468

Evidence of EBV DNA and Adenovirus 2 E1A (Types 2 and 5) in the Mucous Membrane of Bronchial Carcinoma and Pleurarmesothelioma

U. Rüther, C. Nunnensick, H.A.G. Müller, W. Rupp, H. Bader, P. Jipp
Katharinenhospital, Stuttgart, Germany

Issue Investigated:
Within the past decade, we have greatly increased our knowledge of molecular details of cell growth, especially those of tumor cells. However, we still do not fully understand the highly complicated cell growth monitor mechanisms nor, in particular, their disruption in tumor cells. Thus far, it has been established that although the genes involved here number in the thousands, there is a class of specific genes, the oncogenes, which are alone responsible for the expression of major features of carcinoma cells. To date, 40 such oncogenes and a number of related tumors have been identified.
Researchers have found that RNA viruses as carriers of such oncogenes can induce certain forms of neoplasia. Many other tumor viruses have also been identified in humans – including, primarily, RNA viruses – but also some DNA viruses such as Epstein-Barr virus and adenovirus. Since we had already found evidence of EBV and HSV DNA in various kinds of tumors (germ cell tumors and colorectal tumors) in earlier studies, the question arose whether these potentially oncogenic viruses also appear in bronchial carcinoma and pleurarnesothelioma.
Materials and Methods:
The materials studied came from 11 patients. Nine of these patients had bronchial carcinoma of varying histology; the other two had pleurarnesothelioma. In addition, we examined mucous membrane specimens from seven healthy persons. In-situ hybridization was conducted using the Brigatti method. Via avidin-biotin-peroxidase using 3-amino-9-ethylcarbazole as the chromagen, evidence of covalent biotin-marked BAM HIV fragments of EBV DNA was found. Adenovirus (types 2 and 5) was detected immuno-histochemically using monoclonal antibody (Klon M73).
Results:
In the mucous membranes of 7/9 bronchial carcinoma cases and in 1/2 pleurarnesotheliomas, EBV DNA was detected in tumor cell nuclei, while the healthy patients' bronchial mucous membranes showed no EBV DNA. In 8/9 bronchial carcinoma patients, and in 0/2 pleurarnesothelioma cases, we found evidence of adenovirus 2 E1A (types 2 and 5) in the tumor cell nuclei. In the 7 healthy mucous membrane specimens, there was no evidence of adenovirus 2 E1A (types 2 and 5).
Discussion:
The evidence of EBV DNA and adenovirus 2 E1A (types 2 and 5) in the mucous membrane of patients with bronchial carcinoma of various histology and pleurarnesotheliorna may indicate a viral cause of these diseases. Since Epstein-Barr viruses and adenovirus 2 E1A (types 2 and 5) can be involved in malignant cell transformation, the question of their possible role in the development of bronchial carcinomas and pleurarnesotheliomas is significant. If this viral phenomenon does turn out to be an etiopathogenetic factor or co-factor, it will bear strongly on therapeutic practice.
We would like to express our gratitude to M. Potting and G. Hlob for their technical assistance.

Digestive Tract Cancer

Colorectal Cancer

469

UNRESECTED HEPATIC METASTASES (HM) FROM COLORECTAL CANCER (CRC). PROSPECTIVE PROGNOSTIC FACTOR ANALYSIS ON 544 CASES FROM FONDATION FRANÇAISE DE CANCEROLOGIE DIGESTIVE (FFCD).

Ph. Rougier, Ch. Milan, L. Bedenne, F. Lazorthes, G. Fourtanier, C. Partensky, Th. Conroy, M. Parneix, J.L. Gouzi, M. Gignoux, P. Boissel, J. Bourry, A.K.Ben Bouali, M. Ducreux, H. Baumel, J. Faivre - FRANCE

To better evaluate prognostic factors of patients (pts) with HM from CRC 544 pts with unresectable HM from CRC were registered in a national inquiry during one year and were followed up until death. Twenty factors were studied in an univariate analysis (log rank test). All significant factors ($p<0.05$) were then included in a multivariate analysis (cox model) and eight factors independently influenced survival :

Variables	Class	Nb of pts at risk	P-value	RR of death
Performance Status	2-3/0-1	127/411	$<10^{-4}$	1.9
Alkaline Phosphatase	>N/N	309/160	$<10^{-4}$	1.6
Nb of involved segments	≥4/<4	383/138	10^{-3}	1.6
Chemotherapy	no/yes	318/226	10^{-4}	1.4
Extra hepatic metastases	yes/no	200/341	0.003	1.4
CRC primary site	right/other	108/436	0.01	1.4
Prothrombine time (%)	<75/≥75	78/406	0.014	1.4
Primary CRC resected	no/yes	299/245	0.045	1.2

We conclude that life expectancy for pts with non resectable HM from CRC, mainly depends on performance status, liver involvement and chemotherapy and a simple classification will be given taking into account PS and Alkaline phosphatase.(* supported by a grant from the French League Against Cancer)

471

THREE ARMS RANDOMIZED TRIAL COMPARING METHOTREXATE, 5-FU AND LEUCOVORIN (MFL) vs 5-FU, LEUCOVORIN (FL) vs 5-FU (F) IN ADVANCED AND METASTATIC COLORECTAL CANCER. (FINAL RESULTS). Abad A., Garcia P.*, Gravalos C.**, Tusquets I.§, Rosell R, Perez-Manga G.* Cortés-Funes H.** Fabregat X§ , Barnadas A., Sanchez JJ. H. Germans Trias Pujol. *H. Gregorio Marañon. ** H. 12 de Octubre. § H. Esperança. SPAIN.

Based on our experience (Am J Clin Oncol 14:5,1991), we carried out a randomized trial with MFL: Methotrexate 500 mg/sqm iv 1 hour infusion and 10 hours later 5-FU 600 mg/sqm iv bolus plus leucovorin 200 mg/sqm iv 1 hour infusion every 2 weeks vs FL: 5-FU plus leucovorin in equal dose and schedule vs F: 5-FU 1200 mg/sqm iv every 2 weeks. A total of 186 patients are included (172 evaluable). In a preliminary analysis with 92 evaluable patients there was a significant statistical difference concerning toxicity for F arm (MFL vs F p:0.0002; FL vs F p: 0.00001) and for survival with 13 months for MFL and FL and 8 months for F (p:0.01). With these results the F arm was stopped. To date 69 patients for MFL and 70 patients for FL are evaluable. The distribution for prognostic factors shows no difference. The response rate found were 26% (95% CL:16-38) for MFL and 15.7% (95% CL:8-26) for FL (p:0.1). The median survival was 14.9 months for MFL and for FL was 13.8 months. The Hematologycal toxicity were mild without grade 3-4 leukopenia in both arms. The major non-hematologycal toxicity was ocular and non-grade 3-4 diarrhoea had been observed. The biochemical modulation of 5-FU is superior to 5-FU alone in the treatment of colorectal cancer but the double modulation, though it obtains a higher response rate, fails to demonstrate superiority to single modulation in this dose and schedule.

470

High - dose Folinic Acid (HDFA) and Fluorouracil (FU) plus or minus Thymostimulin (TS) for treatment of metastatic colorectal cancer (MCRC): a randomized multicentric study.

G.Mustacchi on behalf of an Italian Cooperative Trials Group*

Rationale : TS has been reported effective in reducing chemotherapy-induced fever and cytopenia (Anticancer Res 9:193,1989) as well as to potentiate efficacy of chemotherapy through immunomodulation in solid tumors(Rec.Progr.Med ; 78:35,1987). Purpose : To compare therapeutic efficacy and tolerability of HDFA-FU versus the same regimen plus TS and to ascertain the possible protective effect of TS on chemotherapy - related febrile episodes and leukopenia. Patients and Methods : from Febr. 1990 to Dec. 1992 two hundred and forty one pts. with histologically proven , progressive MCRC were enrolled and randomly allocated over the phone to one of the following treatment arms : A. - FA (200 mg/m^2 in 60' infusion), followed by FU (375 mg/m^2 bolus iv. from da 1 to 5) q.3 weeks. B. - HDFA-FU plus TS (1 mg/kg/im/daily , concurrently with chemotherapy and 3 times a week thereafter until progression or withdrawal). The pretreatment characteristics of pts. sample were well balanced in terms of age , sex, performance status, previous treatment of primary, free-interval and dominant metastatic site. Results : In 186 fully evaluable pts. , 93 in group A and 93 in gropu B , an objective response (CR + PR) was observed in 16 /93 pts. (17% - C.I.95% = 10-24 %) versus 30 / 93 pts (32% - C.I.95% = 23-41 %) p=0.01 . The best response was recorded in cutaneous and lymph nodes (3/4 pts. in both groups) as well as in viscerale metastases (10/71 vs. 23/66 , p =0.01). The median time to P was 9.5 and 11 mos. respectively , median survival was 10 vs 9.5 months. Toxicity :on a total of 1051 courses of chemotherapy , no difference was observed in terms of hematological toxicity (assessed as number of delayed / total number of administered cycles) , whereas the TS treated-group of pts. experienced a significantly lower (p= 0.02) incidence of mucositis and diarrhea . No difference emerged from the analysis of the incidence of febrile episodes and other systemic toxicity. Conclusions : the addition of TS improves the HDFA-FU regimen's therapeutic efficacy and , by reducing G.I. toxicity , contributes to the improvement of quality of life in pts. with metastatic colorectal carcinoma.
* *Iaffaioli (Napoli) ,Musiacchi (Trieste), Caracò (Napoli) ,Comella (Napoli),.Conzu (Sassari) Farris (Sassari) , Attardo (Mede), Brema (Savona),Beni (Roma) ,Gallotti(Vigevano)Ghezzi (Arezzo) ,Robustelli (Pavia) , Angeli (Torino) ,Bumma (Torino) ,Piazza (Milano), Smerieri (Mantova) , Baroni (Milano) ,Fiore (Novi Ligure)Failla (Catania), Fertitta (Palermo) .*

472

THE OUTCOME OF SURGERY FOR COLORECTAL CANCER IN THE ELDERLY

R D Kingston, J Jeacock, S Walsh, F Keeling
Dept. of Clinical Studies, Trafford General Hospital, Manchester, England.

A colo-rectal database has been developed at Trafford General Hospital which contains a comprehensive set of pre and post-operative parameters for all patients presenting to three general surgeons since 1981. Data on 882 patients have been analysed to assess the influence of patient age on treatment management and outcome. Three age groups were defined; less than 65 years old, 65 years to 75 years and those greater than 75 years.
The percentage of patients who were inoperable at admission was significantly higher in the over 75 group and consequently the resection rate was reduced to 80% in this group. The physical status (ECOG) of these patients was poorer and stage of disease (Dukes) more advanced.
The 'curative' resection rate for the three age groups was comparable; 71%, 74% and 68% respectively, and the post-operative wound infection and leak rates were not different. The number of emergency admissions were also comparable in each group, but length of hospital stay was increased in the over 75s.

	5 YEAR SURVIVAL		
Age group	Any cause	Colon Ca	Colon Ca - Curative Res.only
<65	34%	40%	65%
65-75	30%	38%	60%
>75	24%	31%	59%
	p<0.0001 SIG	p=0.009 SIG	p=0.57 NOT SIG

As a group these data demonstrate the poor survival rate of the more elderly patients from any cause of death and also when censored for non-cancer deaths. However, if the elderly patient is fit for surgery and a 'curative' resection performed the survival rate is as good as those patients in the younger age groups.