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CHEMOTHERAPY — A NEW APPROACH TO THE TREATMENT OF VERRUCOUS CARCINOMA

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Abstract — From 1969 to 1986, 8 patients (7 males, 1 female) age 32-78 with advanced verrucous carcinoma were treated by chemotherapy. Five patients had extensive previously untreated tumors, in 2 patients repeated surgical interventions failed to control the disease, and one patient had a persistent tumor after irradiation. The tumor site was buccal mucosa in 4, lower alveolus, skin of the temporal region, plantar skin and cervix uteri each in one patient. Drugs which had proved to be effective in highly differentiated squamous carcinomas in our previous studies, i. e. Vinblastine, Bleomycin and Methotrexate were used in 6 patients in continuous infusions. In 2 patients Cisplatinum was added to achieve a complete response. In the first patient treated, only Methotrexate was used. Chemotherapy was applied intravenously in 6, intraarterially in 1 and a combination of i. v. and i. a. chemotherapy in 1 patient. Six out of 8 patients had a complete and 2 partial response to chemotherapy. Five patients are alive NED 31 months — 11 years after treatment, among them a patient who was treated with chemotherapy only and has been without evidence of disease 8 years already. Chemotherapy proved very effective in verrucous carcinoma, and could be used either preoperatively for tumor reduction or as an alternative to irradiation in inoperable tumors. This is to our knowledge the first report on an effective chemotherapy in a verrucous carcinoma. For development of ChT schedules cytophotometric DNA measurements and labeled Bleomycin accumulation curves were used.

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Introduction — Verrucous carcinoma (VC) is a distinctive, rare variant of squamous cell carcinoma. It is a locally invasive tumor, regional metastases are exceptional (6, 21). Predilective sites are mucosa of the oral cavity and larynx (14, 19, 21) but VC can occur on cutaneous surfaces in the ano-genital region and extremities (6, 16, 18, 22, 25, 26). The clinical characteristics are slow growth of an exophytic, shaggy, gray-red lesion which can be locally invasive and destructive. Microscopically VC is composed of highly differentiated squamous epithelial cells lacking the usual cytologic criteria of malignancy. Therefore, a close cooperation of pathologist and clinician is mandatory to establish a correct diagnosis (6, 13). In our series patients had repeated biopsies elsewhere before a correct diagnosis of verrucous carcinoma was made.

The treatment of choice is surgery (6, 13, 19). The role of irradiation is controversial. Some authors consider irradiation contraindicated because of the danger of anaplastic transformation (1, 8, 12, 13, 23) and poor response to irradiation (13). Other authors failed to prove an increased anaplastic transformation after irradiation (20, 21, 24). The role of chemotherapy (ChT) in the treatment of VC is unknown. There are only few case reports in the literature describing the use of chemotherapy which was mostly ineffective (9, 10, 17, 25).

Excellent results of individually planned chemotherpay in some of highly differentiated squamous cell carcinomas of non-verrucous type in our series (3) prompted us to explore the effectiveness of ChT in VC as well.

Material and Methods — From 1969 to 1986, 8 patients with verrucous carcinoma were treated by chemotherapy at the Institute of Oncology in Ljubljana. There were 7 male and 1 female patient, age 30—78 years. The tumor site was buccal mucosa in 4, the floor of mouth and lower alveolus, skin of the temporal region, cervix uteri and plantar skin in one patient respectively. The data on tumor site and stage are presented in Table 1. All but one patient had a long history of papillary growth, ranging from 2—12 years. Usually several biopsies were performed before a correct diagnosis could be established. Only one patient (No. 6, Table 1) gave a short history of one-month duration. The rationale for our using chemotherapy was inoperable tumor in 5 patients (No. 1, 4, 5, 6, 7, Table 1). The tumor in these patients involved more than one tumor site, i. e. buccal mucosa with infiltration of the muscles and skin, upper alveolus and floor of the mouth,

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so that even by an extensive mutilating surgery the tumor would be difficult to erradicate. In one patient (No. 3, Table 1) the tumor recurred 3 weeks after radical mutilating surgery (with histologically free margins). One patient refused surgery (No. 2, Table 1) and in another one (No. 8, Table 1) there was a residual, deeply infiltrating tumor after repeated, non-radical surgery performed elsewhere. Five patients were previously untreated (No. 2—6, Table 1), 2 were previously operated on elsewhere (No. 7, 8, Table 1) and one patient (No. 1, Table 1) was repeatedly irradiated for uncontrolled VC of the buccal mucosa elsewhere. All patients had histologic confirmation of the diagnosis according to the criteria redefined by Batsakis (6).

Vinblastine (VLB) 2 mg or Cisplatinum (CDP) 50 mg/m^2 were infused continuously intravenously over 8—12 hours with the aim to perturb the cellular kinetics of the tumor. For an attempt of monitoring the changes in the cellular kinetics DNA cyto-photometric measurements of tumor cells and measurements of the accumulation of labeled Bleomycin in the tumor region were performed. For DNA measurements fine needle aspiration biopsies (FNAB) or scrappings of tumors were used. Smears were stained according to a Feulgen procedure described previously (3, 4). In brief: a hydrolysis in 4n HCl at 28 °C for 60 min was used. Measurements were performed on a Vicker's 85 microdensitometer at wave lengths 560 μm up to 250 tumor cells and 25 leukocytes were measured in each smear. The DNA values of leukocytes were used as a reference for diploid DNA values. FNAB provided enough material for DNA measurements in 3 patients (No. 4, 6, 8, Table 1).

In addition to DNA measurements monitoring of changes in the cell kinetics of tumors was tried in vivo with an original non-invasive method of measuring labeled Bleomycin in the tumor. The accumulation of 99mTc labeled Bleomycin (TcBleo) was measured before and repeatedly after the infusion of VLB which was used with the aim to perturb the cellular kinetics of the tumor. As Bleo is a phase specific agent we assumed that accumulation of TcBleo in the tumor would increase at a certain time after VLB if perturbation of cellular kinetics occurred i. e. if the number of cells in a particular phase of the cell cycle increased. The method of TcBleo measurements was described in detail previously (2, 3, 4, 5). In brief: About 1 mC (0.5 mg) of TcBleo was administered intravenoulsy (i.v.). When a patient had measurements twice a day, the second dose of TcBleo was tripled and appropriate corrections were made for the residual activity on the basis of physical and biological disappearance of the first dose. The tumor region was imaged together with the standard and images processed by a computer. The peak value of TcBleo concentration in the tumor image was determined and time dependency curve of TcBleo covering a 3-day period after VLB infusion was drawn together with a baseline uptake value determined before VLB infusion. TcBleo accumulation curves were measured in 5 patients (No. 2, 3, 5, 6, 7, Table 1).

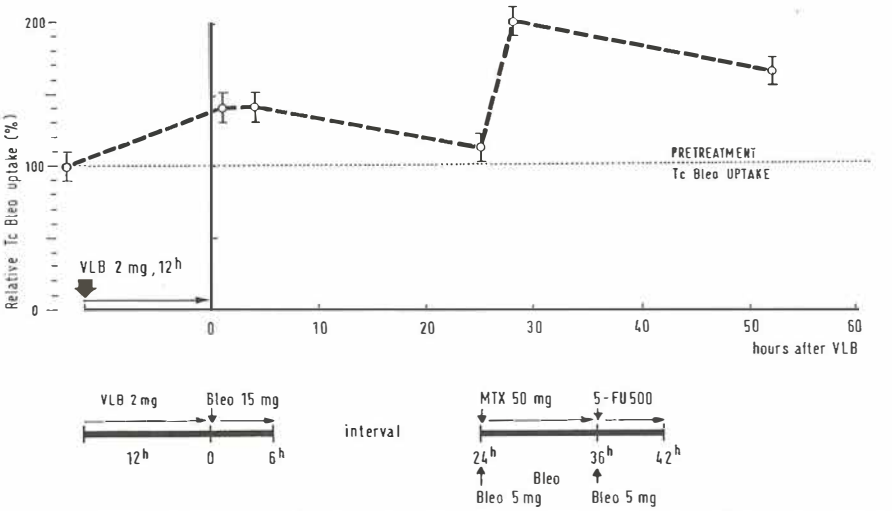

Fig. 1 — An individual 99 m Tc Bleomycin (Tc Bleo) accumulation curve after infusion of Vinblastine 2 mg over 12 hours. Values of Tc Bleo are normalized to the values of Tc Bleo before VLB infusion (case No. 5, Table 1, verrucous carcinoma of the buccal mucosa). Chemotherapeutic schedule is superimposed on Tc Bleo accumulation curve.

Chemotherapy: Drugs effective in highly differentiated squamous cell carcinomas, i.e. VLB, Bleo, Methotrexate (MTX) and 5-Fluorouracil (5-FU) were used. In 2 patients (No. 4, 8, Table 1) CDP was used in addition to achieve a complete response. Low-doses of drugs were used in continuous infusions with the aim to obtain prolonged exposures of tumor cells to the drugs. For the timing of drugs the data of DNA measurements and TcBleo accumulation curves were used. As we found with the DNA measurements performed during the increased TcBleo accumulation, an increased number of cells in S, $G_2 + M$ compartment, we applied infusions of drugs effective in respective phases of the cell cycle, i.e. Bleo predominantly effective in $G_2 + M$, MTX and 5-FU in S phases, accordingly. As we have not enough measurements performed in VC we took into account also DNA measurements performed in highly differentiated squamous cell carcinomas. The DNA measurements showed changes in the DNA distribution pattern during approximately 60 hours after VLB. TcBleo accumulation in the tumors was increased for about the same time. Therefore, infusions of drugs were given over approximately 60 hours, with an individual interval between VLB, Bleo and MTX applications. An example of chemotherapeutic schedule for patient No. 7 (Table 1) is shown in Figure 2.

Fig. 2 — Chemotherapeutic schedule used in case No. 7 (Table 1) — VC of the buccal mucosa.

The effect of chemotherapy was evaluated by measuring two perpendicular diameters of tumors and was classified as: CR — complete disappearance of tumor, PR — 50—100 % reduction of the product of two diameters, MR — less than 50 % reduction of tumor.

Three patients were treated by chemotherapy only (2 for relapses, No. 1, 3, Table 1, and 1 previously untreated, No. 7, Table 1). In 4 patients ChT was followed by surgery (No. 2, 5, 6, 8, Table 1) and in 1 patient by irradiation (No. 4, Table 1).

Results — Clinical: Six out of 8 patients had a CR and 2 patients a PR after ChT. In the 3 patients treated by ChT only the duration of ChT effect could be evaluated: Patient No. 1 (Table 1) treated in 1969 with MTX only had a local relapse at 8 months and died 25 months after ChT of advanced recurrent tumor. Patient No. 3, Table 1) died 2.5 years after ChT of myocardial infarction with no evidence of tumor (NED), and patient No. 7 is alive with NED 8 years after ChT. Patient No. 4 (Table 1) with cervical carcinoma died 8 months after the beginning of ChT of respiratory distress with only microscopic residual disease. Five patients are alive with NED from 31 month + to 11 years + after tretment; 3 of them had surgical resections after chemotherapy.

Complications: One patient had fever during Belo infusion and drop of blood pressure during ChT. This patient (No. 7, Table 1) was suffering from hypopituitarism. Infusions and corticosteroids brought about a prompt relief of symptoms. Patient No. 4, (Table 1) died in respiratory distress with cardiac failure 8 months after the beginning of treatment. Pulmonary fibrosis was found at autopsy.

DNA measurements: Changes in the DNA distribution pattern were found in the DNA histograms after VLB or CDP infusions. A relative increase of cells in the S and $G_2 + M$ compartments were seen both after VLB and CDP.

TcBleo accumulation curves: TcBleo accumulation was found increased up to 200 % over the pretreatment level in 4 of 5 patients, up to 55 hours after VLB. In one patient only evaluation of 2 measurements succeeded.

Discussion — The role of chemotherapy in verrucous carcinoma is rarely addressed in the literature. There are only few case reports mentioning the use of chemotherapy, i.e. the topic use of 5-FU (9), an improvement with Bleo (17). In his compilation of 293 cases from the literature McDonald (20) found a patient treated with podophyllin for 6 years (effect not mentioned). According to Stehman (25) topic podophyllin and 5-FU were without effect. Edelstein described a stabilization of a VC in the temporal bone after high dose MTX for 6 months. In the same patient Cyclophosphamide had no effect. Another patient with the same tumor site failed to respond to ChT with CDP and Amsacrine (10). In summary, there are no reports in the literature on an effective chemotherapy of verrucous carcinoma. In our series of 8 patients, 6 had a CR after chemotherapy. These results are very promising, particularly, as it appears that the effects are long lasting, especially in patients receiving more than 3 courses of ChT (Table 1). The patient No. 7 (Table 1) with a huge carcinoma of the buccal mucosa invading muscles and skin is alive without recurrence 8 years after treatment with chemotherapy only.

No. Age (yrs) Sex	Tumor site TNM	Duration of symptoms	First treatment	Chemotherapy	Effect of ChT	Subsequent treatment	Follow up Survival (yrs)
1. 63 M	buccal mucosa rT4 NO MO	11 yrs	RTX	i.a. MTX 600 mg/34 days	CR	Ir^{92} implant	Recurrence 8 mo dead 25 mo after IAC
2. 75 M	skin of the face T4 MO NO	2 yrs	i.v. ChT	VLB, MTX, Bleo 3 courses	CR	S	Alive, NED 8 yrs +
3. 70 M	buccal mucosa T4 NO MO	2 yrs	i.v. ChT VLB, MTX, Bleo 3 courses + S	i.a. ChT for recurrence VLB, MTX, Bleo, 5-FU 4 courses	CR	—	Dead 2.5 yrs after IAC (myocard. infarct.) NED
4. 78 F	cervix uteri, vagina T3a NO MO	5 yrs	i.v. ChT	VLB, MTX, Bleo — 2 courses CDP, MTX, VLB. Bleo 2 courses	CR	Ra application	Dead 8 mo after ChT (pulm. fibrosis) NED
5. 56 M	buccal mucosa T4 NO MO	12 yrs	i.v. ChT	VLB, MTX, Bleo, 5-FU 2 courses	PR	S + ChT i.v. 6 courses	Alive 11 yrs + NED
6. 54 M	lower alveolus T4 NO MO	1 mo	i.v. ChT	VLB, MTX, Bleo 2 courses	PR	S + i.v. ChT 6 courses	Reccurence 9 mo — salvage S Alive 10 yrs + NED
7. 32 M	buccal mucosa rT4 NO MO	5 yrs	S 2×	VLB, MTX, Bleo 4 courses	CR	Biopsy — no Tu cells	Alive 8 yrs + NED
8. 62 M	plantar skin rT4 NO MO	2.5 yrs	S 3×	VLB, MTX, Bleo 2 courses VLB, CDP, MTX, Bleo 4 courses	CR	S — no Tu cells	Alive 31 mo + NED

i.v. ChT — intravenous chemotherapy
RTX — radiotherapy
S — surgery

Table 1 — Characteristics of 8 patients with verrucous carcinoma treated by chemotherapy

ChT with low doses of drugs and continuous infusions was generally well tolerated. There is no proof that pulmonary fibrosis in patient No. 4 (Table 1) was a complication of ChT. The total dose of Bleo in this patient was only 90 mg, moreover, Bleo was applied in infusions so, pulmonary fibrosis related to the use of Bleo in such circumstances would be highly improbable.

Verrucous carcinoma is a slowly growing, very low-grade tumor, therefore we applied ChT in long infusions rather than in bolus. By this method we protracted the exposure of tumor cells to the drugs and probably overcame the »chemoresistance« of this tumor. In planning chemotherapy the DNA measurements and TcBleo accumulation curves were very useful. DNA measurements showed that the maximum changes in the DNA distribution pattern occurred rather late. In the measurements shown in Figure 3 the maximum changes occurred 52 hours after the end of VLB infusion. TcBleo accumulation curves showed as well a long lasting increase in the uptake of TcBleo in tumors after VLB. These measurements suggested a chemotherapeutic schedule with infusions of drugs covering the time from 0 hours to about 60 hours after VLB. Another reason for good results of ChT in this highly differentiated tumor is probably the incapacity of tumor to repair the damaged DNA. In our previous studies (3) we observed a better effect of ChT in highly differentiated squamous cell carcinomas in comparison with low differentiated ones. In well differentiated tumors cytology showed that the cell damage lasted longer than in low differentiated carcinomas (Us-Krašovec, unpublished data). Planning of ChT with relation to individual cell kinetics of tumors therefore seems to be rational.

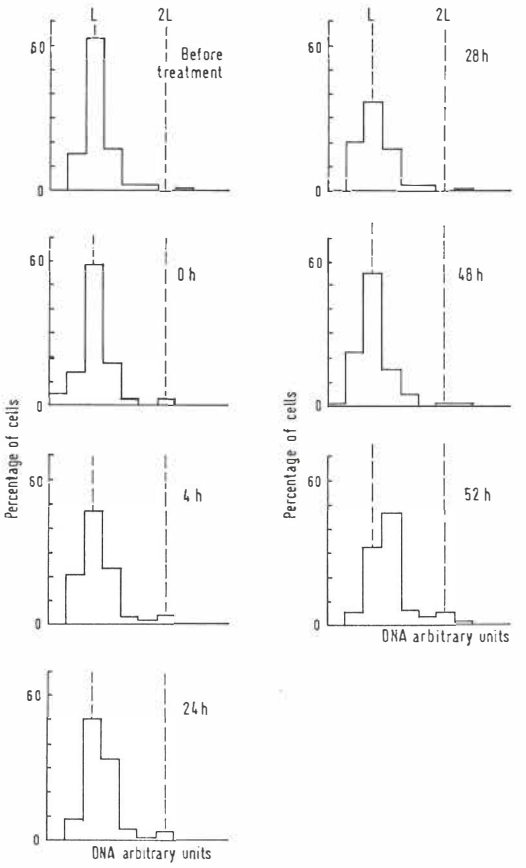

Fig. 3 — DNA histogram of a VC in the lower alveolus (patient No. 6, Table 1), before and after i..v. infusion of VLB 2 mg over 8 hours. There is a relative increase of cells in S and $G_2 + M$ compartments at 4, 24 and 52 hours after VLB.

Conclusions — Chemotherapy with low doses of drugs in long infusions was very effective in verrucous carcinoma of various sites. Cyto-photometric measurements and TcBleo accumulation curves were used in the attempt of planning rational chemotherapeutic schedules.

Povzetek

Od 1969 do 1986 smo zdravili s kemoterapijo 8 bolnikov (7 moških, 1 žensko), starih 32—78 let, ki so imeli verukozni karcinom različnih lokalizacij. Uporabili smo Vinblastin, Metotreksat, Bleomycin in 5-Fluorouracil v nizkih odmerkih in dolgih intravenskih infuzijah. Z Vinblastinom smo skušali vplivati na celično kinetiko tumorjev. Spremembe v celični kinetiki smo zasledovali s citofotometričnimi meritvami DNK in meritvami kopičenja markiranega Bleomycina v tumorjih. Na podlagi teh meritev smo skušali sestaviti individualne, racionalne sheme za kemoterapijo, ki so bile zelo uspešne. Pri 6 bolnikih je tumor popolnoma izginil, pri 2 pa se je zmanjšal za več kot 50 %. Tri bolnike smo zdravili samo s kemoterapijo, 3 so bili po uspešni kemoterapiji še operirani, 2 bolnika smo zdravili s kombinacijo kemo- in radioterapije. En bolnik je umrl zaradi karcinoma, 2 iz drugih vzrokov, 5 bolnikov je živih brez znakov bolezni 31 mesecev + do 11 let + po zdravljenju.

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