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Quality Control of Radiotherapy in Acute Lymphocytic Leukemia Protocol Treatment: Experience with 610 Cases*†

REINHARD HUNIG,‡§ CHRISTINA LANDMANN,‡ JAKOB ROTH,‖ LAWRENCE E. REINSTEIN§¶ and ARVIN S. GLICKSMAN§¶**

‡*Departments of Radiotherapy and* ‖*Radiation Physics, Kantonsspital/University Hospital, Basel, Switzerland and* ¶*Quality Assurance Review Center, Department of Radiation Oncology, Rhode Island Hospital, Providence, RI, U.S.A.*

Abstract—*Quality assurance programs are necessary in multi-institutional cooperative group clinical trials to ensure that possible inter-institutional differences in selection, treatment and evaluation of patients will not erode the statistical assessment of these clinical trials. The Radiotherapy Committee of the Cancer and Leukemia Group B examined the evaluability and appropriateness of treatment of patients entered into two protocols for childhood acute lymphocytic leukemia, 7411 prior to and 7611 after the development of a quality assurance review program. Of the 348 patients entered into 7411, 37% were evaluable and 26% were appropriately treated in 1974 when the protocol opened. This rose to 53 and 35% in the last year of the study. On the other hand, in 7611 with an ongoing quality assurance program, the evaluability rate initially was 63% and rose to 73% and the appropriateness rate rose from 37 to 61%. This change in performance which was statistically significant at the P = 0.001 level is attributed to the impact of the Quality Assurance Review Center correspondence. Improvement in performance occurred almost entirely in the principal centers and not in satellite institutions. This difference in performance was statistically significant at the P = 0.05 level, indicating that adherence to protocol requirements increases with increased participation in studies.*

INTRODUCTION

CURRENT progress in the treatment of cancer depends to a great extent on the successful use of prospect randomized trials in which a carefully designed protocol of two or more treatment regimens may be compared, leading, it is hoped, to the most effective and least toxic treatment of the disease in question. In attempting to do so, a number of conditions have to be met: (1) patient selection, tumor diagnosis and staging have to be well defined and uniform at all participating institutions; (2) treatment must be explicitly spelled out and each patient must be treated strictly according to protocol demands; (3) treatment evaluation must be uniform and carried out at predefined intervals; and (4) patient accrual has to be large enough in a reasonable period of time to allow statistical analysis of the data.

The fulfilment of the last condition implies the need for uniting multiple oncological centers to form multi-institutional national (e.g. Swiss Group for Clinical Cancer Research—SGCCR) or international (e.g. Cancer and Leukemia Group B—CALGB; Eastern Cooperative Oncology Group—ECOG; European Organization for Research on Treatment of Cancer—EORTC; etc.) oncology groups. It is possible, however, that all participating centers may not be equally capable,

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§Radiotherapy Committee of the Cancer and Leukemia Group B.

**To whom requests for reprints and correspondence should be addressed at: Department of Radiation Oncology, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02902, U.S.A.

as far as personnel and technical requirements are concerned, of performing the required protocol treatment in a uniform manner. In order to guarantee the appropriateness of the submitted treatment data, every oncology study group in each oncological discipline requires a quality control system.

The CALGB (with which the SGCCR has been working for many years) was the first group to implement a quality assurance program for radiation oncology treatments [1–3]. In this report we will present the results of quality control in radiation oncology, focusing on two CALGB protocols in which a relatively simple irradiation technique was employed.

Our study is of importance to those who are interested in protocol treatment and it shows that quality control is essential not only for assuring the reliability of data, but also for improving radiotherapy performance of protocol treatments.

MATERIALS AND METHODS

Protocols

In 1974 the CALGB protocol *7411* (Fig. 1) for the treatment of acute lymphocytic leukemia (ALL) of childhood was activated and in 1976 it was replaced by protocol *7611* (Fig. 2). Both protocols prescribe induction and maintenance chemotherapy and cranial irradiation to include the spinal cord down to C2 and the posterior two-thirds of the orbit using parallel opposed fields (Figs 3 and 4—diagram and X-ray). This requires that the caudal border of the irradiation field at the base of the skull has to be individually adjusted with shielding blocks. Preferably the definition of the target volume for each patient was to be accomplished with a simulator and documented by simulator films. Furthermore, a field verification film was required, taken on the treatment machine (^{60}Co or linear accelerator) before the first treatment session. A dose of 2400 rad, with a single dose of 200 rad at midplane, was to be given in 12 sessions in 16 days.

All radiation treatment data, consisting of treatment plans, localization films, verification films and dosimetry calculations, were required to be submitted to the Radiotherapy Quality Assurance Review Center, which was established

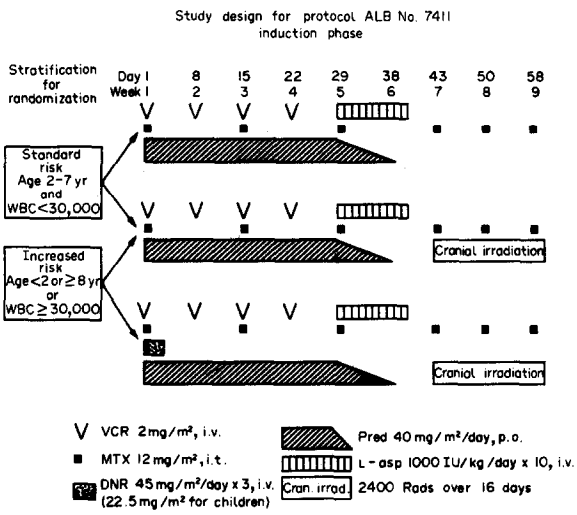

Fig. 1. Protocol design for CALGB 7411, acute lymphocytic leukemia of childhood.

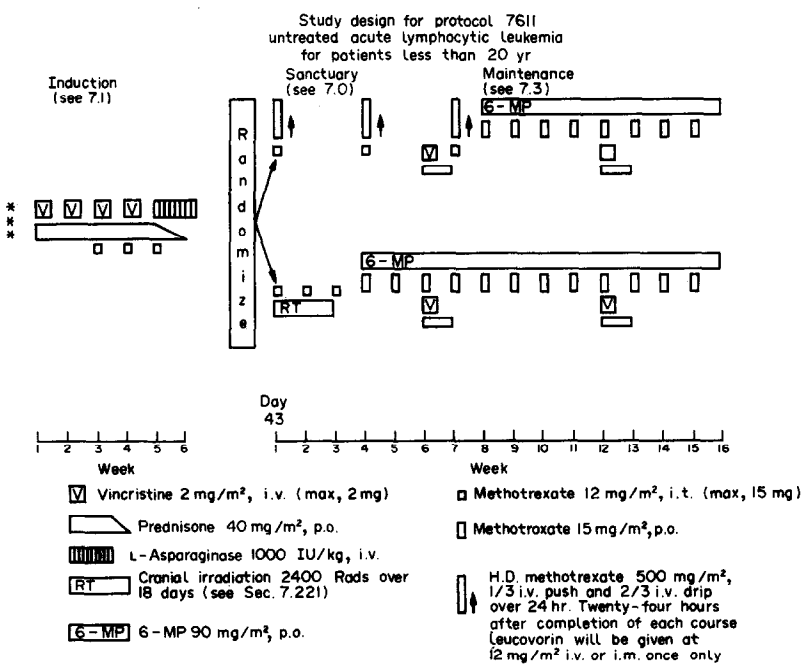

Fig. 2. Protocol design for CALGB 7611, acute lymphocytic leukemia of childhood.

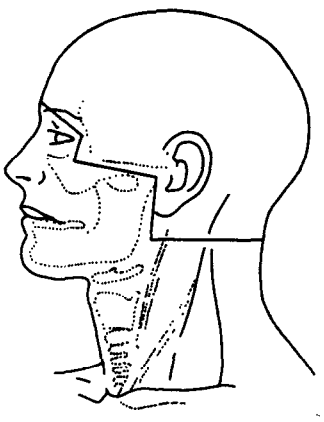

Fig. 3. Analysis of radiation field requirements in protocols 7411 and 7611.

in 1975. The review of cases in *7411* occurred 2–3 yr after the patient completed treatment. In protocol *7611*, on the other hand, the radiotherapist was informed by a letter within a month or two as to the assessment of the treatment and type of deviation if such had occurred.

Materials

Six hundred and ten children were treated on the radiotherapy arms of these studies, 348 on protocol *7411* and 262 on protocol *7611*. Accrual of patients per year is shown in Table 1.

Among the participating oncological institutions, 46 were from the United States, 4 from Switzerland, 1 from Paris and 1 from Copenhagen. Twenty-seven of the 52 institutions were 'principal centers', i.e. members of the CALGB. The remaining 25 institutions had the status of 'satellites' of the principal centers. All of the radiation treatment reviews were performed in Providence, RI by a team of radiotherapists who are members of the CALGB and the chief physicist of QARC.

Assessment of the treatment can only be accomplished if the radiotherapy data submitted are complete and evaluable. This must include a complete description of the treatment plan, simulator (localization) films, verification (treatment) films, isodose plan and departmental treatment sheets so that the dose and volume delivered can be adequately determined. Review of the submitted data by the Quality Assurance Review Center can then determine whether the protocol requirements have been adhered to and the patient has been treated appropriately for the protocol. For example, if an institution enters 10 patients on a study but submits complete data on 8, only these 8 can be evaluated. If, of the 8 patients, 7 are assessed to have been treated according to protocol requirements, only these 7 are classified as appropriate. Finally, then, 70% of the patients entered would be considered evaluable and appropriate. The institution's performance score would then be 70%.

Table 1. Patient accrual to protocol CALGB 7411 and 7611 by year

Year	*7411*	*7611*	
1974	93		
1975	131		
1976	119	2	
1977	5	104	
1978		100	
1979		56	
Total	348	262	(610)

RESULTS

Complete and evaluable data were available in only 47% of the 348 patients treated by 50 institutions in protocol *7411*. The 52 therapy centers which treated 262 children in protocol *7611* achieved an evaluability rate of 69%. Both protocols show a time-dependent improvement of performance: the evaluability of the data rises in *7411* from 37 to 53% and in *7611* from 63 to 73% (Table 2).

Another time-dependent pattern appears when the rate of patients treated according to protocol requirements is reviewed. The improvement with time is clearly seen in protocol *7611*, where for 1977 through 1979 the rate of appropriately treated patients rose from 37 to 61%, whereas no significant pattern was found for protocol *7411*. This improvement is most likely due to the detailed comments which the radiation oncologist received from QARC for each case.

The impact of this 'first letter' can be seen in the performance of institutions in protocol *7611*. The percentage of cases with complete, evaluable data rose from 57 to 87% ($P = 0.001$). Furthermore, the percentage of patients treated appropriately for the protocol after the 'first letter' was significantly higher than before receiving the information, 38 vs 65% ($P = 0.001$) (Table 3).

In protocol *7411* few institutions achieved a 50% or better performance (i.e. half of the cases entered into the study were fully evaluable and appropriately treated). There was no difference between the principal centers or the satellites. In protocol *7611* approximately half of the principal centers had an institutional performance score of 50% or better, but less than one-third of the satellites improved to this level. This change in performance was statistically significant ($P = 0.02$) (Table 4).

Table 2. Time-dependent improvement in protocol performance in 7411 and 7611

	Protocol					
	7411			*7611*		
Year	No.	Evaluable	Appropriate	No.	Evaluable	Appropriate
1974	93	34 (37%)	9 (26%)			
1975	131	63 (48%)	18 (29%)			
1976	124	66 (53%)	23 (35%)			
1977				106	67 (63%)	25 (37%)
1978				100	73 (73%)	38 (52%)
1979				56	41 (73%)	25 (61%)

Table 3. Impact of the first letter from QARC in protocol 7611, showing significant improvement in both evaluation and appropriateness of treatment

	No. entered	Evaluable	Appropriate
Before 1st letter	171	97 (57%)	37 (38%)
After 1st letter received	91	79 (87%) $P = 0.001$	51 (65%) $P = 0.001$

Table 4. Institution performance in 7411 and 7611, showing significant improvement at the principal centers but not satellites

Protocol	Principal centers	Satellites
7411	3/23 (13%)	6/27 (22%)
7611	13/27 (48%)	8/25 (32%)
7411 vs 7611	$P = 0.02$	$P = 0.63$

DISCUSSION

Protocol-prescribed therapies carried out within the structure of oncological working groups are an increasingly important element of current clinical cancer research. It is essential that every aspect of patient selection and therapy be uniform for the definitive evaluation of a treatment method.

This implies the exact work-up and recording of the patient's condition, his disease and all details concerning the performance and effects of the prescribed treatment regimen. As the significance of the various measures applied in a protocol has yet to be established, their reliable execution has to be guaranteed by quality control.

The reasons for deviations remain unclear and cannot be discussed from the data received by the QARC. In the process of evaluating the therapeutic effectiveness of a protocol, we have to keep in mind that a simple deviation recognized by the QARC may be repeated during every treatment session. The simulator and verification films document merely the momentary spatial relation between patient and irradiation source, but do not take into consideration the deviations which might also occur in the course of a complete treatment series. It is assumed that reliable reproducibility in each of the 12 sessions has been achieved and that new verification films for every irradiation session are not required.

As far as we know, this is the first study to demonstrate quantitatively the need for radiotherapy quality control in the performance of a multi-institutional treatment protocol. This study was conducted on the radiotherapeutic component of a multimodal treatment only because the radiation oncologists of the CALGB recognized the problem and reacted with the establishment of a quality control office.

It is still of concern that transmission of evaluable data to the data center remains a problem for some institutions and that there is still too high a rate of deviations from protocol. The radiation oncologist clearly profits from the information he gets from the QARC as to the appropriateness of his treatment. It is, therefore, not surprising that investigators at principal institutions who have frequent contact with the QARC profit from this feedback more than satellite institutions. A similar divergence of performance has been noted by the EORTC in a soft tissue sarcoma protocol. They found that minor participants were in fact deleterious to the scientific and administrative performance of the study [4].

The goal of the CALGB radiotherapy quality control program is to effectively assure that every case entered into a study will ultimately be completely evaluable. The radiation oncologists in the group are concerned and attempting to approach this level of participation. Equally, the other disciplines must establish quality control procedures of comparable effectiveness.

CONCLUSIONS

Quality assurance programs are essential for protocol studies. It is important in assessing the

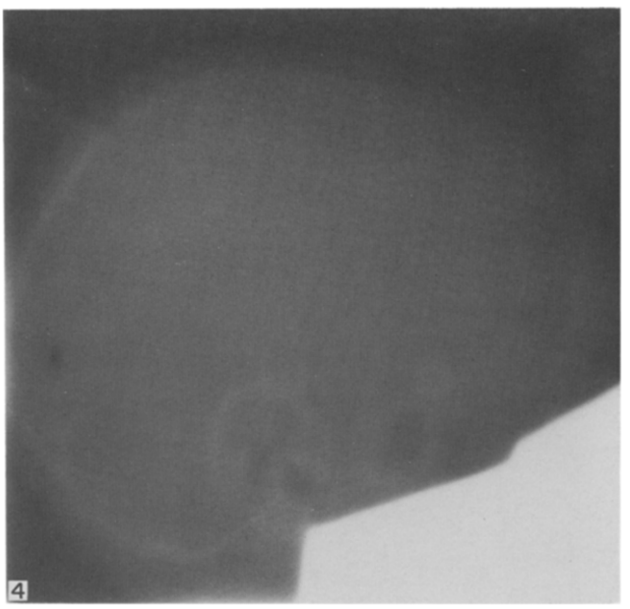

Fig. 4. Portal film of field for cranial irradiation.

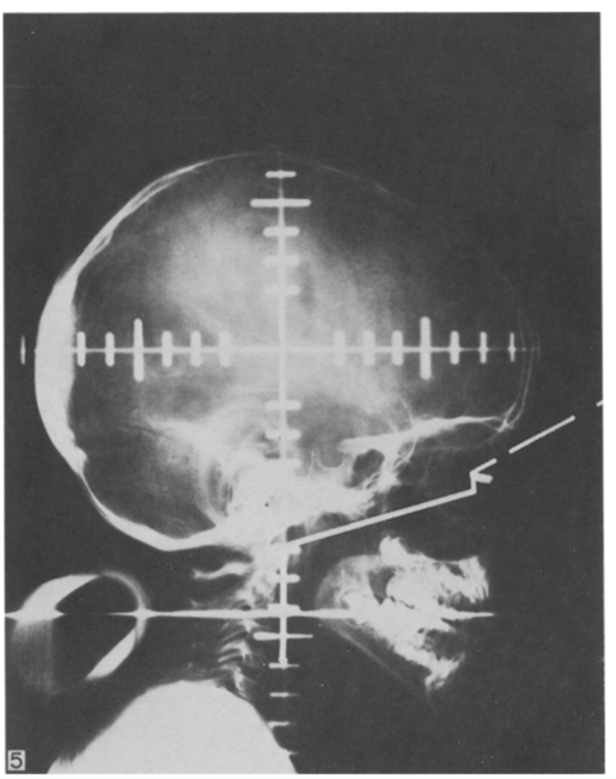

Fig. 5. Simulator film of field for cranial irradiation.

appropriateness of the therapy delivered and enables a uniform evaluation of the end results.

Information the radiotherapist receives from the Quality Assurance Review Center helps to improve his performance of protocol treatments —in effect a learning process takes place. Adherence to protocol requirements increases with increased participation in studies. We believe that quality assurance in multimodal, multidisciplinary protocols should be developed for all disciplines to enhance the evaluability of all cases entered into the studies.

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