Alpha 2-b interferon and farmarubicin in the prophylaxis of recurrence of superficial transitional cell carcinoma of the urinary bladder

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Alfa 2-b interferón a farmarubicín v profylaxii rekurentného povrchového karcinómu tranzitórnych buniek močového mechúra

Abstract

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Objective: **To ascertain the effect of intravesical instillation of Alpha 2-b Interferon (IFN a-2) 10 million I.U. in 50 ml physiological saline as a monotherapy and in combination with Farmarubicin (FRC) 50 mg dissolved together in 50 ml of physiological saline. These substances were administered four times during the first month after TUR-BT and then once monthly for one year either in the form of an IFN a-2 monotherapy or as an IFN a-2 and FRC combination in the therapy of recurrence of transitional cell carcinoma (TCC) of the urinary bladder after transurethral resection of the bladder tumor (TUR-BT).**
Th*eoretical consideration:* One of the causes of malignancy is an irreversible shift in the balance between protooncogens and tumor supressorgens. In the genetical process of the control of cell apoptosis, an important role is played by the tumor-supressorgen p 53. By the means of mutation of protooncogenes, cellular oncogenes(C-MYC) are formed, inducing the proliferation of cells of the tumor and via feedback induce also the p53 mutation. By the reduction of cellular oncogenes, IFN a-2 and FRC intervene by blocking the proliferation of tumor cells.
P*atients and methods:* Authors have checked and treated 33 patients (pts) with recurrent TCC. The first group of 20 pts were after TUR-BT with BCG unsuccessful intravesical therapy, and 13 pts in the second group were with recurrence of TCC, but contraindicated for BCG treatment. These 33 pts (the first and second groups) were compared with 33 pts of the third group after TUR-BT but without intravesical instil-

Abstrakt

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Cieľ štúdie: Na základe poznatkov z výskumu molekulovej genetiky zistiť úspešnosť intravezikálnej instilácie alfa 2-b interferónu (IFN a-2) 10 miliónov medzinárodných jednotiek (I.U.) v 50 ml fyziologického roztoku ako monoterapiu alebo v kombinácii s 50 mg farmarubicínom (FRC) pri liečbe recidivujúceho povrchového tumoru močového mechúra. Táto liečba sa použila u 33 pacientov po transuretrálnej resekcii TUR-BT pre histologicky verifikovaný povrchový tumor močového mechúra(TCC), ktorý recidivoval do jedného roka. V I. skupine (20 pac.) bola po TUR-BT+ po neúspešnej alebo prerušenej liečbe BCG vakcínou z objektívnych príčin (špecifická prostatitída, cystitída, striktúry, febrilné stavy atď.) podaná instilačná intravezikálna liečba IFN a-2. V II. skupine (13 pac.) sme nemohli začať liečbu BCG vakcínou, pretože pre ich ťažkú hypoproteinémiu, hepatopatiu, dekompenzovaný diabetes mellitus (DM) a iné bolo podanie BCG vakcíny kontraindikované z dôvodov vzplanutia generalizovaného špecifického procesu. Uvedených 33 pacientov v prvej a druhej skupine sme porovnali s 33 náhodne vybranými pacientmi v tretej skupine, ktorí boli po TUR-BT, ale bez intravezikálnej liečby a nemali vážnejšie vedľajšie ochorenie. IFN a-2 v množstve 10 mill I.U. a 50 mg FRC, rozpustené v sterilnom fyziologickom roztoku (50 ml), sa podali na dve hodiny intravezikálne 4-krát v 1. mesiaci (raz týždenne) a potom raz mesačne počas jedného roka.
Teoretický podklad: Jedna z príčin vzniku malignity je ireverzibilná zmena rovnováhy medzi protoonkogénmi a tumor-supresorgénmi. V genetickom procese riadenia apoptózy buniek má významné miesto tumor-supresorgén p53. Mutáciou protoonkogénov vznikajú celulárne onkogény (c-myc) podnecujúce proli-

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lation therapy. The pts of the third group did not suffer from any other significant ailment. IFN a-2 monotherapy (10 mill. I.U./ or a combination of IFN a-2+FRC (50 mg/50 ml solution were administered for 2 hours, 1 week after TUR-BT. During the first month, instillations were done weekly, from the second to the twelfth month only once monthly. The results were evaluated for 12 to 33 months (median: 24 months).

Results: **Group I: From 20 pts after TUR-BT + unsuccessful BCG+IFN a-2 monotherapy recurrence was registered in 4 pts (20 %). Group II: Out of 13 pts after TUR-BT+IFN a-2+FRC, recurrence was registered in 3 pts (23 %). Group I+II: Recurrence in both groups was observed in 7 pts (21.2 %). Group III: Out of 33 pts after TUR-BT without immuno– et chemotherapy recurrence was registered in 18 pts (54.5 %). After one year of treatment, patients were checked for 24 months. The transition into an invasive tumor was observed in 4 pts (12.1 %). In the comparative group of 33 pts without instillation after TUR-BT, recurrence was detected after one year in 18 pts (54.5 %) and the transition into an invasive tumor was observed in 7 pts (21.2 %).**

Conclusion: **Intravesical instillation of BCG used to be the most frequently applied therapy following TUR-BT. The toxicity of this vaccine as well as the contraindication of this treatment in some diseases, and also the primary or secondary resistance of TCC to BCG have challenged the search for alternative possibilities of the intravesical instillation treatment. IFN a-2 monotherapy and IFN a-2 in combination with FRC are new alternative approaches in the improvement of TCC treatment. This therapy is also supported by research of molecular genetics. *(Ref. 18.)***

Key words: superficial transitional cell carcinoma, transurethral resection of bladder tumor, immunotherapy alpha 2-b interferon, chemotherapy by farmarubicin, carcinoma in situ, epithelium-limited carcinoma, carcinoma invading only lamina propria.

feráciu buniek nádoru a spätnou väzbou mutáciu p53. IFN a-2 a FRC zasahujú v prospech zastavenia proliferácie nádorovej bunky na základe redukcie celulárnych onkogénov.

Pacienti a metódy sledovania: Od marca 1997 do decembra 1999 sme po TUR-BT podávali a sledovali u 33 pacientov s recidivujúcim TCC buď IFN a-2 ako monoterapiu (20 pac.) alebo v kombinácii IFN a-2+FRC (13 pac.) v 50 ml fyziologického roztoku do prázdneho močového mechúra na dve hodiny. 20 pacientov bolo s recidívami TCC po TUR-BT+BCG neúspešnej liečbe a 13 pacientov s recidivujúcim TCC po TUR-BT nevhodných pre uvedenú liečbu z objektívnych príčin. Uvedených pacientov sme porovnávali s 33 náhodne vybranými pacientmi bez imunoterapie a chemoterapie po TUR-BT. Výsledky liečby sme hodnotili po 12—33 mesiacoch (medián 24 mesiacov).

Výsledky: Skupina I: 20 pac. po TUR-BT+neúspešná BCG terapia+IFN a-2 monoterapia: recidíva zistená u 4 pac. (20 %); skupina II: 13 pac. po TUR-BT+IFN a-2+FRC. Recidíva zistená u 3 pac. (23 %); skupina I+II: recidíva zistená celkovo u 7 pac. (21,2 %); skupina III: 33 pac. po TUR-BT bez imunoterapie a chemoterapie. Recidíva zistená u 18 pac. (54,5 %). V skupine I+II: prechod do invazívneho tumoru sme zaznamenali u 4 pacientov (12,3 %), oproti III. porovnávanej skupine, kde bola konverzia do invazívneho BT u 7 pac. (21,2 %).

Záver: Liečba TCC po TUR-BT bola často doplňovaná intravezikálnymi inštiláciami BCG vakcínou. Jej toxicita a kontraindikácie pri niektorých ochoreniach, ako aj primárna alebo získaná rezistencia TCC buniek na BCG vakcínu a poznatky z molekulovej genetiky nútili hľadať iné možnosti instilačnej intravezikálnej liečby. Liečbu IFN a-2 a FRC pac. znášali dobre. Okrem jednej dramatickej cystitídy u psychicky labilnej pacientky, 6 prípadov prechodnej cystitídy a niekoľkých prípadov diskomfortu močenia sa nezaznamenali nežiaduce vedľajšie reakcie. Autori pokladajú liečbu alfa 2-b interferónom a farmarubicínom za prínos v alternatívnej liečbe rezistentných povrchových tumorov močového mechúra. *(Lit. 18.)*

Kľúčové slová: rezistentné povrchové tumory, transuretrálna resekcia tumoru močového mechúra, imunoterapia alfa 2-b interferónom, chemoterapia farmarubicínom, karcinóm in situ, karcinóm invadujúci do lamina propria karcinómu len v epiteli.

About 80 % of bladder carcinomas are superficial: carcinoma in situ(CIS), epithelium-limited papillary carcinoma (pTA) and carcinoma invading only lamina propria yet not invading the muscular structures of the detrusor (pT1). Their main characteristic feature is the high recurrence rate within one year. Some authors report the recurrence rate of up to 80 % (1, 2, 3, 4). Another threat comes from the transformation of superficial into an invasive tumor which is reported to happen in 30 to 35 % of patients (2, 3, 4). The standard treatment of choice is transurethral resection of the bladder tumor (TUR-BT). After TUR-BT, the most frequently applied therapy used to be the intravesical instillation of BCG vaccine into the bladder (3, 5). The toxicity of this vaccine as well as the contraindication for this treatment in some diseases and the primary or acquired resistance of TCC cells to BCG have urged the search for alternative possibilities of the intravesical instillation treatment (3, 4). Games (6) warns about the possible danger of infection for the staff engaged in administration of Bacille Calmet-Guérin (BCG) as this is a ”live virus”. Bohle et al. (7) have registered a decrease in the quality of sexual life of patients treated with the BCG vaccine. Babjuk et al. (3) observed a most serious granulomatous pneumonitis in one male patient treated with BCG. One of our patients had a grave cystitis and a TBC abscess of the prostate after repeated TUR-BT and BCG vaccine therapy, and had to undergo cystectomy and urine derivation.

Alpha, beta and gamma interferons constitute a system which is a part of the non-specific immune defense system of the organism. They participate in the protection against viral infections and have a pronounced immunoregulatory activity. They also take part in the transfer of the genetic information of cells, they have an antiproliferative effect on healthy cells and inhibit oncogens in tumor cells. Interferon alpha 2-b has the most pronouced antiproliferative effect and interferon alpha is the most frequently used interferon in the treatment of cancer (8, 9).

Farmarubicin (Epirubicini hydrochloridum) is an antibiotic with an antitumor activity and is used for the treatment of various malignant diseases .

Administration of these substances is contraindicated in myelosuppression and patients with a grave heart condition (10).

Patients and methods

From March 1997 to December 1999 we began to administer chemo and immunotherapy to 33 pts after TUR-BT with a histologically verified TCC (either only IFN a-2 alone or in combination with FRC). The majority of patients of group I. consisting of 20 pts were previously unsuccessfully treated with BCG vaccine after TUR-BT. The 13 pts of group II were unsuitable for this treatment because of decompensated diabetes mellitus (DM), chronic hepatopathy, TBC in their anamnesis, hypoproteinemia and other immune and endocrine diseases. Out of 33 pts, 20 pts were treated and checked after monotherapy by 10 million I.U. IFN a-2 and the remaining 13 pts in group II were treated and observed after intravesical instillations with 10 million I.U. of IFN a-2 and 50 mg of Farmarubicin dissolved together in 50 ml of sterile physiological saline. We started with instillations one week after TUR-BT by four weekly administrations which continued for one year with monthly instillations.

Both substances were mixed, then a sterile catheter was applied, the bladder was emptied and the solution was instilled for two hours after which the patients urinated spontaneously, and the ultrasonographic examination showed that no residual fluid remained in the bladder. The patients were checked regularly. The third group consisted of 33 randomly chosen patients with no chemo– or immunotherapy applied after TUR-BT. The described three groups of patients were regularly checked by biochemical, haematological and serological laboratory tests as well as by oncomarkers. Every three months the patients were also checked cystoscopically and by ultrasonography. If needed, the patients were also subjected to intravenous urography every six months.

Results

Group I: 20 pts after TUR-BT+ unsuccessful BCG + IFN a-2, recurrence rate 4 pts (20 %).

Group II: 13 pts after TUR-BT+ IFN a-2+FRC, recurrence rate 3 pts (23 %).

Group I+II: 33 pts after intravesical therapy sum of recurrence rates 7 pts (21,2 %).

Group III : 33 pts after TUR-BT without intravesical therapy, recurrence rate 18 pts (54,5 %).

A recurring TCC with the transition into an invasive tumor in Groups I+II was detected in 4 pts (12.1 %). In the comparative group III, the transition to invasive tumors was observed in 7 pts (21.2 %). In group III, without chemo and immunotherapy, recurrences were detected in 18 pts (54.5 %) and the transition into an invasive tumor was observed in 7 pts (21.2 %). The differences in the results of treatment in the first and second experimental groups were not significant (group I: 20 %, and group II: 23 %).

Discussion

Ferrari et al. (11) have successfully applied the combined chemo– and immunotherapy using IFN a-2 combined with Epirubicin (ERC). Rattanen et al. (12) reports good results achieved by ERC and IFN a-2 monotherapy as well as with their combination in the treatment of patients with BCG vaccine resistant TCC. Schmid (13) has successfully applied a smaller amount of BCG vaccine in combination with 30 million I. U. of alpha 2-b interferon with lower toxicity, and observed a decreased rate of recurrence. Bouffiox et al. (14) administered Mytomycin C (MMC) or ERC, 50 to 80 mg dissolved in 50 ml saline and applied for 2 hours immediately after TUR-BT and continued with weekly instillations for six weeks. Crawford (15) has successfully applied Thiotepa as a monotherapy or in combination with MMC. The solution was instilled into an empty bladder and was kept there for only one hour. Naito et al. (16) report good results in the treatment of TCC by doxorubicin applied before and after resections. They have not registered any signifficant difference in the results after combining the previous treatment with 5-fluorouracil administered per os.

According to Schmitz-Dräger et al. (17) one of the causes of malignancy is the irreversible disturbance of the balance between protooncogenes and tumor-suppressorgenes. In tumors of the bladder inactivation of the tumor-suppressorgene p-53 located on the chromosome 17p 13.1 is often detected. The incidence of p-53 accumulation was slightly higher in muscle — invasive tumors (pT2) than in pT1 bladder cancer. The simultaneous analysis of both genes yielded specific patterns for different tumor stages. Based on DNA-cytometry Rassler et al. (18) divided tumors into “low-risk” and “high-risk” tumors.

In “low-risk” tumors (representing 13 %), chemotherapy is problematic and a ”wait and see” approach can be chosen. In “high-risk” tumors (78 %), topical prophylaxis is needed.

Conclusion

We would like to state that this publication is the beginning of the search to new approaches for the improvement of TCC treatment, and a much higher number of patients participating in multicentric and randomized studies will have to be involved. IFN a-2 and FRC are alternative treatments and form a contribution to the TCC therapy. Molecular and genetic research as well as research on the classification of tumors of the urothelium , will improve the differentiation of biological properties of tumors in the future and thereby enable also a more effective therapy. It can be expected that in the future the study of biochemical activities of tumors “in vitro” after TUR-BT as well as their vital response to the presence of chemotherapeutic and immunologically active agents will improve the treatment of tumors of the urine bladder. A similar result can be also expected owing to the eventually possible preparation of autoimmune vaccines, and as a result of highly probable technical progress.

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