indicated that patients having a blastformation rate over 40% before operation had a favorable prognosis (Fig. 2). In patients without a recurrence, the blastformation rate postoperatively remained above 40% in the majority of cases, whereas the rate was persistently low for the nonresection group. The 40% blastformation rate did, therefore, serve as a useful boundary line for distinguishing between H. MIWA and K. ORITA

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these two groups. This supports our early work on the potential usefulness of the preoperative blastformation rate as a prognostic aid (9).

In patients with a recurrence during the postoperative course, the blastformation rate rose slightly three to four months before confirmation of the recurrence, then fell rapidly during the remaining two months before clinical confirmation (10). This characteristic pattern indicates that the blastformation test may also be very useful in the diagnosis of a recurrence. There are very few reports of long term postoperative monitoring of blastformation rates, so this possibility awaits verification.

The correlation between immunological tests and the prognosis in cancer patients has also been studied by Pinsky (11) and Morton *et al* (12). They stated that a preoperative DNCB test alone correlated well with recurrence at six months postoperatively, and also with the long-term prognosis (up to two years). Krant *et al* (13) reported that patients with positive PPD tests had good prognoses, whereas in those in whom the PPD test turned negative, the prognosis was unfavorable. Orita *et al* (14) used MIF tests to follow the results of immunotherapy in patients immunized with BCG-CWS (cell wall skeleton). They reported that this test both reflected well the postoperative course of cancer patients and served as a useful parameter of the effect of immunotherapy.

Although both specific and nonspecific immune tests reflect well the prognosis of cancer patients, nonspecific immune tests do not require cancer tissue for the test. They are, therefore, easily performed and useful as a parameter in anticancer therapy (15), irradiation therapy (16), and when using immune potentiators (17). Moreover, it is possible to monitor cancer patients postoperatively over an extremely long period of time. They are, therefore, recommended as an excellent clinical aid.

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