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EXPERIENCE GAINED DURING THE INTRODUCTION AND DEVELOPMENT OF INTRA-ARTERIAL CHEMOTHERAPY OF THE HEAD AND NECK TUMORS*

Introduction

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The application range of chemotherapeutics is limited by the tolerance of the highly susceptible normal tissues (bone marrow and intestinal mucosa) for a cytostatic. Dosages producing no appreciable side effects are mostly not high enough to be lethal to cancer cells. Therefore, methods have been designed by which the chemotherapeutic is delivered to the tumor through its arterial supply. Infusion of a cytostatic into small caliber arteries supplying lesser areas (head, neck, liver) allows the concentration of the drug in the tumor to be kept much higher than in intravenous application procedures (1, 2, 3). In arteries of a larger caliber, however, the cytostatic is rapidly diluted to a concentration approximately equal to that ensured by intravenous injection procedures (2).

In spite of the theoretical considerations supporting the application of intra-arterial chemotherapy (IAC), the results achieved by this method have been relatively modest. Sullivan reported that only 26 percent in his series of patients treated with IAC, had shown more than 50 percent of tumor regression; Harrison reported 12 percent, Lachapele 33 percent, and Cachin 17 percent (5). There is no doubt that the reasons for such results are to be sought in the fact that there are still many unsolved problems regarding chemotherapy in general and the regional applications of drugs in particular.

High concentration of the cytostatic in the tumor, the duration of IAC course, the dosage schedule and the tumor sensitivity to the applied cytostatic are generally considered to be the factors primarily responsible for the success of regional chemotherapy.

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It has been pointed out that in order to obtain a high concentration of the cytostatic in the tumor, it is imperative that the arterial catheter be correctly placed, and that all arterial side branches be carefully ligated. In this way it is possible to direct the flow of the cytostatic predominantly into the tumor and to reduce the infusion of the surrounding healthy tissue. The correct position of the catheter and the size of the infused region should be checked by methylene blue or fluoresceine injection into the cannulated artery (1, 5, 16, 23).

The duration of arterial infusion is largely based on experience and published data on the length of therapeutic course range from a few days to several weeks. Nor is there much agreement regarding the dosage schedule (1).

The choice of the cytostatic for intra-arterial chemotherapy is based, in most institutions, on the clinical effect of a cytostatic in tumors of related histology because, in vitro tesing of the cytostatics in each individual case can be done only in few, well equipped laboratories and is very expensive. In addition, the tissue culture of the patient's tumor is not always successeful while a positive correlation between tumor sensitivity determined in vitro and the clinical effect of the drug is found in only something over 50 percent of all cases (6, 7, 22, 24).

The purpose of the present work was to investigate some parameters closely related to the success of IAC i. e. the drug flow to the tumor and the tumor response to the drug.

It was believed that by the use of isotope methods designed for the study of the blood circulation a better understanding of the haemodynamics of the tumor region during infusion could be gained and, in turn, a more exact control of the flow of the cytostatic into the tumor region ensured.

Further, an attempt was made to find out whether a morphologic study of the behavior of the tumor cell population during IAC could yield data on tumor sensitivity which, like an in vivo test, would serve as a guide-line for the choice of the appropriate cytostatic.

Furthermore, we were interested in the tolerance of the normal tissue sourounding the primary site in cases where IAC was followed by a full course radiotherapy.

Materials and methods

In a series of 28 patients with advanced cancer of the head and neck treated by IAC, the flow of the infused drug was studied with the aid of isotopes while the changes occurring in the tumor during chemotherapy were followed by repeated thin needle aspiration biopsy.

Cannulation of the appropriate artery was accomplished in most cases retrogradely via the superficial temporal artery (Stille-Werner teflon catheter). During cannulation the methylene dye injection was used only for an approximate estimation of the catheter position, which subsequently, was accurately determined by isotope examination and corrected if necessary. A daily dose of 50 mg Methotrexate in heparinised saline (1 ml/500 ml)

was continuously infused over the 24-hour day. The cytostatic was neutralised by intramuscular injection of 25 mg Leukovorin daily.

In order to study the regional flow of the IAC we applied a method developped by Wagner et al. (25) for the investigation of the general blood circulation. In our work, the infusate was labeled with radioactive particles large enough to embolise in the first capillary bed. The radioactivity deposited in the tissues is thus proportional to the amount of material delivered locally. In the presence of arteriovenous (a/v) shunts, the labeled infusate partly bypassed the target region and the particles were brought to and trapped by the lung capillaries. Macroaggregated human albumin labeled with I-131 (17) or Tc-99 m (14), iron hydroxide particles labeled with In-113 m (15) and, most recently, microsieved Dowex 50 W resins labeled with In-113 m (10) were used. After the administration of the isotope, color dot scintigrams and body profile curves were made. Details and results achived by this techniques were published elsewhere (8, 9, 11).

The dynamics of the morphological changes in head and neck tumors during IAC was studied by repeated thin needle aspiration biopsy. The aspiration biopsy smears were stained according to the May-Grünwald-Giemsa method. The intensity of morphological changes in the tumor cells was classified into four categories and a retrograde comparison with the tumor regression, which likewise was classified into four categories, was made. In order to exclude a subjective interpretation of the results, the cytologist who classified morphological changes in the coded tumor smears was not made familiar with the clinical picture of the respective tumor.

In cases where the IAC was followed with percutaneous Co^{60} irradiation, the technique consisted in applying two opposite portals covering the primary together with regional nodes. Daily doses varied between 160 to 200 rads, with a total tumor dose of 6000 rads in 35 days. The changes of the irradiated mucosae were evaluated by frequent clinical examination during the radiotherapy. The appearance and severity of the mucosal reaction of the infused and irradiated site were compared to the reaction of the non-infused, but only irradiated mucosae.

Comments on results

Accuracy of catheter position

Even though dye injections indicated a good initial position of the catheter in most of our patients, subsequent isotope examinations showed that it was correct only in about one third of all cases. By repeated (1 to 3) corrections of the catheter position an adequate flow of the infusate was obtained in another third of cases (Fig. 1; a, b). In the remaining cases, however, the catheter could not be positioned satisfactorily even after several attempts (11).

By comparing the distribution of the intra-arterially injected methylene blue with the scintigrams of the same region, some further shortcomings of the dye method for checking the position of the catheter were found:

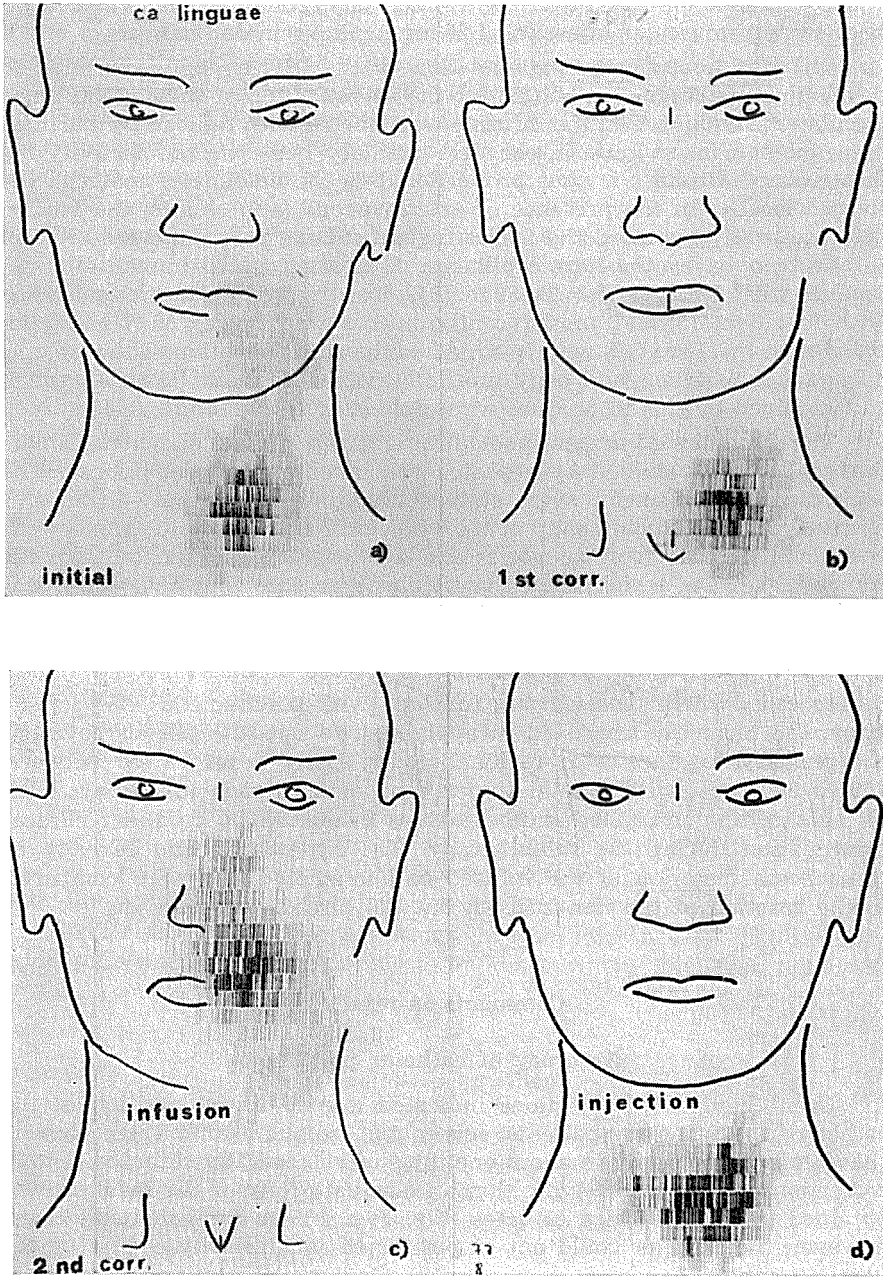

Fig. 1. Tumor of tongue, isotope monitoring of intraarterial chemotherapy: (a) initial distribution is not satisfactory; (b) 1st correction unsuccessful; (c) after 2nd correction the flow of infusion is adequate; (d) a simultaneous rapid injection of another isotope is distributed quite differently.

— the tumor blood supply can be inferred only through the coloration of the skin and mucosae, giving thus no information on the central region of the tumor:

— neither the infused volume nor the concentration ratio between the tumor and the surrounding tissue can be estimated.

In checking the position of the catheter with the dye, the latter is injected at the rate of about 1 ccm per 30 sec., whereas the chemotherapeutic itself is infused at the rate of 5 to 10 drops per min. On the basis of Rush's experiments on a model of plastic tubes (13) we assumed that this difference in the application rate would result also in a difference in the spatial distribution of the infused material. In the literature no related in vivo study could be found, but we supposed that rapid injection would give rise to a turbulent flow in the artery resulting in a thorough mixing of the material with the blood and its fairly uniform distribution along the arteries branching off near the tip of the catheter. Conversely, it was expected that a very slow infusion would produce a laminary flow of the material which the blood counterflow would carry to and unevenly distribute in the peripheral arterial branches. This assumption was verified with the aid of the simultaneous application of two different isotopes, one of which was injected while the other one was slowly infused in the same patient. In 2 out of 5 such experiments, scintigrams actually demonstrated an entirely different distribution pattern of the two isotopes (Fig. 1; c, d), proving that the results of dye check may be erroneous and misleading.

Constancy of drug distribution during IAC and the treatment policy

Observations made during the treatment showed that the spatial distribution of the infused material was extremely variable. At the time of the acute local toxic reaction two different phenomena were observed:

— if the toxic reaction manifested itself predominantly in the form of an oedema, the infused material was diverted to the neighboring arterial branches;

— if, however, an erythema was the leading symptom of the toxic effect, isotope examination showed a leakage of the drug out of the region via a/v shunts, which frequently was, associated with a general toxic reaction.

Besides the shunts appearing during IAC, in more than one-half of examined patients a/v shunts of various extent were discovered already before IAC. Patients with considerable primary shunting tolerated IAC poorly. Some of them developed leukopenia already after a single dose of 50 mg of Methotrexate.

By guiding IAC only on the basis of a relative decrease in the leukocyte count, which according to the reported data indicates that chemotherapy should be discontinued or the dosage lowered, the dangerous bone marrow depression can not be entirely avoided. Our observations showed that the drop in leukocyte counts occured one to two days after the appearence of a/v shunts. Consequently, we believe that a/v shunts are an early and reliable sign indicating the necessity to discontinue IAC.

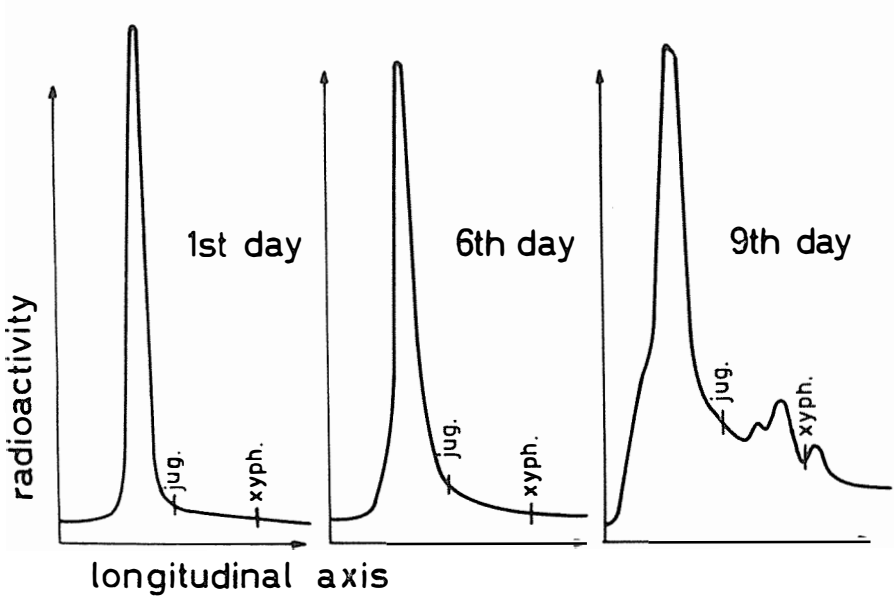

Fig. 2. Body profile curves after infusion of radioactive Dowex-50 W In-113 m (40-60 mikrons diameter) in a case of buccal cancer: onset of arteriovenous shunts detected by appearance of lung activity.

Use of antihistaminics

We believe that the fast desintegration of the tissues brought about by the cytostatic, causes the release of histamine and allied substances which, in turn, may affect the blood vessels, a phenomenon shown by isotopes as »shunts« which anatomically are, in all probability, abnormally dilated capillaries. Recently we attempted to control this phenomenon by applying antihistaminics. It was found that 24 hours after the intra-arterial application of 40 mg of Synopen (Geigy) in heparinised saline the shunts had almost completely disappeared. In cases in which the antihistaminics were not applied, IAC had to be discontinued for 5—18 days before shunts closed down.

In spite of our scanty experience in this regard, it is believed to be possible to influence the shunting mechanism by antihistaminics and thus ensure a more efficient conduct of chemotherapy.

Tumor sensitivity reflected by cell morphology

In a previous work, a morphological study of cells in malignant effusions during chemotherapy was carried out by means of exfoliative cytology. It was recognized that the effect of cytostatics is reflected in the cell morphology and that there is a certain correlation between the grade of cell damage and the clinical effect (3, 4, 18, 19, 20).

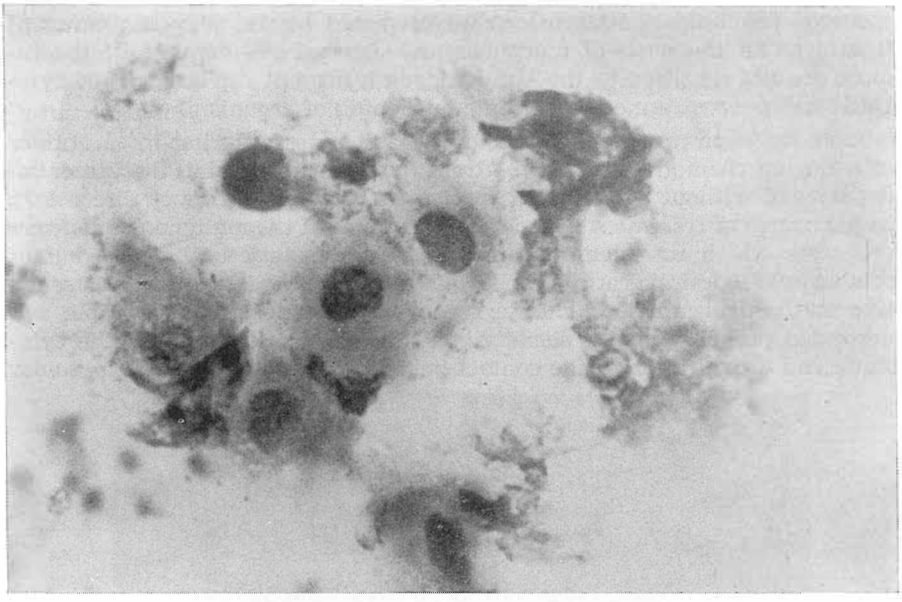

Fig. 3. Tumor of the tongue, aspiration biopsy before treatment: epidermoidal cancer cells.
M. G. G., 45 × 8

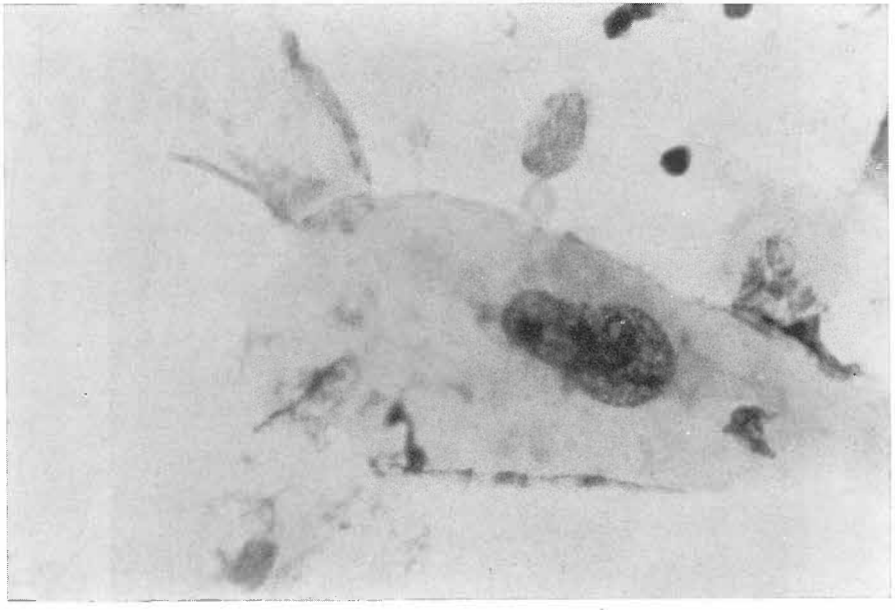

Fig. 4. The same case as Fig. 3 during IAC (150 mg Methotrexate i. c.).
M. G. G., 45 × 8

Hence, an attemyt was made to find out whether in regional chemotherapy the clinical response can be predicted at the very beginning of treatment on the basis of morphological signs of cell damage. If the tumors are not sensitive to the applied drug a prompt replacement of cytostatic will prevent unnecessary toxic burdening of organism.

By the aspiration biopsy cytology the changes occuring in the tumor cells during chemotherapy can be traced without disturbing the tumor integrity and without exposing the patient to any major risk or discomfort. In the course of treatment degenerative changes of the malignant cells were observed, which reflected the effect of the cytostatic and resulted later in a complete desintegration of the cells inasmuch as the tumor was sensitive to the drug applied. The degree of cell alteration was variable and depended probably on the sensitivity of the tumor, the dosis of the cytostatic and the duration of the contact between the cytostatic and the tumor

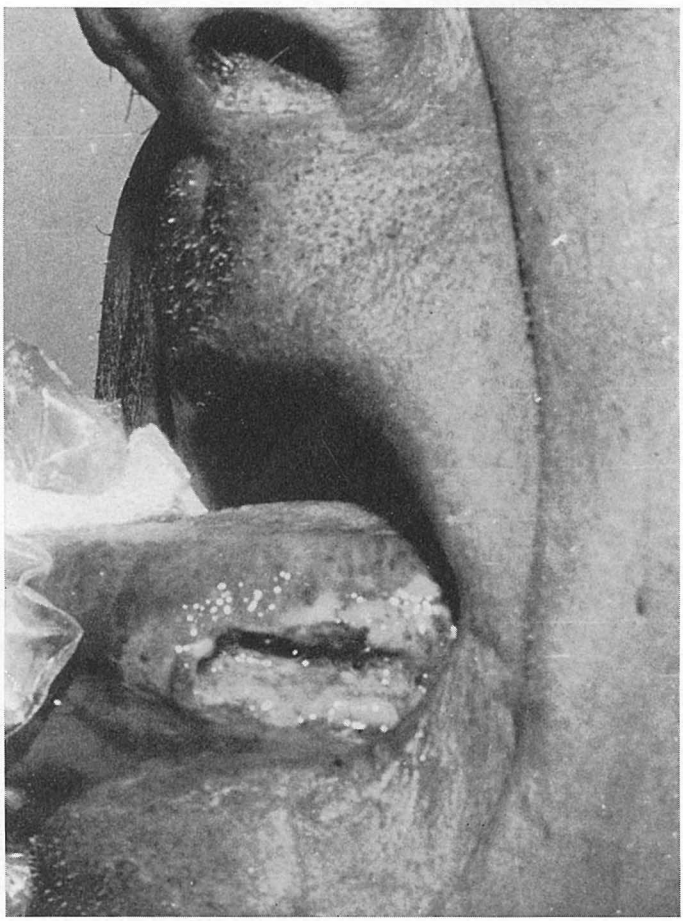

Fig. 5. Tumor of tongue (T_3) before IAC.

tissue. Retrograde comparison disclosed that in cases with marked degenerative changes of malignant cells after the first doses of the cytostatic, the clinical response was most striking.

Early damage in the cells was detectable after the first doses of the drug whereas the clinical response was observed not earlier that on the 8th to 10th. day. In some cases the intensive initial morphological evidence of cell damage did not progress during chemotherapy. This inconsistency turned out to be partly due to the leakage or deviation of the cytostatic. In the remaining cases differently sensitive tumor cell strains or development of tumor resistance must be assumed.

Of 28 patients with head and neck tumors treated by IAC 14 had 50 to 100 percent regression of the tumor. Cytological reports correctly predicted the clinical outcome of therapy in 24 cases, 3 cases could not be

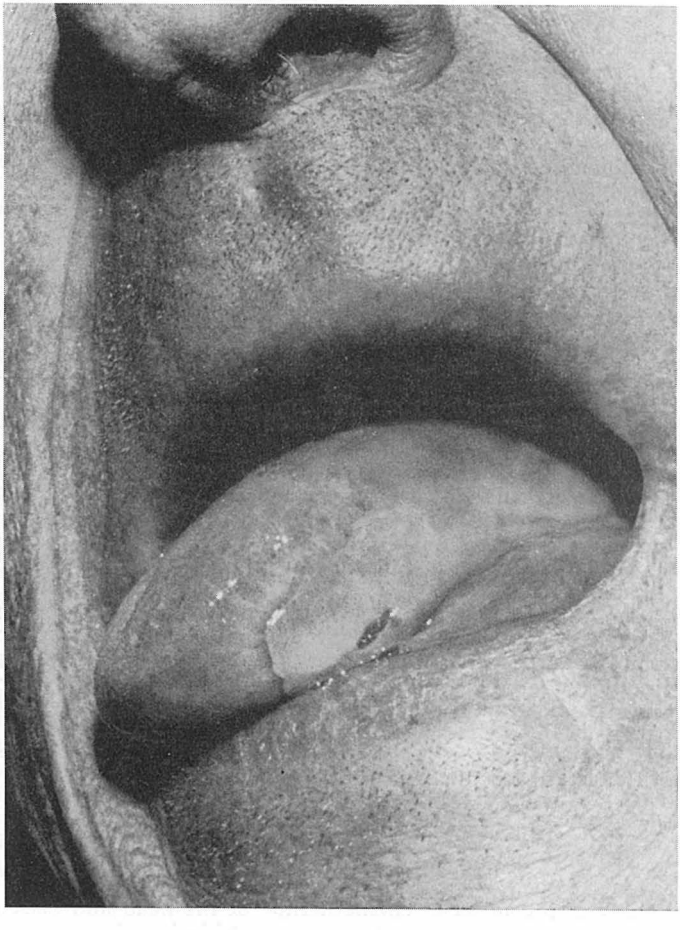

Fig. 6. The same case as Fig. 5.: Complete regression of the tumor after TD of 225 mg of Methotrexate i. a. (Selective infusion of the left lingual artery). Signs of local toxic reaction are seen.

evaluated because of unsuitable material, while in one case the cytological report did not tally with the clinical effect.

The percentage of significant tumor regressions (50%–100%) archieved in our series is considerably higher than that reported in the literature (5). Cytological results have so far not been used in the clinical work. Experience, however, seems to indicate that it will be possible immediately to replace an inadequate cytostatic and by doing so perhaps further improve the results.

According to our observations a full course of radiotherapy can be applied safely on a region previously treated by IAC (12). No gross changes in the severity of radiomucositis of the infused areas, compared to the non-infused side, were noted.

Conclusions

1. The intra-arterial (i. a.) infusion of isotope labeled particles seems to be a feasible method for accurate placement of i. a. catheter for IAC.
2. Primary arterio-venous shunts in the tumor area, or those secondary to chemotherapy, seem to be responsible for the general toxicity of the intra-arterially administered drug. The shunts can be monitored by profile counting after i. a. administration of particulated isotopes.
3. It seems that cytological examination of infused tumors can give important data on tumor sensitivity to the applied drug.
4. We believe that by implementing both methods the results of IAC can be further improved.
5. According to our experience, it seems that the combined treatment of head and neck tumors (IAC plus irradiation) could yield better results than IAC or irradiation alone.

Sadržaj

Kod proučavanja intraarterialne kemoterapije tumora glave i vrata upotrebili smo dve nove metode: intraarterialnu aplikaciju izotopa i uzostopne citološke analize tumora tokom terapije.

Upotreba izotopa omogučila je precizniju kontrolu pozicije katetra i s tim veću koncentraciju citostatika u tumoru u uporedjenju sa metodom intraarterijalnog bojenja tumorske regije.

Upotrebom izotopa došli smo i do nekih novih nepoznatih činjenica, kao tkzv. arteriovenozni šanti i skretanje infundiranog materijala iz tumorske regije, što može biti uzrokom slabih rezultata intraarterijalne kemoterapije.

Retrogradnim uporedjenjem kliničkih rezultata i citoloških promena na ćelijama tokom kemoterapije našli smo u većini primera pozitivnu korelaciju. Izgleda moguće, da bi se citomorfološke promene mogle upotrebiti za rano prognoziranje kliničkog efekta, u koliko tokom kemoterapije ne nastupe promene u distribuciji citostatika u tumorskoj regiji, ni u senzibiltetu tumora.

Summary

In the study of intraarterial chemotherapy of the head and neck two additional methods were used: intraarterial infusion of isotope labeled particles and repeated cytological analysis of tumors during chemotherapy.

Isotope application afforded a more accurate catheter positioning and, in turn, a higher concentration of the cytostatic in the tumor, than dye method.

Further, isotope application revealed some new factors, such as, arteriovenous shunts and deflections of the infused material, into neighboring arteries, which, if not taken into consideration, might become responsible for a certain percentage of failures in intraarterial chemotherapy.

Retrograde anlysis of clinical response and cytological changes occuring during chemotherapy showed a positive correlation in the majority of cases.

It is assumend that cytomorphological changes in tumors after the first doses of cytostatics might be used for an early prediction of the clinical response provided that distribution is kept correct and that no changes of the tumor sensitivity occur.

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