Original Research Article

Articolo che riporta i risultati di studi originali osservazionali o sperimentali

ORIGINAL ARTICLE

High-Dose Chemotherapy and Stem-Cell Rescue for Metastatic Germ-Cell Tumors

Lawrence H. Einhorn, M.D., Stephen D. Williams, M.D., Amy Chamness, B.A., Mary J. Brames, R.N., Susan M. Perkins, Ph.D., and Rafat Abonour, M.D.

ABSTRACT

BACKGROUND

Metastatic testicular tumors that have not been successfully treated by means of initial chemotherapy are potentially curable with salvage chemotherapy.

METHODS

We conducted a retrospective review of 184 consecutive patients with metastatic testicular cancer that had progressed after they received cisplatin-containing combination chemotherapy. We gave 173 patients two consecutive courses of high-dose chemotherapy consisting of 700 mg of carboplatin per square meter of body-surface area and 750 mg of etoposide per square meter, each for 3 consecutive days, and each followed by an infusion of autologous peripheral-blood hematopoietic stem cells; the other 11 patients received a single course of this treatment. In 110 patients, cytoreduction with one or two courses of vinblastine plus ifosfamide plus cisplatin preceded the high-dose chemotherapy.

RESULTS

Of the 184 patients, 116 had complete remission of disease without relapse during a median follow-up of 48 months (range, 14 to 118). Of the 135 patients who received the treatment as second-line therapy, 94 were disease-free during follow-up; 22 of 49 patients who received treatment as third-line or later therapy were disease-free. Of 40 patients with cancer that was refractory to standard-dose platinum, 18 were disease-free. A total of 98 of 144 patients who had platinum-sensitive disease were disease-free, and 26 of 35 patients with seminoma and 90 of 149 patients with nonseminomatous germ-cell tumors were disease-free. Among the 184 patients, there were three drug-related deaths during therapy. Acute leukemia developed in three additional patients after therapy.

CONCLUSIONS

Testicular tumors are potentially curable by means of high-dose chemotherapy plus hematopoietic stem-cell rescue, even when this regimen is used as third-line or later therapy or in patients with platinum-refractory disease.

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N Engl J Med 2007;357:340-8.

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ORIGINAL ARTICLE

Vaccine for Prevention of Mild and Moderate-to-Severe Influenza in Children

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ABSTRACT

BACKGROUND

Commonly used trivalent vaccines contain one influenza B virus lineage and may be ineffective against viruses of the other B lineage. We evaluated the efficacy of a candidate inactivated quadrivalent influenza vaccine (QIV) containing both B lineages.

METHODS

In this multinational, phase 3, observer-blinded study, we randomly assigned children 3 to 8 years of age, in a 1:1 ratio, to receive the QIV or a hepatitis A vaccine (control). The primary end point was influenza A or B confirmed by real-time polymerase chain reaction (rt-PCR). Secondary end points were rt-PCR–confirmed, moderate-to-severe influenza and rt-PCR–positive, culture-confirmed influenza. The vaccine efficacy and the effect of vaccination on daily activities and utilization of health care resources were assessed in the total vaccinated cohort (2584 children in each group) and the per-protocol cohort (2379 children in the QIV group and 2398 in the control group).

RESULTS

In the total vaccinated cohort, 62 children in the QIV group (2.40%) and 148 in the control group (5.73%) had rt-PCR–confirmed influenza, representing a QIV efficacy of 59.3% (95% confidence interval [CI], 45.2 to 69.7), with efficacy against culture-confirmed influenza of 59.1% (97.5% CI, 41.2 to 71.5). For moderate-to-severe rt-PCR–confirmed influenza, the attack rate was 0.62% (16 cases) in the QIV group and 2.36% (61 cases) in the control group, representing a QIV efficacy of 74.2% (97.5% CI, 51.5 to 86.2). In the per-protocol cohort, the QIV efficacy was 55.4% (95% CI, 39.1 to 67.3), and the efficacy against culture-confirmed influenza 55.9% (97.5% CI, 35.4 to 69.9); the efficacy among children with moderate-to-severe influenza was 73.1% (97.5% CI, 47.1 to 86.3). The QIV was associated with reduced risks of a body temperature above 39°C and lower respiratory tract illness, as compared with the control vaccine, in the per-protocol cohort (relative risk, 0.29 [95% CI, 0.16 to 0.56] and 0.20 [95% CI, 0.04 to 0.92], respectively). The QIV was immunogenic against all four strains. Serious adverse events occurred in 36 children in the QIV group (1.4%) and in 24 children in the control group (0.9%).

CONCLUSIONS

The QIV was efficacious in preventing influenza in children. (Funded by GlaxoSmithKline Biologicals; ClinicalTrials.gov number, NCT01218308.)

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This article was published on December 11, 2013, at NEJM.org.

DOI: 10.1056/NEJMoa1215817

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CASE REPORT

- *E' la forma di comunicazione più vecchia e basilare in medicina*
- *Il report deve descrivere dettagliatamente cosa è accaduto al paziente secondo un ordine cronologico e quale trattamento particolare è stato scelto*
- *Lo scopo è quello di aiutare il lettore a riconoscere e trattare un problema simile*

CASE REPORT

- Titolo
- Autori
- Introduzione breve
- Descrizione del caso (fotografie o altre illustrazioni)
- Discussione
- Bibliografia
- Ringraziamenti
- La riservatezza nei confronti del paziente deve essere assoluta

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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Case 38-2013: A 30-Year-Old Man with Fever and Lymphadenopathy

Alaka Ray, M.D., Victorine V. Muse, M.D., and Daniel F. Boyer, M.D., Ph.D.

PRESENTATION OF CASE

Dr. Jennifer M. Rosenbluth (Medicine): A 30-year-old man was seen in an outpatient clinic at this hospital because of fever and lymphadenopathy.

The patient had been well until approximately 2 weeks before presentation, when an enlarging, tender lump developed at the posterior base of the neck on the right side. Two days before presentation, fever to a temperature of 39.4°C, a mild headache, myalgias, chills, and fatigue developed. He took ibuprofen, but his condition did not improve, and he came to this hospital for evaluation.

The patient reported no history of sore throat, coryza, or earache. He had had a low hemoglobin level in the past but was otherwise healthy. He reportedly had had a negative tuberculin skin test in the past, and he had not received an influenza vaccine during the previous year. He took no other medications and had no known allergies. He was born in India and came to the United States 4 years previously to attend school; his most recent visit to India was 6 months before presentation. He worked in an office and lived with a roommate. He was not sexually active and had no known exposures to sick contacts, animals, or blood products. He had stopped smoking 2 years before this presentation, drank alcohol occasionally, and did not use illicit drugs. His parents had diabetes mellitus; there was no family history of autoimmune or connective-tissue diseases.

On examination, the temperature was 38.9°C, the blood pressure 129/80 mm Hg, and the pulse 104 beats per minute. A group of five tender lymph nodes, each approximately 1 cm in diameter, was present in the posteroinferior cervical chain on the right side; the lymph nodes in the posterior cervical chain on the left side and in both inguinal regions were nontender, and there were no abnormal lymph nodes in the supraclavicular or axillary regions. A systolic ejection murmur (grade 1 out of 6) was heard at the cardiac base; the remainder of the examination was normal. During evaluation, the temperature rose to 39.5°C and was associated with chills. Blood levels of glucose, total protein, albumin, and globulin were normal, as were results of tests of liver and renal function; testing for heterophile antibodies and rapid tests for streptococcal pharyngitis and influenza virus were negative. Additional test results are shown in Table 1. A blood culture was sterile. The administration of acetaminophen alternating with ibuprofen was recommended, as were fluids

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N Engl J Med 2013;369:2333-43.
DOI: 10.1056/NEJMcpc1310002

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Folgori et al. Italian Journal of Pediatrics 2010, 36:29
http://www.ijponline.net/content/36/1/29

ITALIAN JOURNAL OF PEDIATRICS

CASE REPORT Open Access

Cutaneous granulomatosis and combined immunodeficiency revealing Ataxia-Telangiectasia: a case report

Laura Folgori[1*], Alessia Scarselli[1], Giulia Angelino[1], Francesca Ferrari[2], Antonio Antoccia[3], Luciana Chessa[2], Andrea Finocchi[1]

Abstract

Ataxia-telangiectasia (A-T) is a complex multisystem disorder characterized by progressive neurological impairment, variable immunodeficiency and oculo-cutaneous telangiectasia. A-T is a member of chromosomal breakage syndromes and it is caused by a mutation in the *ataxia-telangiectasia mutated* (*ATM*) gene. Because of a wide clinical heterogeneity, A-T is often difficult to diagnose in children.

We report an unusual case of a 3-year-old boy affected by A-T who presented exclusively with extensive cutaneous granulomatosis and severe combined immunodeficiency, without neurological abnormalities, at the time of diagnosis. This case clearly emphasizes the variable presentation of A-T syndrome and highlights the difficulties in the early diagnosis of A-T.

A-T should be considered in children with evidence of combined humoral and cellular immunodeficiency associated with unexplained skin granulomatous lesions, even in the absence of the classic features of this syndrome.

Introduction

Ataxia-telangiectasia (A-T) is an autosomal recessive genomic instability syndrome characterized by progressive cerebellar ataxia, oculo-cutaneous telangiectasia, increased radiosensibility, predisposition to lymphoid malignancies and a variable degree of immunodeficiency. The prevalence is estimated to be between 1:100.000 [1] and 1:40.000 [2]. Both males and females are equally affected.

A-T results from mutations of a single gene, *ATM* (*ataxia-telangiectasia mutated*), located on chromosome 11q22-23 [3,4], encoding a large basic protein involved in cell cycle control and DNA damaging repair.

The diagnosis of A-T is based primarily on clinical findings. Determination of serum alpha-fetoprotein (αFP) is an important diagnostic marker as raised αFP level is found in more than 90% of A-T patients. Confirmatory tests for A-T include colony radiosensitivity assay and identification of the ATM protein by immunoblotting [2,5,6].

We report the case of a 3-year-old boy affected by A-T who presented exclusively with extensive cutaneous granulomatousis and severe combined immunodeficiency, without neurological abnormalities.

Case Report

A 3-year-old boy was referred to our Department of Pediatrics with a history of cutaneous lesions, recurrent otitis, repeated episodes of fever of unknown origin and suspected immunodeficiency. He was born full term as the second child of healthy non consanguineous parents.

At the age of 2, the child had chickenpox without complications except for a residual erythematous, scaly dermatitis characterized by small, red and indured lesions on face, arms and legs [Fig. 1]. In the suspect of hypersensitivity to insect bites, he was treated with topical treatment (steroids and tacrolimus) and oral antihistamines without improvements.

Our first clinical examination revealed a failure to thrive below the third percentile for height and below the tenth for weight. Chest x-ray showed a lobar pneumonia. Neurological development was normal. Complete blood count (CBC) revealed lymphopenia (range 840-920/ml). Quantitative Polymerase Chain Reaction (PCR) for EBV showed a massive proliferation (1.600.000

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL): A patient from Sri Lanka

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ARTICLE INFO

Article history:
Received 2 September 2008
Accepted 16 January 2009

Keywords:
CADASIL
NOTCH 3
C260G
Indian subcontinent
Sri Lanka

ABSTRACT

We report the first patient from Sri Lanka (the third patient from the Indian subcontinent) with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The patient experienced a young onset familial stroke with an 856T>G missense mutation in exon 5 of the *NOTCH3* gene resulting in a C260G mutation in the sixth epidermal growth factor-like repeat. We believe this is the first reported Sri Lankan patient. CADASIL is probably underdiagnosed in the region.

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1. Introduction

Ischemic stroke in young adults (aged 15–45 years) is proportionately more common in Sri Lanka (34%) and India (19–32%) than in Western countries (3–5%), and the etiology of most strokes in young adults in Sri Lanka is unexplained.[1] Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most commonly known classic Mendelian form of stroke. The responsible gene is *NOTCH3*, which has been mapped to chromosome 19q12.[2] We report a CADASIL patient with young onset familial stroke with a confirmed C260G mutation of *NOTCH3*. To our knowledge this is the first reported Sri Lankan patient.

2. Case report

A 45-year-old male presented with a 2-year history of difficulty in walking and progressive memory impairment. His father and four older sisters also suffered similar symptoms and recurrent strokes. His eldest and the youngest sister had normal cognitive function with no previous stroke episodes.

There was no family history of diabetes, hypertension or hypercholesterolaemia. A neurological examination revealed pseudobulbar palsy, asymmetrical spastic tetraplegia and dementia (Mini-Mental State Examination: 9/30). He was diagnosed as having mild hypertension with type 2 diabetes mellitus. MRI showed diffuse leukoencephalopathy in the periventricular, deep hemispheric, centrum semiovale, temporopolar and external and internal capsular areas. Similar signal abnormality also involved the corpus callosum. Multifocal infarctions of varying sizes and shapes were also seen within the abnormal areas as well as in the left side of the pons (Fig. 1).

2.1. Mutation analysis

Genomic DNA was extracted from peripheral blood lymphocytes using a DNA extraction kit (Qiagen; Germantown, MD, USA) after obtaining ethical clearance from the Faculty of Medical Sciences, University of Sri Jayawardenepura, and informed consent. Each exon of the *NOTCH3* gene was directly sequenced using an ABI Prism 377 DNA sequencer (Applied Biosystems; Foster City, CA, USA). Mutations were confirmed by polymerase chain reaction (PCR), followed by restriction fragment length polymorphism (RFLP) assay and were compared with 50 healthy patient controls from Sri Lanka.

The patient possessed an 856T>G missense mutation in exon 5 of the *NOTCH3* gene, which resulted in an amino acid change from cysteine to glycine at codon 260. Because this mutation yields a new Eae1 (Cfr1) recognition site, it could be confirmed by RFLP. This mutation was not seen on PCR-RFLP analysis in 50 control patients in Sri Lanka (data not shown).

3. Discussion

Over 500 CADASIL families have been identified worldwide. Three patients, two from India[3,4] and our patient from Sri Lanka, have been reported from the Indian subcontinent, which is home to 20% of the world's population. Many patients with CADASIL in Sri Lanka possibly go undiagnosed due to the inaccessibility of MRI facilities; this is particularly so for the rural population. This could also be true for other developing countries on the Indian subcontinent in which confirmation diagnostic testing for CADASIL is unavailable.

Over 130 different mutations in the *NOTCH3* gene have been described in patients with CADASIL and around 70% of the mutations cluster in exons 3 and 4.[5] Of the three patients with CADASIL reported from the Indian subcontinent, the Indian study[4] reported a heterozygous mutation in exon 4 resulting in an R141C mutation in the third epidermal growth factor (EGF)-like repeat which has been reported worldwide. In our patient, the mutation was in exon 5, resulting in a C260G mutation in the sixth EGF-like repeat. A C260Y mutation has been reported in a German family;[6] however, C260G is the first report of this mutation in a patient with CADASIL.

Most of the mutations in CADASIL have been linked to an odd number of cysteine residues within the EGF-like repeats. Joutel et al. speculated that replacement of the highly conserved cysteine residues with another amino acid in the EGF-like repeats would

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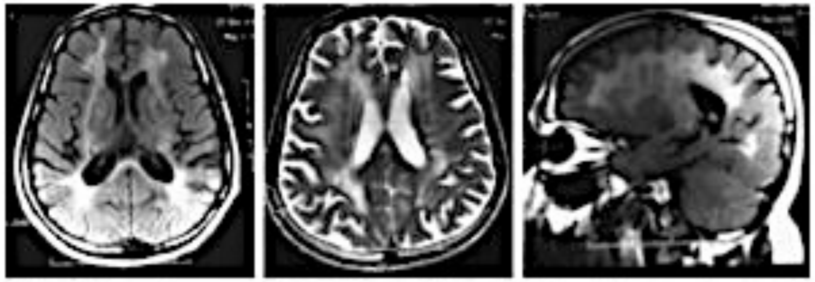

Fig. 1. (left) Axial fluid attenuated inversion recovery (FLAIR) MRI, (right) sagittal FLAIR MRI, (middle) axial T2-weighted MRI showing leukoencephalopathy in the periventricular, deep hemispheric, centrum semiovale, temporopolar and external and internal capsular areas. Similar signal abnormality also involved the corpus callosum. Multifocal infarctions of varying sizes and shapes were also seen within the abnormal areas as well as in the left side of the pons.

change the conformation of EGF-like repeats due to altered covalent bonding between cysteine residues.[5] Any amino acid replacing cysteine residues could cause CADASIL in codon 183 (C183R, C183S, C183F)[6] or codon 440 (C440R, C440G, C440S).[6,7] These mutations support that the C260G mutation could be a causative mutation in CADASIL. In addition, the two different mutations in the Indian subcontinent patients suggested no founder effect for CADASIL in this area.

4. Conclusion

CADASIL is probably underdiagnosed. We recommend that genetic testing for DNA mutation of *NOTCH 3* should be considered for patients presenting with stroke of young onset, cognitive impairment and a positive family history of stroke in Sri Lanka.

doi:10.1016/j.jocn.2008.01.009

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REVIEW ARTICLE

o

REVISIONE

- *Gli articoli di revisione sono quelli maggiormente letti*
- *Permettono di aggiornarsi rapidamente sull'argomento*
- *Il revisore è un esperto del campo*

REVISIONE

Riassume in forma esaustiva le evidenze su un determinato argomento su dati della letteratura e delle conoscenze dell'autore.

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Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management

*Katharine Bushby, Richard Finkel, David J Birnkrant, Laura E Case, Paula R Clemens, Linda Cripe, Ajay Kaul, Kathi Kinnett, Craig McDonald, Shree Pandya, James Poysky, Frederic Shapiro, Jean Tomezsko, Carolyn Constantin, for the DMD Care Considerations Working Group**

Duchenne muscular dystrophy (DMD) is a severe, progressive disease that affects 1 in 3600–6000 live male births. Although guidelines are available for various aspects of DMD, comprehensive clinical care recommendations do not exist. The US Centers for Disease Control and Prevention selected 84 clinicians to develop care recommendations using the RAND Corporation–University of California Los Angeles Appropriateness Method. The DMD Care Considerations Working Group evaluated assessments and interventions used in the management of diagnostics, gastroenterology and nutrition, rehabilitation, and neuromuscular, psychosocial, cardiovascular, respiratory, orthopaedic, and surgical aspects of DMD. These recommendations, presented in two parts, are intended for the wide range of practitioners who care for individuals with DMD. They provide a framework for recognising the multisystem primary manifestations and secondary complications of DMD and for providing coordinated multidisciplinary care. In part 1 of this Review, we describe the methods used to generate the recommendations, and the overall perspective on care, pharmacological treatment, and psychosocial management.

Lancet Neurol 2010; 9: 77–93

Published Online November 30, 2009 DOI:10.1016/S1474-4422(09)70271-6

See In Context page 37

See Online/Review DOI:10.1016/S1474-4422(09)70272-8

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Introduction

Duchenne muscular dystrophy (DMD; Online Mendelian Inheritance in Man [OMIM] reference 310200) is an X-linked disease that affects 1 in 3600–6000 live male births.[1–3] Affected individuals can have mildly delayed motor milestones and most are unable to run and jump properly due to proximal muscle weakness, which also results in the use of the classic Gowers' manoeuvre when arising from the floor. Most patients are diagnosed at approximately 5 years of age, when their physical ability diverges markedly from that of their peers.[4] Untreated, muscle strength deteriorates, and boys require the use of a wheelchair before their teens. Respiratory, orthopaedic, and cardiac complications emerge, and without intervention, the mean age at death is around 19 years. Non-progressive cognitive dysfunction might also be present.[5]

or even exclusively affect cognitive and/or cardiac function.[13–15] Although the disorder in affected girls is usually much milder than in boys, a few cases do have disease severity similar to that seen in affected boys.[13–15] Apart from a few cases associated with chromosomal rearrangements, most girls are assumed to be affected as a result of skewed X inactivation.

The molecular basis of DMD has been known for over 20 years.[16,17] Many promising therapeutic strategies have since been developed in animal models.[18] Human trials of these strategies have started, leading to the hope of definitive treatments for this currently incurable disease.[18] Although specific treatments for DMD have not yet reached the clinic, the natural history of the disease can be changed by the targeting of interventions to known manifestations and complications. Diagnosis can be swiftly reached; the family and child can be well

REVIEW ARTICLE

CURRENT CONCEPTS

Nanomedicine

Betty Y.S. Kim, M.D., Ph.D., James T. Rutka, M.D., Ph.D., and Warren C.W. Chan, Ph.D.

From the Institute of Biomaterials and Biomedical Engineering (B.Y.S.K., W.C.W.C.), Terrence Donnelly Centre for Cellular and Biomolecular Research (B.Y.S.K., W.C.W.C.), the Department of Materials Science and Engineering (W.C.W.C.), and the Department of Chemical Engineering (W.C.W.C.), University of Toronto (B.Y.S.K., J.T.R., W.C.W.C.); and the Division of Neurosurgery (B.Y.S.K., J.T.R.) and the Arthur and Sonia Labatt Brain Tumour Research Centre (J.T.R.), Hospital for Sick Children (B.Y.S.K., J.T.R.) — both in Toronto. Address reprint requests to Dr. Chan at the Institute of Biomaterials and Biomedical Engineering, Donnelly Centre for Cellular and Biomolecular Research, 164 College St., 407, University of Toronto, Toronto, ON M5S 3G9, Canada, or at warren.chan@utoronto.ca.

N Engl J Med 2010;363:2434-43.
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MANY DISEASES ORIGINATE FROM ALTERATIONS IN BIOLOGIC PROCESSES at the molecular or nanoscale level. Mutated genes, misfolded proteins, and infections caused by viruses or bacteria can lead to cell malfunction or miscommunication, sometimes leading to life-threatening diseases. These molecules and infectious agents are nanometers in size and may be located in biologic systems that are protected by nanometer-size barriers, such as nuclear pores 9 nm in diameter. Their chemical properties, size, and shape appear to dictate the transport of molecules to specific biologic compartments and the interactions between molecules.

Nanotechnology is defined as the "intentional design, characterization, production, and applications of materials, structures, devices, and systems by controlling their size and shape in the nanoscale range (1 to 100 nm)."[1] Because nanomaterials are similar in scale to biologic molecules and systems yet can be engineered to have various functions, nanotechnology is potentially useful for medical applications. The field of nanomedicine aims to use the properties and physical characteristics of nanomaterials for the diagnosis and treatment of diseases at the molecular level.

Nanomaterials are now being designed to aid the transport of diagnostic or therapeutic agents through biologic barriers; to gain access to molecules; to mediate molecular interactions; and to detect molecular changes in a sensitive, high-throughput manner. In contrast to atoms and macroscopic materials, nanomaterials have a high ratio of surface area to volume as well as tunable optical, electronic, magnetic, and biologic properties, and they can be engineered to have different sizes, shapes, chemical compositions, surface chemical characteristics, and hollow or solid structures.[2,3] These properties are being incorporated into new generations of drug-delivery vehicles, contrast agents, and diagnostic devices, some of which are currently undergoing clinical investigation or have been approved by the Food and Drug Administration (FDA) for use in humans. Examples of the nanomaterials most commonly used in medicine are provided in Figure 1 and Table 1. This overview describes the properties of nanomaterials, their principal medical applications, and the future possibilities for this emerging field.

PROPERTIES OF NANOMATERIALS

Over the past three decades, physical scientists have developed strategies to reproducibly synthesize nanomaterials and to characterize their unique, size-dependent properties.[2,3] An understanding of these fundamental physical and chemical properties is necessary for the optimal use of nanomaterials in medical applications.

Nanomaterials generally consist of metal atoms, nonmetal atoms, or a mixture of metal and nonmetal atoms, commonly referred to as metallic, organic, or semiconducting particles, respectively. The surface of nanomaterials is usually coated with polymers or biorecognition molecules for improved biocompatibility and selective

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Articolo di Metanalisi

I risultati di più studi clinici vengono combinati e analizzati con appropriate procedure statistiche

Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials

Kausik K Ray, Sreenivasa Rao Kondapally Seshasai, Shanelle Wijesuriya*, Rupa Sivakumaran*, Sarah Nethercott*, David Preiss, Sebhat Erqou, Naveed Sattar*

Summary

Background Whether intensive control of glucose reduces macrovascular events and all-cause mortality in individuals with type 2 diabetes mellitus is unclear. We undertook a meta-analysis of randomised controlled trials to determine whether intensive treatment is beneficial.

Methods We selected five prospective randomised controlled trials of 33 040 participants to assess the effect of an intensive glucose-lowering regimen on death and cardiovascular outcomes compared with a standard regimen. We gathered information about events of non-fatal myocardial infarction, coronary heart disease (fatal and non-fatal myocardial infarction), stroke, and all-cause mortality, and did a random-effects meta-analysis to obtain summary effect estimates for the clinical outcomes with use of odds ratios calculated from the raw data of every trial. Statistical heterogeneity across trials was assessed with the χ^2 and I^2 statistics.

Findings The five trials provided information on 1497 events of non-fatal myocardial infarction, 2318 of coronary heart disease, 1127 of stroke, and 2892 of all-cause mortality during about 163 000 person-years of follow-up. The mean haemoglobin A_{1c} concentration (HbA_{1c}) was 0·9% lower for participants given intensive treatment than for those given standard treatment. Intensive glycaemic control resulted in a 17% reduction in events of non-fatal myocardial infarction (odds ratio 0·83, 95% CI 0·75–0·93), and a 15% reduction in events of coronary heart disease (0·85, 0·77–0·93). Intensive glycaemic control had no significant effect on events of stroke (0·93, 0·81–1·06) or all-cause mortality (1·02, 0·87–1·19).

Interpretation Overall, intensive compared with standard glycaemic control significantly reduces coronary events without an increased risk of death. However, the optimum mechanism, speed, and extent of HbA_{1c} reduction might be different in differing populations.

Funding None.

Lancet 2009; 373: 1765–72

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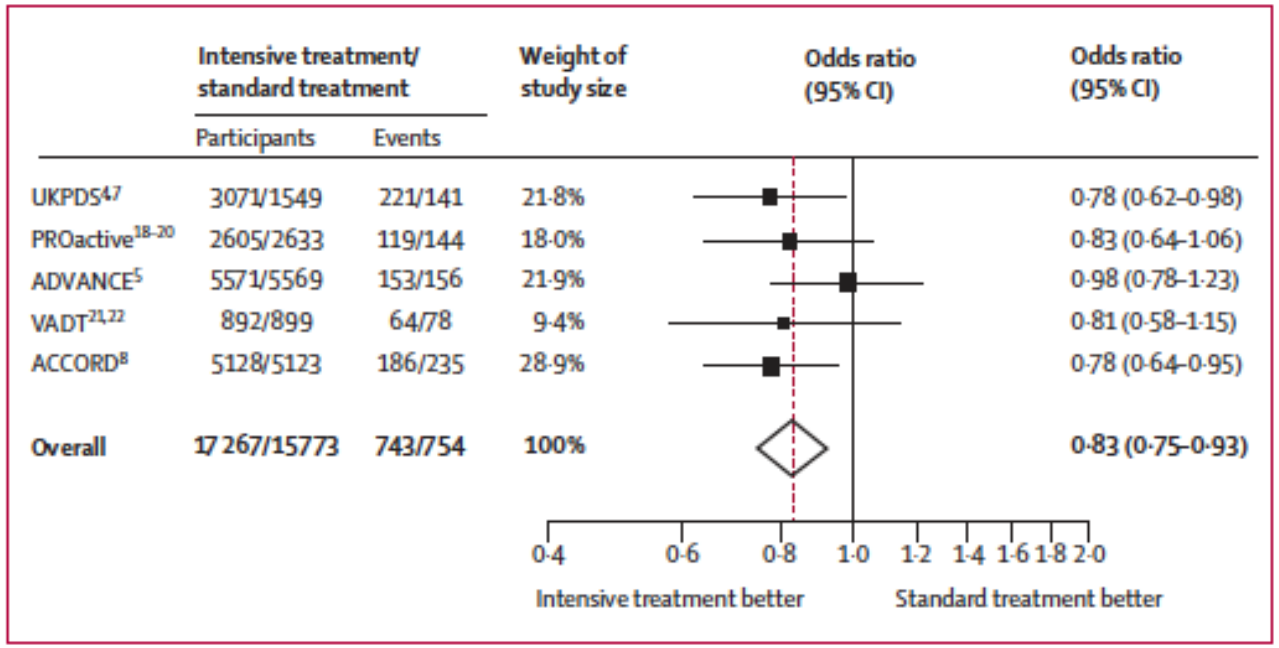

Figure 1: **Probability of events of non-fatal myocardial infarction with intensive glucose-lowering versus standard treatment**

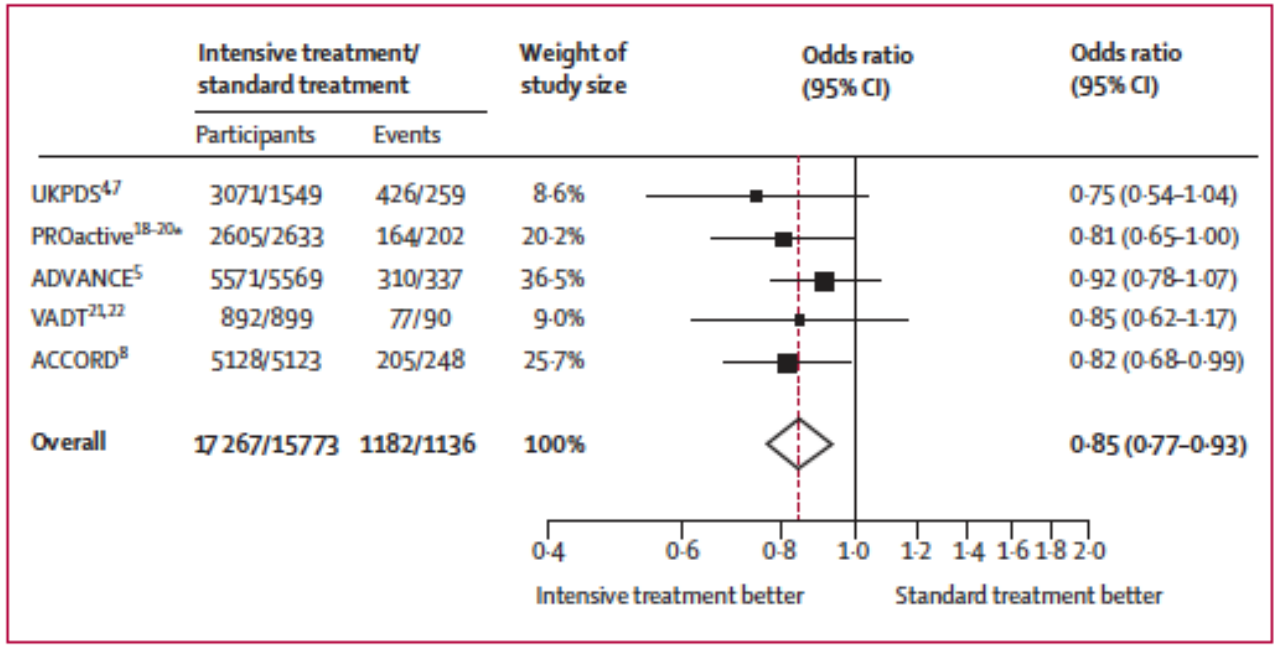

Figure 2: **Probability of events of coronary heart disease with intensive glucose-lowering versus standard treatment**

*Included non-fatal myocardial infarction and death from all-cardiac mortality

Lettera

Commentare o partecipare al dibattito scientifico su un articolo pubblicato o su un tema di attualità.

Lunghezza e bibliografia limitate.

British Journal of Cancer (2012) 106, 240
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www.bjcancer.com

Letter to the Editor

Aspirin as adjuvant therapy in childhood cancer?

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British Journal of Cancer (2012) **106,** 240. doi:10.1038/bjc.2011.467 www.bjcancer.com
Published online 10 November 2011
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Sir,

The mini review on aspirin and cancer questions whether the medicine has been overlooked as an adjuvant therapy (Langley *et al*, 2011). Although the focus of the mini review was on adult cancer, perhaps aspirin might also be helpful in childhood cancer. There is evidence that childhood cancer survivors have increased risks of both cancer and cardiovascular disease when compared with the general population (Mulrooney *et al*, 2009; Reulen *et al*, 2011). Given the evidence supporting aspirin reducing the risk of both cancer and cardiovascular disease (Rose *et al*, 2011), potentially the medicine could be helpful in the proactive health care of survivors. Such potential does need to take into account the undesirable effects of aspirin.

Aspirin is not recommended for children, hence compared with adults, it is more difficult to make a case for aspirin as adjuvant therapy in childhood cancer. This does not mean it should not be considered at all, and perhaps the ethical aspects of low doses of aspirin as adjuvant therapy in childhood cancer need further exploration. In the meantime, perhaps a readily available alternative might be also considered. Salicylate is the putative active component of aspirin against cancer cells through several mechanisms and it might be ingested through diet. Perhaps a diet rich in salicylate, such as fruits and vegetables, could be considered as adjuvant therapy. This might also help promote the general health and wellbeing of children with cancer.

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Editoriale

Commento redatto dall'editor di una rivista su un tema rilevante in un ambito specifico

MICROBIOME

Shaping the gut microbiome

Human genetic variation influences the abundances of specific members of the gut microbiota, suggests a new study published in *Cell*.

High-throughput sequencing analyses have previously revealed substantial inter-individual microbiome variation at the same anatomical sites, although related individuals seem to have more similar microbiotas. Until now, this observation had been attributed to environmental factors such as diet, lifestyle and exposures.

To discern whether any members of the gut microbiota are heritable, the researchers compared microbiotas across >1,000 faecal samples obtained from 977 individuals, including 171 monozygotic (that is, identical) and 245 dizygotic (that is, fraternal) twin pairs. Indeed, Ley and colleagues found that certain components of the microbiota were more similar between twin pairs than between unrelated individuals. Importantly, monozygotic twins had more highly correlated microbiotas than dizogytic twins, suggesting that some members of the microbiota are heritable.

Heritability of microbiota was estimated using the twin-based ACE model, which partitions the total variance into genetic effects (A), common environment (C), and unique environment (E). The investigators identified a number of microbial species that were heritable, including the most highly heritable taxon Christensenellaceae, a family within the bacterial phylum Firmicutes. This family, and the heritable microorganisms that co-occur with it — including the archaeal family Methanobacteriaceae, the bacterial family Dehalobacteriaceae and several unclassified species within the Firmicutes and Tenericutes phyla — were enriched in lean versus obese individuals. Notably, transplantation of human faecal samples containing *Christensenella minuta* into germ-free mice induced a leaner phenotype than transplants lacking this species or those containing a heat-killed version of it.

Taken together, these findings lend support to the notion of a host genetic effect on the microbiome that can affect health. The next step will be to identify the genes that drive the heritability of different microbial taxa and to elucidate the mechanisms by which Christensenellaceae impacts host phenotype.

Linda Koch, Chief Editor,
Nature Reviews Genetics

This article is modified from the original in *Nature Rev. Genet.* (http://dx.doi.org/10.1038/nrg3869).

ORIGINAL RESEARCH PAPER Goodrich, J. K. *et al.*, Human genetics shape the gut microbiome. *Cell* **159**, 789–799 (2014)