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Twelve Years of Experience with Cytotoxic Therapy in Malignant Tumors of the Neck and Head

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Zwölf Jahre Erfahrung mit zytotoxischer Therapie maligner Tumoren an Kopf und Hals

Zusammenfassung. Zwischen 1968 und 1981 wurden 164 bösartige Tumoren an Kopf und Hals, 151 davon als unheilbar eingestuft, mit Chemotherapie isoliert oder mit Radiotherapie bzw. Chirurgie kombiniert behandelt. Chemotherapeutische Protokolle, Behandlungsmethode und Ergebnisse werden ausführlich besprochen. In einigen Fällen wurde die Heilung nur mit Zytostatika erreicht. In anderen Fällen ist es uns gelungen, mit Radio- und Chemotherapie ausgedehnte Operationen zu vermeiden.

Schlüsselwörter: Zytotoxische Therapie – Krebs an Kopf und Hals

Summary. Since 1968 we have treated with antiblastic drugs 164 malignant tumors recurrant or incurable by surgery or radiotherapy in 151 cases. Different therapeutic methods were employed. Today we have the possibility of selecting alternative options with incipient or relatively delimited carcinomas, principally the substitution of radical surgery by initial associated physical and chemical treatment, so that if there is a cure the consequences of radical surgery can be avoided. We emphasize the cure of two primary cancers of the uvula with 300 mg bleomycin exclusively and the results observed in oropharyngeal and laryngeal carcinomas by using three intermittent Schabel cycles and 4,000 rad Telecobalt, avoiding a radical surgery.

Key words: Cytotoxic therapy – Cancer of the neck and head

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Introduction

Since 1968 we have utilized antiblastic drugs in the treatment of carcinomas and other malignant tumors, which are encountered in our speciality.

In one group we have applied this therapy exclusively, in a another group of terminal patients this treatment has been solely of a palliative nature. In many cases this therapy has been used in conjunction with surgery and radiotherapy.

In this paper, we intend to revise our experience and the results obtained, considering that in the majority of cases (151), the carcinomas were recurrent or incurably by surgery or radiotherapy.

Material and Methods

Patients

The number of patients treated with cytotoxic drugs and controlled between October 1968 and April 1981 are presented in Table 1 according to the initial lesion.

In Table 2 we present the percentage distribution of the different evolution stages in TNM notation.

We have gradually changed our methods of treatment as we have seen the results.

Our experience can be divided into four stages:

Stage I, 1968–1974: In this stage we treated two groups of patients differently. The first group of 50 patients was treated with polychemotherapy (cyclophosphamide – vinblastine) to complement the surgery and with postoperative radiotherapy (Table 3). A second group of 25 patients was treated with monotherapy (bleomycin) to complement surgery and radiotherapy (Table 4).

Stage II, 1974–1977: In the second stage we treated 30 patients exclusively with bleomycin associated with surgery and radiotherapy. This group consisted solely of cancers of the larynx and hypopharynx (Table 5).

Stage III, 1977–1980: In this stage were treated 29 patients with bleomycin (Table 6). In two cases we used bleomcin without surgery or radiotherapy. Polychemotherapy was employed only in cases of Hodgkin's disease (MOPP and ABVD).

Stage IV, 1980–1981: This stage was begun in April 1980 stimulated by the results obtained in the previous stages. In the new stage we treated cancers which were thought to be initially incurable and also patients who were curable with radiotherapy and surgery. In this final stage we studied 30 cases distributed as shown in Table 7.

Therapeutic Methods

Polychemotherapy with Vinblastine and Cyclophosphamide. Vinblastine: 10 mg i.v. weekly for 4 weeks (i.e., a total dosage of 40 mg). Genoxal: 50 mg orally every 8 h during 1 month. Control of leukocytes every 3 days. At the end of the treatment cycle, we stopped the medication for 1 month. The treatment was repeated or not, depending on the patient's condition and the stage of the lesion.

Table 1. Neck and head cancers treated with chemotherapy (1968–1981)

Larynx and hypopharynx	108
Nasopharynx	13
Oropharynx (palatotonsillar)	12
Base of tongue and floor of mouth	16
Nose and paranasal sinuses	5
Lip	4
Hodgkin's desease	4
Lymphocarcinoma of the neck	1
Reticuloendothelioma of A. carotis	1
Total	164

Table 2. Per cent of staging in TNM notation

	%		%
T_1	3.77	T_3N_2	7.54
T_1N_2M	1.88	T_3N_3	7.54
T_2	7.54	T_4	9.43
T_2N_2	5.66	T_4N_2	3.77
T_2N_3	3.77	T_4N_3	22.64
T_3	7.54	T_4N_3M	9.43
T_3N_1	9.43		

Table 3. Polychemotherapy (cyclophosphamide-vinblastine)

Larynx and hypopharynx	40
Nasopharynx	3
Oropharynx	3
Lip	1
Reticuloendothelioma	1
Hodgkin's desease	2
Total	50

Table 4. Monotherapy (bleomycin) (1968–1974)

Larynx and hypopharynx	10
Nasopharynx	3
Oropharynx	2
Tongue and floor mouth	5
Lip	3
Nose	1
Lymphocarcinoma of the neck	1
Total	25

Table 5. Monotherapy (bleomycin) (1974–1977)

Vestibulum laryngis	5
Vocal cords	1
Ventricles	7
Pyriform fossae	2
Pharyngoepiglottic fold	3
Vallecullae	5
Lateral pharyngeal wall	3
Posterior pharyngeal wall	4
Total	30

Table 6. Monotherapy and Polychemotherapy (1977–1980)

Larynx and hypopharynx	12
Nasopharynx	3
Oropharynx	3
Base of tongue and floor of mouth	6
Nose and paranasal sinuses	3
Hodgkin's desease	2
Total	29

Table 7. Polychemotherapy (Schabel cycles) (1980–1981)

Larynx and hypopharynx	16
Nasopharynx	4
Oropharynx	4
Base of tongue and floor of mouth	5
Nose and paranasal sinuses	1
Total	30

Table 8

0 h	Vincrisul, 2 mg i.v.
6 h	Bleomycin, 30 mg i.v.
24 h	Methotrexate, 200 mg i.v. during 6 h
48 h	Leucovor, 9 mg i.m. every 6 h until a total dosage of 45 mg

Monotherapy with Bleomycin. Bleomycin: 15 mg i.v. daily for 20 days (i.e., a total dosage of 300 mg). In some cases we altered the dosage depending on the evolution of the carcinoma, patient's tolerance to the drug, and subsequent complication. The minimum dosage achieved was 150 mg and the maximum in one case only 1,515 mg.

Polychemotherapy in Hodgkin's Disease. Eight alternative cycles of MOPP and ABVD in odd and even cycles, respectively. The international convention of treatment was followed.

Table 9

Results	Cure	Improvement	Failure	Total	Decease
Polychemotherapy 1968–1974	3	0	47	50	47 = 94%
Monotherapy (Bleomycin) 1968–1974	5	16	4	25	20 = 80%
Chemotherapy (Bleomycin) 1974–1977	6	7	17	30	24 = 80%
Chemotherapy 1977–1980	13	5	11	29	16 = 55.17%
Polychemotherapy (Schabel cycles) 1980–1981	12	15	3	30	4 = 13.33%

Polychemotherapy with Schabel Cycles. We began with one Schabel cycle. One week later we started to irradiate the patients reaching 4,000 rad in 21 days. Subsequently, we repeated new Schabel cycles at 3- and 6-week intervals until the end of the radiotherapy (Table 8).

If the patient underwent surgery, the Schabel cycle was applied after the operation field had cleared.

Continuous Intraarterial Perfusion with Sullivan's Technique. We employed this technique in two incurable cases of the oropharyngeal region.

All patients treated with cytotoxic drugs were isolated, and we adopted all the control of secondary manifestation and possible repercussion in different parts of the body. Periodically, we performed hematologic tests and determined creatinine levels, bilirrubin, TGO and TGP, total proteins, proteinograms, immunoelectrophoresis, etc.

Results

The results are presented in Table 9, but they must be evaluated in two separated groups. Until April 1980 we applied the cytotoxic drugs in carcinomas of different locations which were initially thought to be incurable by surgery or combined radiotherapy. As indicated previously, they were recurrent or extensive carcinomas with the exception of the cases of Hodgkin's disease and the primary cancer of the uvula.

After April 1980 we used cytotoxic drugs to treat cancers that were susceptible to cure with others therapies, with the intention to evaluate the real possibilities of cure solely with these drugs. Thus, we cannot be surprised about the divergent results in the two groups.

In an earlier paper (Bartual 1980) we studied the results obtained in cancers of the pharynx and larynx in relation to the TNM stage. We do not think it necessary to repeat this study here.

Discussion

The first conclusion that can be drawn from the results is evident. We can still observe malignant tumors of the neck and head that are incurable with surgery or radiotherapy. In these cases the physician resorts to the application of cytotoxic drugs as palliative therapy and the patient's psychologic well-being.

The second conclusion is a confirmation of previous studies which have shown that the solid tumors of the neck and head are more sensitive to bleomycin, as non-phase-specific antiblastic drug, than to the other cytotoxics (Cline and Haskell 1977). Its capacity to inhibit the growth of the tumor is greater than that of the other antiblastic drugs. This inhibitive power increases when bleomycin is given along with the alkaloids of Vinca rosea and methotrexate (Schabel) and also combined with radiotherapy, because bleomycin has a marked radiomimetic effect (Jorgensen, 1972; Fernandez and Errazquin 1973; Bartual et al. 1975).

Since April 1980 we have applied the cytotoxics for the human necessity of helping terminal patients who had been previously treated with radiotherapy or surgery. At the same time, we do empirical testing of drugs of new cytotoxic ability, and we test the tolerance of the patients to the new drugs and to different methods of administration. We also intend to develop protocols of treatment with the information supplied by different authors (Ansfield 1962; Higuero and Aljama 1970; Rossi 1974; Galioto and Germana 1975).

We know that the reaction of the solid tumors of neck and head depends upon many factors, such as the extension of the tumor, lymphatic participation, infection of the tumor, general condition of the patient, method of the drug administration, singular or multiple dosage, hepathic or renal toxicity of the drug, etc.

Thus, between 1974 and 1977, we have studied 30 cases of carcinomas of the larynx and hypopharynx and the possible relationship between TNM stage and the response of the tumor to bleomycin. We have seen that the response of the tumor and of the patient to cytotoxic drugs generally and in particular to bleomycin is independent of the evolution stage of the lesion.

The experience of previous years has induced us to try new therapies. We know that all the drugs used can be administred either directly i.v. or in continous perfusion without accidents. Actually, we employ associated drugs that are well tolerated, effective, and do not cause depression of hematopoiesis. We also know the rate at which to administer antiblastic drugs to obtain the greatest inhibition of cellular growth and also the effects of the drugs in combination with radiation.

As has been discussed in this paper, the number of clinical cures and improvement were greater in the last group of patients than in the first. The immediate consequence of this experience is the possibility of selecting alternative options with incipient or relatively delimited carcinomas. That is, our therapeutic arsenal against cancer has been enlarged, and we can make use of the following possibilities:

1. Clear indications for primary and exclusive radiotherapy.
2. Clear indication for functional conservative surgery.

3. Clear indication for radical surgery.
4. Substitution of radical surgery by initial combined physical and chemical treatment, so that if there is a cure the consequences of radical surgery can be avoided.
5. Rattrapage surgery in cases of failure of the option explained in point 4.
6. Possibility of exclusive initial treatment by cytotoxic drugs in cancers in stages TS and T_1 of the velopalatal region and vocal cords.
7. Palliative management in incurable patients.

Thus, we can explain why after April 1980 we began to treat with cytotoxic drugs and radiotherapy some cases of laryngeal cancer subsidiary to total laryngectomy and also malignant tumors of the base of tongue and oropharynx that need extensive surgery followed by a difficult and always problematic plastic reconstruction.

We emphasize in our cases the cure of two primary cancers of the uvula in stages T_1 an T_2, respectively, with 300 mg bleomycin exclusively. In a third case of primary cancer of the uvula in stage T_2, the size of the tumor was reduced by 50% with 300 mg bleomycin and cured totally with 3,000 rads as complementary Telecobalttherapy.

In the larynx, we must emphasize the cure of two cases of vocal cord carcinomas in stage T_3N_{1a} with three Schabel cycles and 4,000 rad in 21 days. We also cured two cases of ventricular cancers in stage T_3 and one case of commissural cancer in stage T_3, avoiding total laryngectomy in all cases.

In the oropharynx we attained clinical and histological cure in three cases T_4N_3 with the associated treatment (radical neck dissection + three Schabel cycles + complementary 4,000 rad radiotherapy) thus avoiding the removal in monoblock of the cervical lymph nodes with the mandibula, the lateral oropharyngeal wall, the soft palate, and part of the oral floor.

The intra-arterial continous perfusion of cytotoxics with Sullivan's technique, applied to oropharyngeal carcinomas by Galioto and Germana (1975), presents difficulties. In our cases we have observed that 24 h after the beginning of treatment two patients died suddenly, and the autopsy could not explain the cause of death.

Conclusions

1. We have applied cytotoxic drugs as a complementary treatment to radiotherapy and surgery to 164 cases of malignant tumors of the neck and head. One hundred fifty-one cases were considered incurable; in 39 cases we attained a clinical cure, and in 43 cases arrested further growth of the tumor.
2. Of all the antiblastics applied, bleomycin seemed to have the greatest inhibitory effect on the cellular growth of epithelial tumors. With 300 mg of bleomycin exclusively we cured two primary cancers of the uvula in stages T_1 and T_2.
3. Bleomycin alone and associated with vincrisul and methotrexate shows a marked radiomimetic effect. The radiotherapy must begin 1 week after the administration of the bleomycin.

4. The response of the tumor does not depend on its evolutive stage. Probably, the most important determinants are immune conditions, constitutional factors, and tolerance to the drug.
5. The most brillant results were observed in the oropharyngeal cancers in stage T_4N_3, in vocal cords carcinomas in stage T_2, and in ventricular carcinomas of the larynx in stage T_3. In these cases we attained a clinical cure by the application of three intermittent Schabel cycles and 4,000 rads of Telecobalttherapy, avoiding total laryngectomy.
6. The application of antiblastic drugs alone or combined with radiotherapy does not exclude the possibility of future surgical treatment and increases the possibilities of cure without initial radical surgery.
7. We think it necessary to persist in the pharmacologic treatment of cancer of the neck and head and to achieve its cure by bloodless procedures.

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