
Selected published abstracts of Baylor researchers

AMERICAN JOURNAL OF CARDIOLOGY

Late (≥ 6 years) results of combined coronary artery bypass grafting and mitral valve replacement for severe mitral regurgitation secondary to acute myocardial infarction

Theleman KP, Stephan PJ, Isaacs MG, Hebler RF Jr, Henry AC III, Roberts WC

(*Am J Cardiol* 2003;92:1086–1090) Reprinted with permission from Elsevier.

Analysis of outcomes in 31 patients who had combined mitral valve replacement (MVR) and coronary artery bypass grafting (CABG) for ischemic mitral regurgitation (MR) disclosed that 12 patients had MR because of papillary muscle rupture and that 19 patients had MR because of papillary muscle necrosis or fibrosis without rupture. Of the 12 patients with rupture, 6 died within 2 months of operation and the other 6 lived ≥ 6 years postoperatively; of the 19 patients without rupture, none died within 2 months of operation and 11 (58%) lived at least 6 years.

Weights of operatively-excised stenotic unicuspid, bicuspid, and tricuspid aortic valves and their relation to age, sex, body mass index, and presence or absence of concomitant coronary artery bypass grafting

Roberts WC, Ko JM

(*Am J Cardiol* 2003;92:1057–1065) Reprinted with permission from Elsevier.

This study was designed to evaluate weights of operatively-excised stenotic aortic valves and to compare them with age, sex, body mass index, and presence or absence of concomitant coronary artery bypass grafting. Weights of operatively-excised stenotic aortic valves have not been previously reported. We weighed operatively-excised stenotic valves in 499 patients (aged 19 to 91 years, mean 70), none of whom had mitral valve replacement. The 499 aortic valves ranged in weight from 0.45 to 11.30 g (mean 2.67). The mean weights of the unicuspid and bicuspid valves were heavier than those of the tricuspid valves (4.36 vs 3.34 vs 2.04 g, $P < 0.05$). Mean valve weights were greater in the 304 men than in the 195 women (3.19 vs 1.87 g, $P < 0.001$), in the younger patients than in the older patients (3.13 g in patients ≤ 40 years old vs 2.89 g in patients 41 to 70 years old and 2.47 g in patients 71 to 91 years old, $P < 0.05$), and in the 230 patients who did not undergo simultaneous coronary artery bypass grafting compared with the 269 patients who had this additional procedure (2.94 vs 2.45 g, $P < 0.001$). The mean weights of the valves were similar in patients whose body mass index was < 25 , 25 to 30, and > 30 kg/m² (2.62 vs 2.76 vs 2.57 g). Weights of operatively-excised stenotic aortic valves provide objective evidence of valvular stenosis.

AMERICAN JOURNAL OF GASTROENTEROLOGY

Rapid intestinal transit as a primary cause of severe chronic diarrhea in patients with amyloidosis

Guirl MJ, Högenauer C, Santa Ana CA, Porter JL, Little KH, Stone MJ, Fordtran JS

(*Am J Gastroenterol* 2003;98:2219–2225) Reprinted with permission from Elsevier.

Objective: The cause of severe diarrhea in patients with systemic amyloidosis is obscure. We therefore performed pathophysiological studies in three such patients in an effort to determine the mechanism of amyloid diarrhea.

Methods: Epithelial cell absorption rate of electrolytes was measured during steady state GI perfusion of a saline-mannitol solution. GI transit time of PEG and absorption of radiolabeled bile acid were measured simultaneously while subjects ingested three meals per day. To obtain a diarrhea control group for transit time and bile acid absorption, normal subjects were studied when they had diarrhea caused by ingestion of Milk of Magnesia (MOM).

Results: Diarrhea could not be explained by malabsorption of ingested nutrients, bacterial overgrowth, bile acid malabsorption, or epithelial cell malabsorption of electrolytes. However, 25% of polyethylene glycol (PEG) ingested with a standard meal was recovered in stool in 45 min, which is 10 times faster than in normal subjects with equally severe diarrhea caused by ingestion of MOM. All of the patients had autonomic neuropathy that remained unrecognized for 15–36 months after onset of chronic diarrhea; it seems likely that this was the cause of rapid transit.

Conclusions: Severe chronic diarrhea in three patients with systemic amyloidosis was mediated by extremely rapid transit of chyme and digestive secretions through the intestine.

AMERICAN JOURNAL OF SURGERY

Clinical benefits of leukocyte filtration during valve surgery

Patel AN, Sutton SW, Livingston S, Patel A, Hunley EK, Hebler RF, Henry AC III, Hamman BL, Wood RE, Urschel HC Jr.

(*Am J Surg* 2003;186:636–640) Reprinted with permission from Excerpta Medica Inc.

Background: The accumulation of activated leukocytes in the pulmonary circulation plays an important role in the pathogenesis of lung dysfunction associated with cardiopulmonary bypass (CPB). Patients undergoing valve surgery have prolonged CPB owing to the complexity of the surgery. The goal of this study is to determine if arterial leukocyte filters during CPB improve clinical outcomes after valve surgery.

Methods: A prospective analysis of all patients receiving only valve surgery with leukocyte arterial filters from June 1999 to June 2002 was compared with a case-matched cohort during the same time period. Two hundred fifty patients were identified and compared with a cohort who did not have leukocyte filters used during CPB. The following study points were evaluated preoperatively and postoperatively: white blood cell count, platelet count, arterial blood gas, time to extubation, intensive care unit stay, and total length of hospital stay.

Results: There were 500 patients in the study. The following valve operations were performed: 92 mitral valve replacements, 168 aortic valve replacements, 152 mitral valve repairs, 80 combined valve repair/replacements, and 8 tricuspid valve repairs, all evenly divided between the two treatment limbs. Patients with leukocyte filters had the following findings compared with nonfilter patients: the time to extubation 10.3 vs 16.2 hours ($P = 0.009$), postoperative respiratory quotient 407 vs 320 ($P = 0.02$), total length of stay 5.4 vs 7.2 days ($P = 0.04$).

Conclusions: The use of arterial leukocyte filters in patients undergoing valve surgery leads to earlier extubation, improved oxygenation, and a decreased length of stay. Leukocyte filters should be used during CPB for patients having valve surgery.

Patterns of recurrence after sentinel lymph node biopsy for cutaneous melanoma

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(*Am J Surg* 2003;186:675–681) Reprinted with permission from Excerpta Medica Inc.

Background: Previous sentinel lymph node (SLN) studies for cutaneous melanoma have shown that the SLN accurately reflects the nodal status of the corresponding nodal basin. However, there are few long-term studies that describe recurrence site patterns, predictors for recurrence, and overall survival and disease-free survival after SLN biopsy.

Methods: A retrospective review of patients over a 6-year period was performed to determine patient outcomes and the patterns of recurrence. In all cases, Tc-99 sulfur colloid along with isosulfan blue dye was injected at the primary melanoma site. After resection, the SLN was serially sectioned and evaluated by hematoxylin and eosin staining and immunohistochemistry.

Results: One hundred ninety-eight patients were identified who underwent SLN biopsy for cutaneous melanoma including T1 ($n = 21$), T2 ($n = 88$), T3 ($n = 75$), and T4 ($n = 14$) primary tumors. Of these patients, 38 had a positive SLN. Of the 38 patients with a positive SLN (mean follow-up 38 months), recurrent disease was identified in 10 (26.3%) at a mean interval of 14.2 months. The site of first recurrence was distant ($n = 4$) and local ($n = 6$). Regional lymphatic basin recurrence was not identified. Of the 160 patients with a negative SLN (mean follow-up 50 months), recurrent disease was identified in 16 (10.0%) at a mean interval of 31.3 months. The site of first recurrence was systemic ($n = 11$), local ($n = 4$), and nodal ($n = 1$). Overall survival and disease-free survival for patients with a positive SLN at 55 months was 53.3% and 47.7% respectively, while overall survival and disease-free survival for patients with a negative SLN at 53 months was 92.2% and 87.7% respectively ($P < 0.01$). Univariate and multivariate analysis of the entire cohort ($n = 198$) identified primary tumor depth and positive SLN status as significant predictors of recurrence.

Conclusions: The incidence of nodal basin recurrence after SLN biopsy was found to be 0.6%. Primary tumor depth and pathological status of the SLN are significant predictors of local and systemic recurrence. Long-term follow-up indicates that patients with a positive SLN clearly recur sooner and have decreased overall survival than those with a negative SLN.

ARCHIVES OF DERMATOLOGY

Histopathologic features of alopecia areata: a new look

Whiting DA

(*Arch Dermatol* 2003;139:1555–1559)

Background: A peribulbar lymphocytic infiltrate is the expected histologic feature of alopecia areata, but it is absent in many scalp biopsy specimens. Other diagnostic criteria are needed.

Objective: To establish the histologic features of alopecia areata in scalp biopsy specimens taken from different types of alopecia areata, using follicular counts to relate biopsy findings to stages of the disease.

Methods: Fifty consecutive new patients with alopecia areata were studied. Four-millimeter punch biopsy specimens were taken from the scalp in areas of recent, active hair loss; old, inactive hair loss; or recent hair regrowth. Specimens were sectioned horizontally. Terminal and vellus-like hairs were counted. Inflammation and fibrosis around lower and upper follicles were rated.

Results: The histopathologic features of alopecia areata were not significantly affected by the sex, age, and race of the patient or by the type, percentage of hair loss, total duration, or regression of alopecia areata. The major factor affecting the histopathologic features was the duration of the current episode of alopecia areata. In the acute stage, bulbar lymphocytes surrounded terminal hairs in early episodes and miniaturized hairs in repeated episodes. In the subacute stage, decreased anagen and increased catagen and telogen hairs were characteristic. In the chronic stage, decreased terminal and increased miniaturized hairs were found, with variable inflammation. During recovery, increasing numbers of terminal anagen hairs from regrowth of miniaturized hairs and a lack of inflammation were noted.

Conclusions: The histopathologic features of alopecia areata depend on the stage of the current episode. Alopecia areata should be suspected when high percentages of telogen hairs or miniaturized hairs are present, even in the absence of a peribulbar lymphocytic infiltrate.

BONE MARROW TRANSPLANTATION

Total parenteral nutrition vs oral diet in autologous hematopoietic cell transplant recipients

Roberts S, Miller J, Piñero L, Jennings L

(*Bone Marrow Transplant* 2003;32:715–721)

Autologous HCT patients often have poor oral intake for 2–4 weeks posttransplant. To compare outcomes between patients provided prophylactic total parenteral nutrition (TPN) or an oral diet (OD), 55 well-nourished breast cancer/hematopoietic cell transplantation (HCT) patients were randomized to TPN ($n = 27$), beginning day –1, or OD ($n = 28$). Parameters studied include length of stay (LOS), engraftment, infections, survival, weight, anthropometrics, handgrip strength, and quality of life (QOL). In all, 50% of OD patients were given TPN due to poor oral intake for 10 consecutive days. No significant differences were found between the groups for any of the above parameters except weight and anthropometrics, which were better maintained in the TPN group than the OD group. Trends were seen for increased infections, more stable handgrip strength, and improved QOL in the TPN group vs the OD group. Prophylactic TPN did result in a more intact nutritional status and preservation of lean body mass posttransplant but did not impact LOS or survival when compared to OD. For this reason, TPN should be reserved for autologous HCT patients with pretransplant nutritional depletion, complications posttransplant, or prolonged poor oral intake. These results should not be extrapolated to allogeneic HCT

patients but are likely applicable to other well-nourished autologous HCT patients.

CANCER GENE THERAPY

Pilot trial of genetically modified, attenuated *Salmonella* expressing the *E. coli* cytosine deaminase gene in refractory cancer patients

Nemunaitis J, Cunningham C, Senzer N, Kuhn J, Cramm J, Litz C, Cavagnolo R, Cahill A, Clairmont C, Sznol M

(*Cancer Gene Ther* 2003;10:737–744)

We performed a pilot trial in refractory cancer patients to investigate the feasibility of intratumoral injection of *TAPET-CD*, an attenuated *Salmonella* bacterium expressing the *E. coli* cytosine deaminase gene. A total of three patients received three dose levels of *TAPET-CD* (3×10^6 – 3×10^7 CFU/m²) via intratumoral injection once every 28 days as long as progression of disease or intolerable toxicity was not observed. From days 4 to 14 of each 28-day cycle, patients also received 5-fluorocytosine (5-FC) at a dose of 100 mg/kg/day p.o. divided three times daily. Six cycles of treatment were administered. No significant adverse events clearly attributable to *TAPET-CD* were demonstrated. Two patients had intratumor evidence of bacterial colonization with *TAPET-CD*, which persisted for at least 15 days after initial injection. Conversion of 5-FC to 5-fluorouracil (5-FU) as a result of cytosine deaminase expression was demonstrated in these two patients. The tumor-to-plasma ratio of 5-FU for these two colonized patients was 3.0, demonstrating significantly increased levels of 5-FU at the site of *TAPET-CD* colonization and insignificant systemic spread of the bacteria. In contrast, the tumor-to-plasma ratio of 5-FU of the patient who did not show colonization of *TAPET-CD* was less than 1.0. These results support the principle that a *Salmonella* bacterium can be utilized as a delivery vehicle of the cytosine deaminase gene to malignant tissue and that the delivered gene is functional (i.e., able to convert 5-FC to 5-FU) at doses at or below 3×10^7 CFU/m².

DIABETES, OBESITY & METABOLISM

Addition of pramlintide to insulin therapy lowers HbA_{1c} in conjunction with weight loss in patients with type 2 diabetes approaching glycaemic targets

Hollander P, Ratner R, Fineman M, Strobel S, Shen L, Maggs D, Kolterman O, Weyer C

(*Diabetes Obes Metab* 2003;5:408–414)

Aim: Two long-term, randomized, double-blind, placebo-controlled clinical trials in insulin-using patients with type 2 diabetes, spanning a wide range of baseline glycaemic control, have shown that the addition of pramlintide, an analogue of the beta-cell hormone amylin, to preexisting insulin regimens results in reductions in HbA_{1c} that are accompanied by weight loss.

Methods: To assess whether this profile of pramlintide is observed in patients approaching, but not yet reaching, glycaemic targets, we conducted a pooled post hoc analysis of the two trials, including all patients with an entry HbA_{1c} between 7.0% and 8.5%. Within this subset of patients, 80 were treated with placebo + insulin [baseline HbA_{1c} 8.0 ± 0.3%, weight 87.3 ± 19.3 kg (mean ± s.d.)] and 86 with pramlintide (120 µg bid) + insulin [HbA_{1c} 8.0 ± 0.4%, weight 92.5 ± 20.4 kg (mean ± s.d.)]. Endpoints included changes from baseline to week 26 in HbA_{1c}, body weight, and the event rate of severe hypoglycaemia.

Results: Adjunctive therapy with pramlintide resulted in significant reductions in both HbA_{1c} and body weight from baseline to week 26 (–0.43% and –2.0 kg differences from placebo, respectively, both $P < 0.001$). These changes were achieved without a concomitant increase in the overall rate of severe hypoglycaemic events (0.13 pramlintide vs 0.19 placebo, events/patient year of exposure).

Conclusions: The data from this post hoc analysis indicate that the addition of pramlintide to insulin therapy may help patients with type 2 diabetes who are approaching, but not yet reaching, glycaemic targets to achieve further reductions in HbA_{1c} without concomitant weight gain and increased risk of severe hypoglycaemia.

GENOMICS

Characterization of the bidirectional promoter region between the human genes encoding VLCAD and PSD-95

Zhang LF, Ding JH, Yang BZ, He GC, Roe C

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Bidirectional promoters are widely known among lower organisms but rare in mammals. A shared promoter between the two human genes encoding very long chain acyl-CoA dehydrogenase (VLCAD) and postsynaptic density protein 95 (PSD-95) is an ideal model to investigate bidirectional transcription in mammals. VLCAD associates with the inner mitochondrial membrane and catalyzes the initial step in mitochondrial long-chain fatty acid β-oxidation. PSD-95, a component protein of the PSD, plays an essential role in clustering the transmembrane proteins in synaptic membranes. Interestingly, the human genes encoding VLCAD (*ACADVL*) and PSD-95 (*DLG4*) are adjacently located in the head-to-head orientation on chromosome 17p. The transcribed regions of the two genes overlap, while the two transcription start sites stand ~220 bp apart. To analyze the common transcriptional control region shared by the two genes, we generated serial promoter partial deletion constructs using firefly luciferase as the reporter gene. Our results showed that the essential promoter activity of PSD-95 is carried within an ~400-bp region, which covers the entire ~270-bp minimal promoter of VLCAD. The results from di-(2-ethylhexyl) phthalate (DEHP)-treated HepG2 cells revealed that the minimal VLCAD promoter is able to up-regulate VLCAD expression in response to DEHP treatment. Site-directed mutagenesis experiments showed that a mutated activator protein 2-binding site markedly reduced the transcriptional activity of both promoters and abolished the minimal VLCAD promoter's response to DEHP treatment.

HEPATOLOGY

Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C

Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J

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Interferon-based regimens for the treatment of chronic hepatitis C have become increasingly effective and are able to eradicate virus in more than one half of cases. Early identification of patients who will not respond is desirable because treatment might be stopped, thereby avoiding the expense and inconvenience of unnecessary therapy. We examined the accuracy of different degrees of viral inhibition during the early weeks of treatment (early virologic response [EVR]) with pegylated interferon alfa-2b and ribavirin (PEG/R) in identifying patients who would not respond to therapy. The best definition of EVR was a reduction in hepatitis C

virus (HCV) RNA by at least 2 logs after the first 12 weeks of treatment compared with baseline. Between 69% and 76% of patients achieved this threshold, depending on the treatment regimen, and sustained virologic response (SVR) occurred in 67% to 80% of these patients. Patients who did not reach EVR did not respond to further therapy. If treatment had been stopped in patients without EVR, drug costs would have been reduced by more than 20%. In conclusion, early confirmation of viral reduction following initiation of antiviral therapy for chronic hepatitis C is worthwhile. It provides a goal to motivate adherence during the first months of therapy and a milestone at which to reassess the need for continued treatment. Most patients who are able to complete the first 12 weeks of therapy achieve EVR and have a high probability of SVR. Patients who fail to achieve EVR will not clear virus even if an additional 9 months of therapy is received. Therapy can be confidently discontinued in those cases.

INTERNATIONAL JOURNAL FOR QUALITY IN HEALTH CARE

Indicators to improve clinical quality across an integrated health care system

Ballard DJ

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Purpose: To describe key historical and operational elements of change that may assist an organization to develop quality indicators for implementing a strategic plan to improve care, align health care improvement efforts with national directions, and examine the types of medication indicators used to assess these changes.

Setting: The Baylor Health Care System (BHCS) is an integrated health care delivery organization in Dallas–Fort Worth, Texas. It includes 11 hospitals with 83,000 admissions per year and 47 primary care and senior centers with more than 500,000 visits annually.

Intervention: Following a charter by the BHCS Board of Trustees to develop a health care quality improvement strategic plan, BHCS undertook a systemwide effort to improve care supported by the use of clinical quality indicators.

Results: Consistent with the direction of the US Institute of Medicine, BHCS has implemented a clinical indicator system focused on measures of health care underuse, overuse, and misuse. These indicators demonstrated the accomplishments of specific process of care improvements throughout BHCS. Despite implementing Web-enabled error reporting systems and pilot work with an adverse drug event hospital medical record abstraction tool, BHCS indicators of medication misuse continue to be in a formative stage, much like the national consensus.

Conclusion: Organizational, compensatory, and cultural commitments may be important for successful implementation of clinical indicator initiatives by health care systems. Using clinical indicators to establish baseline performance and to assess the effectiveness of proposed quality improvements provides quantitative and qualitative means to identify and disseminate best care practices. Although indicators to measure underuse of clinically necessary care are well established, there remains a need to achieve consensus regarding practicable medication quality indicators for overuse, misuse, and adverse drug events.

JAMA

Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial

Gordon KB, Papp KA, Hamilton TK, Walicke PA, Dummer W, Li N, Bresnahan BW, Menter A, for the Efalizumab Study Group

(*JAMA* 2003;290:3073–3080)

Context: Because T-cell interactions are involved in the pathophysiology of psoriasis, therapy with a T-cell modulator may have beneficial effects on psoriasis severity and health-related quality of life (HRQL).

Objective: To assess the efficacy and safety of efalizumab, a T-cell modulator, in patients with plaque psoriasis.

Design, setting, and patients: Phase 3 randomized, double-blind, parallel-group, placebo-controlled trial involving 556 adult patients with stable, moderate to severe plaque psoriasis and conducted at 30 study centers in the United States and Canada between January and July 2002.

Interventions: Patients were randomly assigned in a 2:1 ratio to receive 12 weekly doses of subcutaneous efalizumab, 1 mg/kg (n = 369), or placebo equivalent (n = 187).

Main outcome measures: At least 75% improvement on the Psoriasis Area and Severity Index (PASI-75); improvement on the overall Dermatology Life Quality Index (DLQI), Itching Visual Analog Scale (VAS), and Psoriasis Symptom Assessment (PSA) at week 12 vs baseline.

Results: Efalizumab-treated patients experienced significantly greater improvement on all end points than placebo-treated patients. Twenty-seven percent of efalizumab-treated patients achieved PASI-75 vs 4% of the placebo group ($P < .001$). Efalizumab-treated patients exhibited significantly greater mean percentage improvement than placebo-treated patients on the overall DLQI (47% vs 14%; $P < .001$), Itching VAS (38% vs -0.2%; $P < .001$), and PSA frequency and severity subscales (48% vs 18% and 47% vs 17%, respectively; $P < .001$ for both) at the first assessment point. Efalizumab was safe and well tolerated, with primarily mild to moderate adverse events.

Conclusion: In this 12-week study, efalizumab resulted in significant improvements in clinical end points, including physician-assessed and dermatology-specific patient-reported HRQL measures, in patients with moderate to severe plaque psoriasis.

JOURNAL OF ASTHMA

A randomized controlled trial using the school for anti-inflammatory therapy in asthma

Millard MW, Johnson PT, McEwen M, Neatherlin J, Lawrence G, Kennerly DK, Bokovoy JL

(*J Asthma* 2003;40:769–776)

This study investigated the impact of providing low-dose inhaled corticosteroids (ICS) at school or at home to asthmatic inner-city children over a 14-week period, compared with the existing community standard. Eight elementary schools in the Dallas Independent School District with a high incidence of asthma located in predominantly urban African American communities were randomly assigned to one of four groups. The treatment arms were school-based delivery of inhaled steroids, home-based delivery of inhaled steroids, and home-based delivery of inhaled steroids with school-based asthma education, and the control group was no change in current therapy. Fifty students were objectively diagnosed with mild, persistent asthma and participated in the study. Students in the treatment arms received beclomethasone (42 mcg/puff) 4 puffs, twice a day, either at school or at home. Students in the control, “community

standard of care” group received no additional medical intervention. Higher peak flows for the treatment groups were seen in the first week and maintained throughout the study ($P = .047$). By week 5 significant differences were found in frequency of bronchodilator use ($P = .025$), episodes of nocturnal awakening with asthma symptoms ($P = .022$), and visits to the primary health care provider ($P = .022$). Treatment groups rated their asthma as “better than the week before” more frequently than the control group ($P = .001$). Delivering ICS in school is associated with improved asthma control than when anti-inflammatory medication was delivered to children with asthma in a home-based setting, and both are superior when compared with a control, “community standard of care” group in which no additional medical intervention occurred.

JOURNAL OF IMMUNOTHERAPY

Single injection of CD34⁺ progenitor-derived dendritic cell vaccine can lead to induction of T-cell immunity in patients with stage IV melanoma

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(*J Immunother* 2003;26:432–439)

There is evidence that dendritic cell (DC) vaccines induce tumor-specific immune responses that correlate with clinical responses. Little is known, however, about the kinetics of T-cell responses to antigens presented on DC vaccines. The authors vaccinated 18 HLA A*0201⁺ patients with stage IV melanoma with CD34 HPC-derived DCs pulsed with six antigens: influenza matrix peptide (Flu-MP), KLH, and peptides derived from the four melanoma antigens: MART-1/Melan A, gp100, tyrosinase, and MAGE-3. A single DC vaccination was sufficient for induction of KLH-specific CD4 T-cell responses in five patients and Flu-MP-specific CD8 T-cell responses in eight patients. A single DC vaccine was sufficient for induction of tumor-specific effectors to at least one melanoma antigen in five patients. Thus, a single injection of CD34 HPC-derived DCs can lead to rapid immune response to CD4 epitopes or to melanoma antigens.

JOURNAL OF THE NATIONAL CANCER INSTITUTE

Granulocyte-macrophage colony-stimulating factor gene-modified autologous tumor vaccines in non-small-cell lung cancer

Nemunaitis J, Sterman D, Jablons D, Smith JW II, Fox B, Maples P, Hamilton S, Borellini F, Lin A, Morali S, Hege K

(*J Natl Cancer Inst* 2004;96:326–331) Reprinted with permission from Oxford University Press.

To evaluate the feasibility, safety, and efficacy of vaccination with autologous tumor cells genetically modified with an adenoviral vector (Ad-GM) to secrete human granulocyte-macrophage colony-stimulating factor (GM-CSF), we conducted a phase I/II multicenter trial in patients with early and advanced stage non-small-cell lung cancer (NSCLC). Vaccines were generated from autologous tumor harvests. Intradermal injections were given every 2 weeks for a total of three to six vaccinations. Tumors were harvested from 83 patients, 20 with early-stage NSCLC and 63 with advanced-stage NSCLC; vaccines were successfully manufactured for 67 patients, and 43 patients were vaccinated. The most common toxicity was a local injection-site reaction (93%). Three of 33 advanced-stage patients, two with bronchioloalveolar carcinoma, had durable complete tumor responses (lasting 6, 18, and ≥ 22 months). Longer survival was observed in patients receiving vaccines secreting GM-CSF at more than 40 ng/24 h per 10^6 cells (median survival = 17 months, 95% confidence interval [CI] = 6 to 23 months) than in patients receiving vaccines secreting less GM-CSF (median survival = 7 months, 95% CI = 4 to 10 months) ($P = .028$), suggesting a vaccine dose-related survival advantage.