REGIONAL PERFUSION FOR SOFT TISSUE SARCOMAS AND MALIGNANT MELANOMAS*

*JOHN S. STEHLIN (Jr.), M. D.***

Experience with perfusions for soft tissue sarcomas and malignant melanomas arising on the extremities of patients observed at the M. D. Anderson Hospital and Tumor Institute has convinced us that this procedure has real merit as a treatment for these types of tumors. When regional perfusion was instituted at this hospital eight years ago, little was known about the problems involved. For this reason, the procedure was initially employed only for locally advanced or disseminated tumors. As more was learned about the dosages and the techniques of administration were improved, its use was broadened to include more favorable cases. At present, the extremities lend themselves best to perfusion, in that they can be more successfully isolated than any other part of the body, and the danger of leakage of the chemotherapeutic drug into the general circulation is thus minimized.

TECHNIQUE

For soft tissue sarcomas, phenylalanine mustard is combined with actinomycin D, whereas for melanomas phenylalanine mustard alone is administered. Whether these are the most effective currently available chemotherapeutic agents is not known. They were chosen in order that as many variables as possible could be eliminated, and their usage has been continued so that meaningful data might be accumulated. In the future, trials of new drugs will be conducted.

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* Department of Surgery, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

The basic techniques of perfusion, as introduced by Creech et al. (1, 2) have been described in detail in earlier communications (3, 7). The dosages and flow rates of the drug and the duration of the procedure have been followed consistently as described.

Two Sigmamotor pumps and a small disposable bubble oxygenator are employed. The latter is primed with 500 ml. of heparinized blood, and a mixture of 95% oxygen and 5% carbon dioxide is delivered at a rate of 3 to 5 L. per minute. Immediately before the perfusion itself is begun, the patient is given heparin intravenously in a dose of 2 gm./kg. of body weight.

SOFT TISSUE SARCOMAS

In our early experience with perfusion for soft tissue sarcomas, a significant number of these tumors, even the far advanced, exhibited an impressive response which lasted a few months. It seemed, therefore, that the procedure might be employed as an adjuvant to excision or irradiation, or both, for potentially controllable tumors of this type on the extremities. It was hoped that the incidence of local recurrence, and perhaps of dissemination, might be reduced by perfusing the extremity before the tumor was excised, and perhaps combining irradiation with either or both of these operations. Of paramount importance was the possibility that fewer amputations would be necessary following the use of combined treatment. Thus, for the past few years, patients with soft tissue sarcomas arising on an extremity have received perfusion together with either wide local or radical excision of the tumor, or with irradiation, or with all three of these modalities. Perfusion has been performed before excision, and irradiation with 1500 rads has been administered both before and after perfusion and followed six weeks later by radical excision of the tumor.

To the present time, 37 patients have been treated for soft tissue sarcomas by one of these combined methods. The primary tumors have been controlled for varying periods of time, from nine months to more than five years. Also, the combined approach has served to obviate the necessity for amputation of the affected extremity of 80 per cent of the 37 patients. No significant increase in the five-year survival rate has been observed. Since the number of patients in the series is relatively small, the value of the procedure as a treatment for these tumors has not been established. At this time, however, the responses suggest that, as an adjuvant to excision of the primary tumor or irradiation, or to both, perfusion offers highly favorable possibilities.

MALIGNANT MELANOMA

In this hospital, surgical treatment for melanoma arising on an extremity formely consisted of the conventional wide local excision of the primary lesion or its excisional scar, with or without prophylactic or therapeutic dissection of the regional lymph nodes. These conventional methods were often inadequate, in that they merely attacked the disease distally and proximally; they did not affect metastases within the cutaneous or subcutaneous lymphatics b etween the site of the primary melanoma and the axilla or groin. In January 1958 an experimental clinical program which included perfusion with phenylalanine mustard, with or without regional lymphadenectomy, was instituted principally for control of melanoma within the extremity. The surgical procedure has been varied according to 1) whether the tumor arose on the upper or lower extremity, 2) its location on the extremity, and 3) wheter the regional lymph nodes exhibited clinical evidence of metastasis.

After a trial of the perfusion program over a period of almost six and a half years ending June 1, 1964, the records of all patients with melanoma of an extremity who had been treated according to this method were reviewed. In addition, the records of all patients who had received conventional treatment without perfusion were reviewed. Thus, the study included every patient for whom definitive surgical treatment of any type had been performed at this hospital for melanoma arising on an extremity, exclusive of the shoulder and gluteal regions, the total number being 339. Patients who were merely observed or who were referred for consultation and those who received therapy were omitted from the study.

The conventional therapy most commonly employed consisted of wide excision of the primary melanoma or its excisional scar, combined with prophylactic or therapeutic lymphadenectomy. Perfusion was combined most often with both excision of the primary melanoma or the scar and lymphadenectomy. Although primary melanomas are still widely excised, since the institution of the perfusion program we have generally been more conservative than previously in excising these lesions. Skin grafts were necessary in 27 (23 per cent) of 118 patients who were treated by conventional methods and in 16 (7 per cent) of 221 who received perfusion. Major amputations were performed for 20 patients.

The results of our treatment of the 339 patients were analyzed, first, with respect to recurrent melanomas within the involved extremity, and second, with respect to the survival rates. In order to obtain a more up-to-date picture, the records

of these patients have recently been reviewed again. The figures shown in Table I therefore reflect the number of recurrences to the present time, and those in Table II, the survival rates of the 339 patients. It is noteworthy that the perfused group contained 15 per cent more patients with advanced tumors, i.e., Stages II, III and IV, than the group who were treated surgically.

In our experience, melanomas which recur within a reasonable period of time subsequent to definitive therapy carry an ominous outlook, even though the recurrent tumor may appear clinically insignificant. The fact that 36 of 41 patients (88 per cent) in this series who had recurrences after definitive therapy, whether conventional or perfusion, died of melanoma within a short time supports this view.

From a strictly statistical standpoint, a comparison of the merits of perfusion with those of conventional treatment for melanomas on the extremities based upon the findings in this review is not possible. First, the patients were not selected at random. Second, the number of patients, especially of those with tumors in some stages of development, was too small to permit valid conclusions. Despite the fact that the study did not meet these essentials for a statistically accurate analysis, certain standards were observed. Not only did the review cover every patient who received definitive surgical treatment at this hospital, but each tumor was classified according to its stage at the time of the patient's initial treatment at this hospital, and the perfusion varied little or not at all with respect to the type and dosage of the drug, duration of the procedure, and technic. Finally, all perfusions were performed by the same surgeon or under his direct supervision.

At present, only two conclusions can be drawn. First, perfusion is unquestionably of value in the treatment of patients with recurrent melanomas. Second, in our experience, the morbidity, mortality, and complications after the procedure have been reasonable and acceptable. From a rather extensive experience with chemotherapy for cancer in general, it is believed that conclusions regarding the relative efficacy of perfusion and conventional treatment are not warranted at this time; indeed, they might prove not only erroneous, but dangerous as well. Personal experience with both methods of treatment for melanoma, however, strongly suggests the following trends.

1. Perfusion reduces materially the incidence of recurrence within the extremities, particularly in the lower extremity. The advantage of perfusion as an adjuvant procedure becomes especially obvious if one considers the incidence of recurrence without evidence of distant metastasis after conventional treatment.

2. If recurrences are to develop after lymphadenectomy and perfusion, the latter seems at least to forestall their appearance until systemic disease becomes overwhelming.

3. Perfusion reduces significantly, although it does not eliminate, the necessity for radical amputation.

4. The five year survival rate after our experimental program, including perfusion, is at least equal to that of conventional therapy, and perhaps will prove to be 10 per cent higher.

If our observations have been correctly interpreted and if the current trends continue unaltered over the next few years, we believe perfusion will prove to be a valuable adjunct to the surgical treatment of patients with melanomas arising on the upper extremities in the epitrochlear region and below, and of all patients with melanomas arising on the lower extremities. Efforts must be continued to discover a more effective chemotherapeutic agent for malignant melanoma.

RESUMEN

Las respuestas obtenidas en los sarcomas originados en los tejidos conjuntivos de sostén, sugieren que la perfusión ofrece posibilidades altamente favorables como terapéutica adyuvante a la excisión del tumor primario o la irradiación.

La sobrevida a los cinco años de los enfermos con melanoma maligno sometidos a un estudio experimental con perfusión, demuestra que es por lo menos igual a la que se logra con la terapéutica convencional y quizás revele ser superior en un 10%.

Si nuestras observaciones han sido interpretadas correctamente y si la tendencia actual se mantiene incambiada en los próximos años, creemos que la perfusión resultará ser una terapéutica adyuvante valiosa a la cirugía en los melanomas que se originan en el miembro superior a nivel de la región epitroclear o por debajo y en el miembro inferior de cualquier localización. Debe perseverarse en los esfuerzos de descubrir un agente quimioterapéutico más efectivo para el melanoma maligno.

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