Summary

Two clinical trials now in progress are described: Stage I and Stage II patients were treated with radical radiotherapy and subsequently randomized into 2 groups; 1 group had no further treatment and the other received weekly injections of Vinca-leucoblastine. Patients with generalized disease but without visceral involvement were treated first with chemotherapy. In the case of incomplete remission or cessation of chemotherapy as a result of intolerance, a course of radiotherapy was undertaken. The patients were randomized between minimal radiotherapy (3500 rads to territories with residual lesions) or maximal radiotherapy (3500 rads to all regions initially affected as well as intervening regions). These 2 protocols seem practicable and without undesirable side effects.

Introduction

This study has been organized under the sponsorship of the Section of Clinical Radiobiology of the Groupe Européen de Chimiothérapie Anticancéreuse. Five treatment centers are presently affiliated with this group, and it is hoped that several other centers will be joining soon. The collaborative study began in July 1964.

Improvement of the treatment of Hodgkin’s disease is the aim of 2 clinical trials now in progress at Villejuif. Both of these attack the problem of the combined modalities of chemotherapy and radiotherapy. In all cases the patients are assigned in a random manner to the various treatment groups.

I. Patients with Local or Regional Involvement (Stages I and II).

The patients in this group have 1 or more groups of lymph nodes involved, but the affected nodes are restricted to 1 side of the diaphragm. It has been apparent to us that the basic treatment for this group must be radiotherapy, but the question to be answered is whether protracted chemotherapy following radiotherapy is likely to improve the long term results of treatment.

Even the best radiotherapeutic statistics demonstrate that a significant percentage of patients with disease first treated in Stage I or II die within the 1st 5 years after treatment, especially when general systemic symptoms such as fever are present. The failures may be due to either incomplete control of all malignant tissue irradiated, or may be the result of undetected dissemination of the disease outside of the irradiated volume; in both cases chemotherapy may be useful.

Technic

Patients were included in the trial if the following conditions were met:

(a) The diagnosis was confirmed by biopsy and cytologic examination. (b) The patient had not received previous treatment for this disease. (c) The patient was judged to be in Stage I or Stage II after a careful clinical and radiologic examination, which included: a successful iliolumbar lymphangiogram; X-ray of the mediastinum and tomography; liver function tests and liver biopsy, if indicated.

Radiotherapy was carried out by telecobaltherapy according to a technic based on that of Kaplan (3). All of the target volume is irradiated in a single field, which is defined by lead screens in such a fashion that areas of demonstrable disease, as well as adjacent and intervening areas containing lymph node, are included. However, if the mediastinum is involved, the lumbar nodes are not irradiated, and conversely, if the lymphangiogram indicates involvement of the lumbar nodes, the mediastinum is not irradiated. The diaphragm is always the limit of the irradiated volume.

A dose of 3500-4000 rads is delivered in 4 weeks, 1000 rads/week in 3 sessions of 330 rads each. Anterior and posterior fields are used alternately. If the tumor mass is large, a small supplementary field is superimposed to raise the tumor dose to 4500 rads.

Four to 6 weeks after the end of the irradiation, those patients who are in complete remission are randomly assigned to 2 groups: (a) patients who receive no further treatment; (b) patients who receive a weekly injection of Vinca-leucoblastine.

The treatment is continued as long as it is tolerated, and at least for several years. The particular chemotherapeutic agent was chosen because it is generally well tolerated for long courses of treatment. A WBC is made each week immediately before each injection; if this count is below 3000/cu mm the treatment is temporarily suspended.

Results

Since the beginning of the study in July 1964, a total of 83 new cases of Hodgkin’s disease have been seen at the I.G.R. Of these, 21 fulfilled the requirements set forth above, and 13 have been randomly assigned to the treatment subgroups prior to July 1965.

In the other cooperating centers 8 patients have been randomized and 3 await assignment to their treatment sub-
groups. As the number of cooperating centers increases we hope to have 50 or so patients per year entering the study.

It is, of course, much too early to make any judgments relative to the 2 modes of treatment. It can only be said that:

1. The radiotherapy has always been well tolerated. All of the patients irradiated in the trial group, except 2, were in complete remission 4 weeks after the last session of radiation, and were thus suitable for inclusion in the group for randomization. One of the 2 patients was excluded because a lung metastasis was apparent at the completion of the irradiation. The other case, who had a lesion of the groin, developed a splenomegaly which was apparent 4 weeks after the termination of irradiation, although the spleen was initially normal. The sedimentation rate in this patient was higher than before treatment. If, after a splenic irradiation, he can be brought into complete remission, he will be included in the study.

2. Long-term chemotherapy by weekly injections of 5-10 mg of Vincaleucoblastin is well tolerated. It has occasionally been necessary to interrupt the administration of the drug for 1-2 weeks due to a transient leukopenia (<3000), but it has been possible to recommence the therapy without complications.

II. Study of Generalized Disease (Stage III)

We have previously reported (4) that for patients with generalized Hodgkin's disease (Stage III) radiotherapy may be usefully employed as an adjunct to chemotherapy. Out of 43 Stage III cases only 3 were in complete remission after chemotherapy, incomplete remission being obtained in the remainder. In this latter group of 40 cases subsequent radiotherapy achieved a complete remission in 3 of cases.

This does not hold for Stage IV disease. In those patients who fail to remit with chemotherapy subsequent radiotherapy achieves a remission in only 1 of the cases. It is why those cases with hepatic, cutaneous, osseous, or visceral involvement are excluded; however, the existence of splenomegaly, relapse, or previous treatment are not reasons for exclusion.

In all cases the treatment begins with an intense course of chemotherapy; generally with methyl hydrazine. This is continued until a complete remission is obtained or signs of intolerance to the drug develop. If complete remission is accomplished, no other treatment is instituted and the patient is kept under close observation. In the case of incomplete remission or cessation of chemotherapy as the result of intolerance, a course of radiotherapy is undertaken.

The 1st session of radiotherapy is either 8-10 days after the termination of chemotherapy in those cases where the lesions are continuing to increase; or 21 days later if the disease is stationary. The choice between 2 modalities of radiotherapy is made by randomization.

MINIMAL RADIOTHERAPY. Those areas in which clinically or radiologically evident lesions still exist are given 3500 rads in 4 weeks.

MAXIMAL RADIOTHERAPY. All those regions affected at the time that chemotherapy is commenced, as well as all intervening regions, are given 3500 rads. For example, an initial involvement of the right axilla, the left cervical region, and the lumboaortic chain would require irradiation, in addition to these sites, of the mediastinum and right subclavicular region.

Since, in these cases, a large tissue volume is involved, and the patients are generally already strongly affected by the prior chemotherapy, the irradiation is managed in a careful and progressive manner. Generally, it is carried out in 2 sessions, delivering 3500 rads to the 2 halves of the trunk successively. The irradiation is protracted to approximately 8 weeks and is stopped temporarily if the number of granulocytes falls below 1000 or the number of platelets is below 50,000.

Results

The trial commenced on the 1st of February, 1964, and prior to July 1, 1965, 17 patients had been taken into the study at the completion of chemotherapy. By random assignment, 8 have been put in the minimal radiotherapy class and 9 have been assigned to maximal radiotherapy.

Even though it is obviously too early to draw any general conclusions, the following remarks may be made:

1. The minimal course of radiotherapy is generally well tolerated. In 2 cases only it has been necessary temporarily to interrupt the irradiation.

2. The maximal course is much more difficult to complete. It is estimated (1, 2) that in those patients in whom the super and subdiaphragmatic lymphatic regions are irradiated, approximately 55% of the hematopoietic tissues receive doses close to 3500 rads. However, as we have previously observed (5) in most of these patients, the treatment is well tolerated.

In 7 of the 9 patients it has been necessary to interrupt the irradiation because of the appearance of leukopenia and/or thrombopenia. However in 6 of these cases it has been finally possible to achieve the prescribed dose, and in all cases but 1 the blood picture was normal 3 months after the completion of treatment. In 3 of the patients it was necessary a few months later to repeat the course of chemotherapy, but in all instances this was without untoward effects.

3. Two patients died in the minimal group, 1 in the maximal. A complete remission lasted more than 6 months in 3 of the patients of the minimal group and in 4 of those of the maximal group.

Conclusion

After more than a year of experience with these 2 protocols it has been shown that both were practicable and without undesirable side effects. Many years of experience will be required to tell which of these treatment modalities gives the most significant survival.

References


Current Clinical Trials in the Radiotherapy of Hodgkin’s Disease at Institut Gustave Roussy

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