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CHEMOTHERAPY WITH SYNCHRONIZATION IN ADVANCED CANCER OF THE HEAD AND NECK*

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Sažetak: 66 bolesnika s lokalno uznapredovalim karcinomom u području glave i vrata bili su liječeni uz radioterapijske i/ili kirurške metode i intravenozno apliciranim Methotrexatom, Bleomycinom i Adriamycinom po različitim shemama nakon Vinblastina, koji je bio apliciran s ciljem, da sinhronizira populaciju tumorskih ćelija. Akumulacija 99m-Tc Bleomycina u tumoru bila je indeks sinhronizacije. Rezultati opisanog terapijskog postupka bili su usporedjivani s rezultatima 83 bolesnika, od kojih je 38 bilo liječeno samo zračenjem, a 45 dodatno je primilo još i intraarterijsku kemoterapiju. Regresija tumora i preživjeće bilo je veće u grupi s kemoterapijom. Sama regresija tumora (a ne i preživjeće) bila je izrazitija kod intraarterijske nego li kod intravenozne kemoterapije, te bolja uz sinhronizaciju. Liječenje je bilo uspešnije kada je kemoterapija bazirala na individualnim, nego li na kumulativnim krivama akumulacije 99m-Tc Bleomycina.

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Deskriptori: karcinom glave, karcinom vrata, radioterapija, kemoterapija, sinhronizacija

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Introduction. — In spite of technical advances in the surgery and radiation therapy of locally advanced cancer of the head and neck the results remain poor. Fletcher had 60 % local failures in T_4 tumors of the tongue and 79 % failures in those of the floor of the mouth (7). Wang had 10 % 3-year survival in T_3 tumors of the oral cavity and 12 % survival in those of the oropharynx (14).

Surgery for cancer in these regions is often mutilant and therefore not always acceptable. Advanced age, poor general health, lack of cooperation (chronic alcoholics) are further limiting factors.

Combination of radiation with chemotherapy results mainly in better tumor regresssion (6, 8), improvement of survival has been shown in tumors of the oral cavity (9) combining 5-Fluorouracil with radiation (6, 8).

Some clinical trials have been conducted lately with attempts to schedule the chemotherapy on the base of cellular kinetics (11). Most chemotherapeutics are cell-cycle or phase specific, i. e. they act only on the cells which devide or are in a certain phase of the mitotic cycle at the time. The effect of the chemoterapeutic is thus limited by the fact that the cells of a tumor are in different phases of the

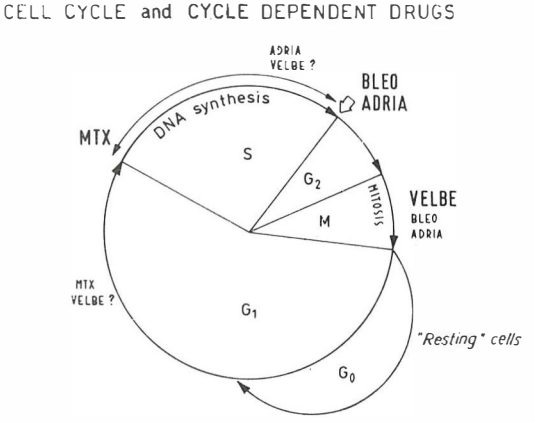

Fig. 1 — The phases of the cell cycle where cytotoxic drugs exert their effects

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cycle at any given time and a phase-specific agent can only affect a fraction of the cell population. Moreover, only a small fraction of the cell population is undergoing the cyclic changes, the rest are »dormant, and out of reach of chemotherapy. (Fig. 1)

Synchronization of tumor cell population is defined as »passage of larger than average portion of cells simultaneously through various cell phases« (11). If this could be achieved, a phase specific drug might affect a larger number of cells and the results of chemotherapy might conceivably be improved.

A synchnonizing agent should be able to cause a phase-specific cell-cycle block as well as rapid release of the cells from the block. The tumor treated should have a large proportion of cycling cells. The synchronization is brought about by either blocking or destroying selectively the tumor cells, within a phase or by recruiting »dormant« cells into the cycle. Vincristine (1, 10), Methotrexate (10), 5-FU (1), Bleomycin (5) have been used as synchronizing agents in recent clinical trials.

The aim of this study was to improve the results of chemotherapy in some advanced tumors of the head and neck by

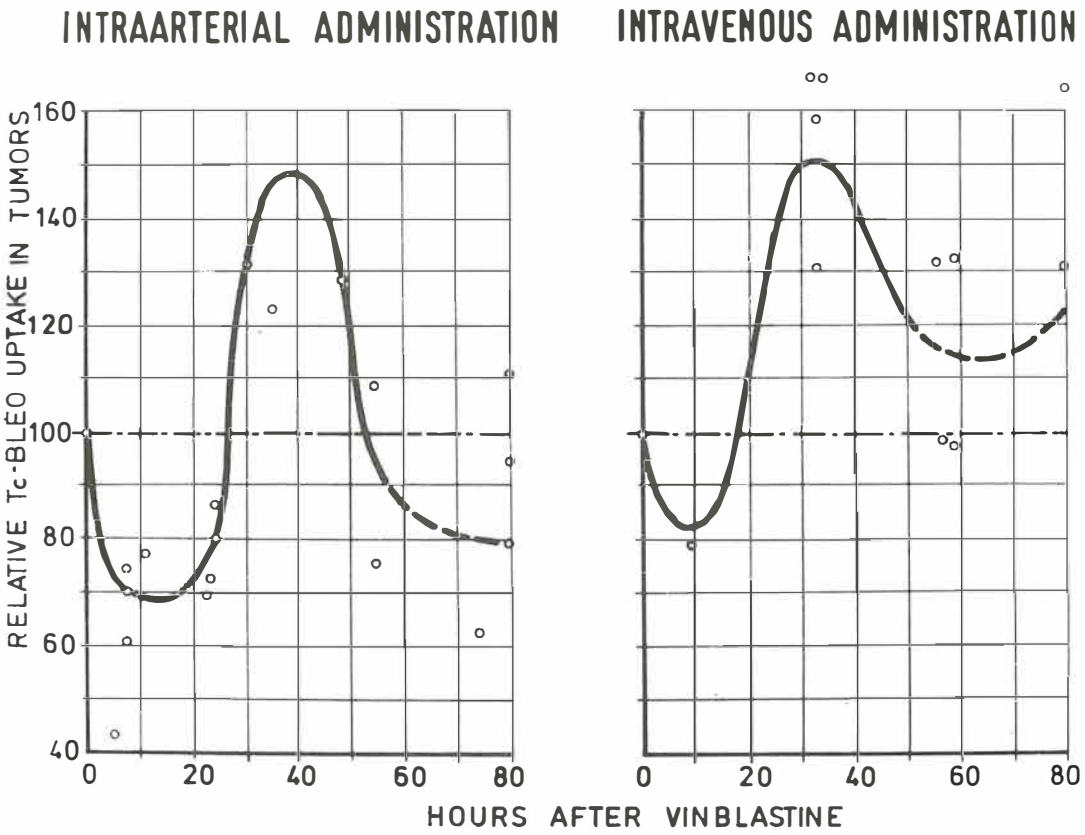


Fig. 2 — Cumulative curve of 99m-Tc Bleomycin uptake in tumors (intra-arterial — 20 measurements on 6 patients, intravenous 12 measurements on 4 patients). The absolute values of measurements are normalised to the uptake of Tc-Bleo in tumors before the infusion of Vinblastine

introducing new combination of cytotoxic drugs while attempting to synchronize the tumor cell population.

Methods and material. — Surgery: Cryosurgery was used in 10 patients when the tumor became resistant to chemotheray. Radiation therapy: Cobalt 60 teletherapy was used with split-dose technique, the tumor dosis being about 7600 rads in 10 weeks in most patients. Details published elsewhere (4). Chemotherapy: when applied intra-arterially, the temporal artery was used, the infusion was continuous through 24 hours, gravity was used to counteract the blood pressure. SP-I, Methotrexate, Bleomycin were used as monochemotherapy or in combination of two drugs. Recently, Vinblastine (Velbe), Methotrexate (MTX) and Bleomycin (Bleo) were used in combination: — Velbe with the aim of synchronizing the tumor cell population (2). When applied intravenously, Velbe, MTX and Bleomycin or Velbe, Adriamycin (Adria) and Bleo were used as shown on Fig. 3. The schedules were based either on cumulative or individual 99m Tc-Bleomycin uptake curves. The first 3 courses of chemotherapy were given with 7—10 days intervals, subsequent courses with 20—30 days intervals, depending on drug toxicity. Velbe was used with the aim of synchronizing the tumor cells.

An original method has been developed for monitoring the synchronization effect of Velbe in vivo: quantitative scintigraphy of the accumulation of 99m Tc-labelled Bleomycin (15). Bleomycin being a phase-specific agent it was our assumption that its accumulation within the tumor cells will increase with their synchronization (2, 3).

Freshly eluted radioopertechnate was reduced with $Sn Cl_3$ and incubated with commercially available Bleomycin (Bleo-

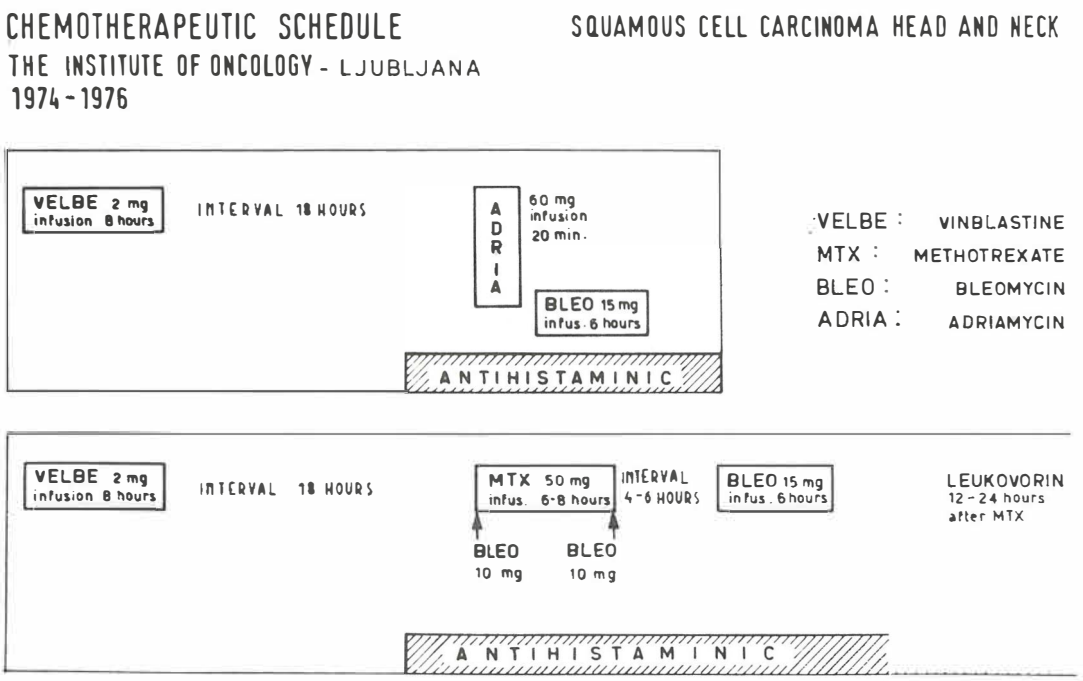


Fig. 3 — Chemotherapeutic schedule for squamous cell carcinoma (head and neck) based on the cumulative curve of Tc-Bleo uptake in tumors

cn Krka at pH 2,2 according to Toru Mori (12). The complex was neutralized, separated from the ubound technetium on an ion exchange resin and sterilized with microfilters (Swinex 22). The yield of the procedure was 30—40 %. Ten percent of released technetium was found after 4 hours and 40 % after 9 hours at room temperature in vitro. The stability of the Bleomycin complex in vivo could not be measured. To inhibit the excretion of technetium through the saliva the patients were as a rule blocked with 0,4 perchlorate one hour prior to the injection of 0,3—3,0 mC of Tc 99. Scintigraphy of the tumor area was performed 4 hours after the injection. One percent of the given dose was put into a syringe and included within the scanning field as standard. Scanning data were computerized and expressed as percentage of the dose administered per image-surface unit.

This method of quantitation was accompanied by a margin of error below 10 % on phantom trials, in 9 patients it was reproducible within $\pm$ 15 % of the average value of 2—3 consecutive measurements at 24 hours intervals.

One or two scintigrams were made on the patients before the infusion of Velbe and up to 5 within about 60 hours after the infusion. When more than one scintigram was made in one 24^h period, the patient received a three times higher dose of radoactivity the second time while the results were corrected and evaluated for residual activity in the tumor after the first dose.

The accumulation of Tc-Bleo was noted to be:

a) up to 150 % of that on the healthy side of the neck in highly differentiated tumors;

b) lower than on the healthy side or none at all in low differentiated tumors.

A cumulative curve of accumulation was done on 4 patients after intravenous and on 6 patients after intraarteerial application of Tc-Bleo and is presented in fig. 2.

Chemotherapy was, accordingly, based on:

a) empirism without attempt at synchronization;

b) cumulative curve of Tc-Bleo uptake, wtih attempt at synchronization;

c) individual curve of Tc-Bleo uptake, with attempt at synchronization.

The treatment was scheduled after cumulative curve when:

a) an individual Tc-Bleo uptake curve was not measured;

b) when there was no appreciable uptake of Tc-Bleo in the tumor region;

c) when there was uptake of Tc-Bleo but no change in it after administration of Velbe.

The effect on the tumor cell population of Velbe, applied with the aim of synchronizing the cell cycle, has been studied from aspiration biopsy specimens.

The specimens were dyed according to May—Grunewald—Giemsa. They were aspirated before the application of Velbe and at uneven intervals, from 4 to 30 hours after that, 3 times in most patients. When obvious degenerative changes were observed on tumor cells, they were interpreted as probable toxic effect of Velbe, the dosage of which was then reduced at subsequent attempts at synchronization.

The clinical effect was evaluated 24 hours after the course of chemotherapy and before the next course. It was expressed as:

zero regression of the tumor
0—50 % regression of the tumor
50—100 % regression of th etumor
100 % regression of the tumor

This was evaluated by 2 examiners; when there was disagreement, the patient was allotted to the lower effect group.

The results were evaluated by the chi^2 method. The survival was counted from the start of the therapy.

There were 4 groups of patients:

1. Thirty-eight patients with T_3 squamous cell carcinomas (13) of the oral cavity and oropharynx, all treated by radiation.

This randomized group has been previously published (4).

2. Fort-five patients with T_3 squamous cell carcinomas of the oral cavity and oropharynx, treated by radiation and intraarterial chemotherapy:

a) 36 patients had T_3 primary tumors; 23 of them were given chemotherapy after empirical schedule, 13 with attempt at synchronization and based on the cumulative curve. These patients were randomized.

b) 9 patients with residual or recurrent tumors after radiation therapy and/or surgery, were not randomized. Six of them received chemotherapy after empirical schedule, three after cumulative curve with synchronization attempt (4).

3. Twenty-eight patients with residual or recurrent, locally advanced tumors of the head and neck, after radiotherapy and/or surgery have failed. They received intravenously applied chemotherapy with attempt at synchronization, the drugs used were Velbe, Methotrexate and Bleomycin. Different chemotherapy schedules were tried out on each of these patients, which were not randomized. (Fig. 4)

15 patients were treated after cumulative curve, 10 after individual curve, (fig. 5) 5 after both, i. e. an individual uptake curve was used after when chemotherapy based on the cumulative curve was no longer effective. (Or vice versa).

4. Thirty-eight patients of the same kind as those in the group 3. These patient, however, were allotted to groups of treatment by random number and were treated with intravenous chemotherapy:

Scheme A — 20 patients — Velbe-Adria-Bleo-cumulative curve as base:

Scheme B — 18 patients — Velbe-MTX-Bleo cumulative curve as base. (Fig. 3)

After resistance or failure to respond 7 patients of group A received treatment B. and 12 patients resistent to treatment B received scheme A.

Tumor sites in the groups 3 and 4 are presented in table 1 and 2.

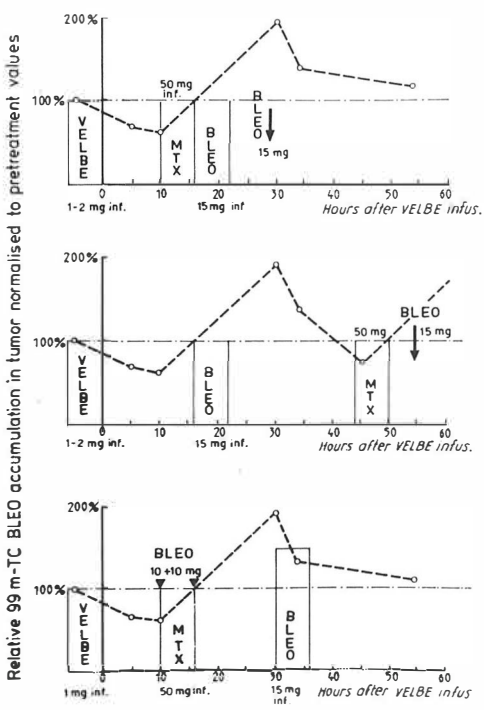


Fig. 4 — Chemotherapeutic schedules for squamous cell carcinoma (head and neck) based on individual curves of Tc-Bleo uptake in tumors

Oral cavity	
Tongue	5
Buccal mucosa	1
Floor of mouth	7
Lower alveolus	0
Oropharynx	8
Hypopharynx	1
Maxillary antrum	2
Skin	1
Lip	2
Larynx	1
Total	28

Table 1 — Primary tumor site in 28 recurrent or residual head and neck tumors (group 3)

23 patients from the groups 3 and 4 had T_3 tumors of oral cavity and oropharynx and only these are presented in the results of survival after intravenous chemotherapy.

Oral cavity	Adria	Mtx
Tongue	4	3
Buccal mucosa	0	2
Floor of mouth	2	1
Lower alveolus	1	0
Oropharynx	7	5
Hypopharynx	0	2
Maxillary antrum	4	3
Skin	0	1
Lip	0	1
Larynx	2	0
Total	20	18

Table 2 — The primary tumor site in 38 residual or recurrent head and neck tumors

Results. — The tumor cell reaction to Velbe administred for synchronization was o follows:

a) minimal reaction or none;

b) enlargement of cells, mainly the nuclei, sometimes to more than double size;

c) degenerative changes as with therapeutic doses of the drug;

d) in 7 out of 10 cytologicaly evaluable patients mitoses were noted 5 or 10 hours after the administration of Velbe, 20 % of cells were in the mitotic phase in one patient;

e) the sensitivity of tumor cells to Velbe has a rule increased with repeated synchronization attempts in the same patient.

Results of intra-arterial chemotherapy:

a) scheduled after cumulative curve, with synchronization: tumor regression of more than 50 % in all 16 patients, 100 % regression in 10 of these;

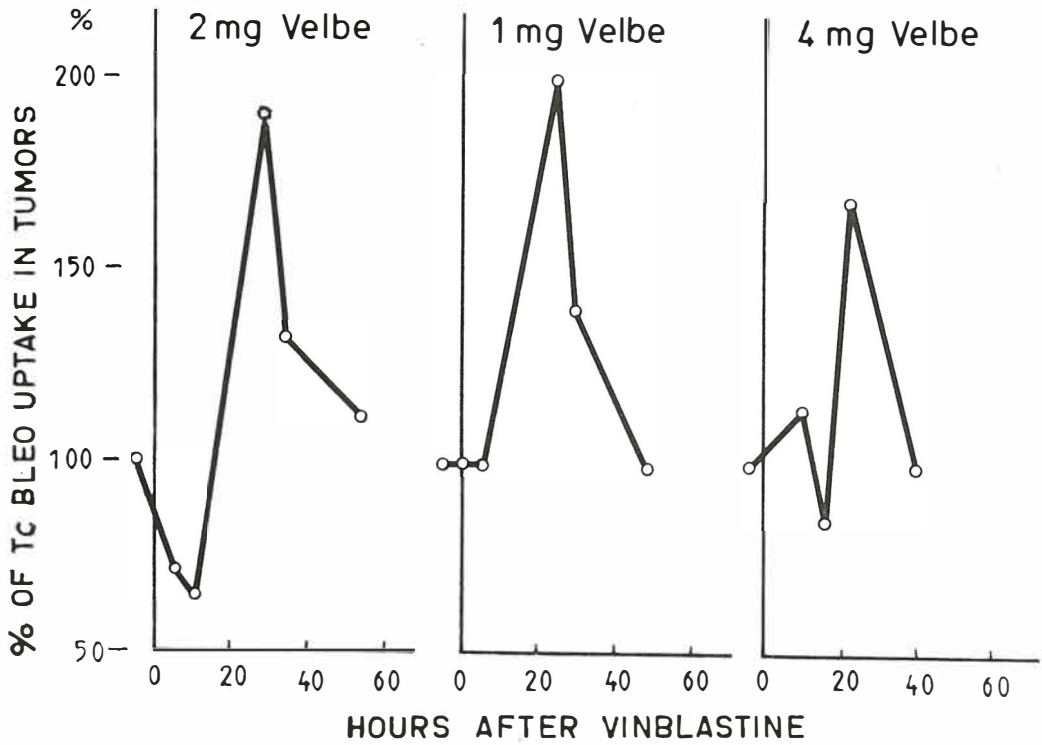


Fig. 5 — Individual Tc-Bleo accumulation curves in a squamous cell carcinoma of the tongue (Patient No. 1998/74, 1th, 2nd, 4th synchronization)

b) administered empirically (without synchronization): tumor regression of more than 50 % in 21 out of 29 patients, 100 % regression in 8 of these patients. ($p < 0,05$)

There was no appreciable difference in the survival in these two groups of patients. Fig. 6).

Results of chemotherapy (intravenous) with synchronization in patients with residual or recurrent disease after radiation therapy and/or surgery:

Tumor regression of more than 50 % in 28 out of 53 patients, 100 % regression in 5 of these.

a) 15 of these patients were treated with Velbe, Methotrexate, Bleomycin scheduled after individual curve. Tumor regression of more than 50 % in 13 of these 15 patients. 100 % tumor regression in one.

b) 38 of these were treated with Velbe, Methotrexate, Bleomycin scheduled after cumulative curve. Tumor regression of more than 50 % in 15 of these patients. 100 % tumor regression in 4 patients. ($p < 0,05$)

Scheme A (with Adriamycin): 20 patients.

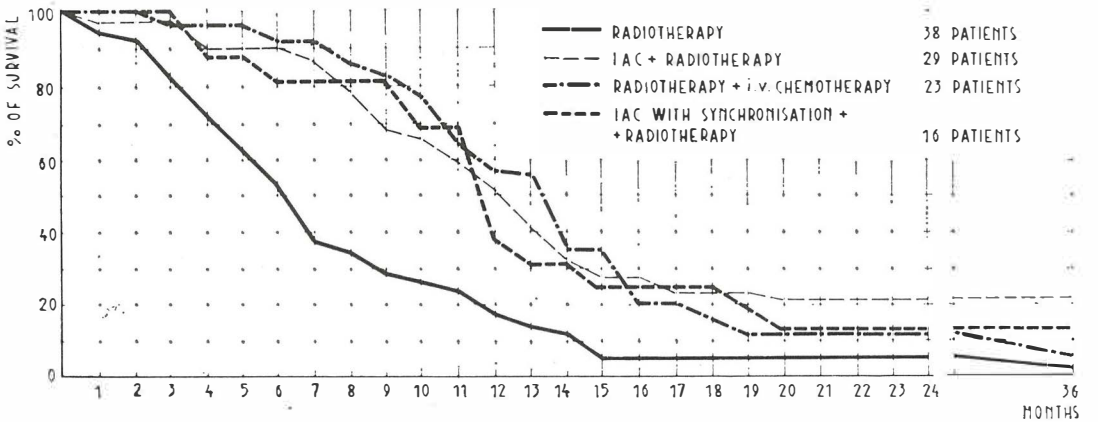
Regression of tumor of more than 50 % in 3 of these; average duration of the therapeutic effect 2,9 months, in good responders 4,7 months.

Scheme B (with Methotrexate): 18 patients.

Regression of tumor more than 50 % in 11 of these; average duration of the therapeutic effect 4,2 months, in good responders 6,4 months. ($p < 0,05$)

Figure (6) shows survival after different combinations of chemotherapy with radiation therapy as opposed to radiation therapy only. With addition of chemotherapy, the survival is significantly improved during the first 16 months. (Fig. 6).

The complications of intravenous chemotherapy are summarized in table 3.



CRUDE SURVIVAL IN PATIENTS WITH T_3 CANCER OF THE ORAL CAVITY AND OROPHARYNX

Fig. 6 — Survival of patients by therapy. The difference between curves after chemotherapy and radiation is not statistically significant. The difference between radiotherapy and IAC plus radiotherapy is significant from the 5th—16th month./at 5th month $p < 0,05$, 6th to 12th month $p < 0,01$, 13th—16th month $p < 0,05$

	VELBE MTX BLEO (53 pts.)	VELBE ADRIA BLEO (32 pts.)
Hematological toxicity	1/53	5/32
Mucositis	2/53	2/32
Gastrointestinal toxicity	7/53	6/32
Gastric ulcer	2/53	—
Fever, Headache	2/53	—
Pulmonary infection	3/53	5/32
Flush	2/53	—
Fibrosis, Hyperpigmentation	1/53	6/32
Alopecia	—	3/32
Stenocardia	1/53	2/32

Table 3 — Complications of intravenous chemotherapy for recurrent or residual head and neck carcinoma

Discussion. — There is no proof that increased uptake of Tc-Bleo in the tumor is actually due to the synchronization effect. It might be due to a pharmaco-dynamic effect of the »synchronizing drug«. An indication, that synchronization actually occurs, may be the fact that lower doses of the synchronizing drug seem to result in higher Tc-Bleo uptake in the same patient (fig. 5). Also, sometimes a considerable number of mitoses was found after attempts at synchronization, while as a rule no or only few mitoses were found in our material from aspiration biopsies. Besides, there are some sources of error at this stage of the »quantitative« method:

a) The Tc-Bleo complex is unstable, its decay is rather irregular and unpredictable. Meanwhile, the conclusions are based on the assumption that it is constant at least in a single patient within one cell cycle.

b) The accumulation within the tumor has been recorded at rather long, often irregular intervals. Peak values thus might have been missed, the curve rendered unrepresentative.

c) The »quantitation« was done without regard to either the attenuation of radio activity within the tissue or to the size of the tumor. Therefore, while observations on a single patient and within one cell cycle may be valid, no conclusion can be drawn as to a possible change in the Tc-Bleo accumulation in a tumor after chemotherapy and regression.

The results of chemotherapy scheduled on the basis of individual Tc-Bleo uptake curves were better than when a cumulative curve was used ($p < 0,05$). The latter was mostly used when there was no significant rise or no uptake to begin with in an individual patients curve. A bias may thereby have been introduced in that these two groups may not be comparable as to the biological properties of the tumor.

The results of intra-arterial chemotherapy with »synchronization« being somewhat better than those of the intravenous one, especially in terms of 100 % regression of tumors often confining the need for subsequent surgery to the extirpation of residual lymph nodes, it should be the first choice of chemotherapy. It is, however, technically rather difficult, requires cooperative patients and 3—4 weeks hospitalization. It may also interfere with subsequent reconstructive surgery, e. g. prevent the use of the temporal skin flap when the temporal artery had to be cannulated.

We have therefore chosen the intravenous route for routine use and reserved the intra-arterial route for patients with poor response to the intravenous chemotherapy, to poor risk patients in order to minimize toxicity and to some patients, who had significantly higher uptake of Tc-Bleo after intra-arterial application.

Conclusions. —

1. Chemotherapy, when added to radiation therapy, increased the percentage of significant tumor regressions and improved the crude survival under the first 16 months in patients with locally advanced

tumors of oral cavity and oropharynx. (Fig. 6).

2. The combination Velbe-Methotrexate--Bleomycin was better than the combination Velbe-Adriamycin-Bleomycin.

3. There is no proof that synchronization of the cell cycle actually takes place.

4. Chemotherapy, based on synchronization attempt, was better than without it. It was better, when based on individual uptake curves than on a cumulative curve.

5. The Tc-Bleomycin method for monitoring the »synchronization« process cannot be regarded as truly quantitative in its present form.

Summary

CHEMOTHERAPY WITH SYNCHRONIZATION IN ADVANCED CANCER OF THE HEAD AND NECK*

Sixty-six patients with locally advanced cancers of the head and neck region were treated, in addition to radiation therapy and/or surgery, with intravenously applied Methotrexate, Bleomycin and Adriamycin in different schedules, after application of Vinblastine with the aim of synchronizing the tumor cell population. 99m-Tc Bleomycin accumulation in the tumor was used as an index of the synchronization. The results of this treatment were compared to the results in 83 patients, 38 of whom treated by radiation only while 45 received additional chemotherapy, applied intra-arterially. The tumor regression and crude survival was better in chemotherapy groups. The tumor regression but not the survival was better with intra-arterially than with intravenously applied chemotherapy, was better with attempt at synchronization than without and was better when chemotherapy was based on individual rather than cumulative 99m-Tc Bleomycin accumulation curves.

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