Novità in Ematologia ed Oncologia Pediatrica

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Vittoria 26/03/2011

Novità su molti fronti

- **Diagnosi**
- **Terapia**
- **Terapia di supporto**
- **Prognosi**

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Novità nella diagnosi

- Citofluorimetria
- Immunoistochimica
- Biologia molecolare
- TC – RM – PET

Vittoria 26/03/2011

Novità nella diagnosi

- **Citofluorimetria**
- Biologia molecolare
- TC – RM – PET

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Giovanni: 2 anni

- Pancitopenia grave (leucociti 500/mmc)
- Lieve splenomegalia
- Iperpiressia
- Sospetto: leucemia acuta

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Giovanni: 2 anni

Sangue periferico

- Striscio non valutabile

Midollo

- Striscio non valutabile per ipocellularità
- Citofluorimetro: 65% di elementi CD10+CD19+

Diagnosi: leucemia linfoblastica acuta Common

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Novità nella diagnosi

- Citofluorimetria
- **Biologia molecolare**
- TC – RM -PET

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Francesca: 5 anni

- Neoformazione mandibolare
- Istologia su biopsia: Sarcoma di Ewing/PNET
- Biologia molecolare: negativa per i trascritti del sarcoma di Ewing: t(11;22) e t(21;22)
- Revisione istologica: **Prognoma melanotico**

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Ancora biologia molecolare

- **Leucemia linfoblastica acuta**
  - **t(9;22) con trascritto BCR/ABL detto anche cromosoma Philadelphia**
    - **Trattamento specifico con IMATINIB**
    - **Prognosi nettamente migliorata**

Novità nella terapia

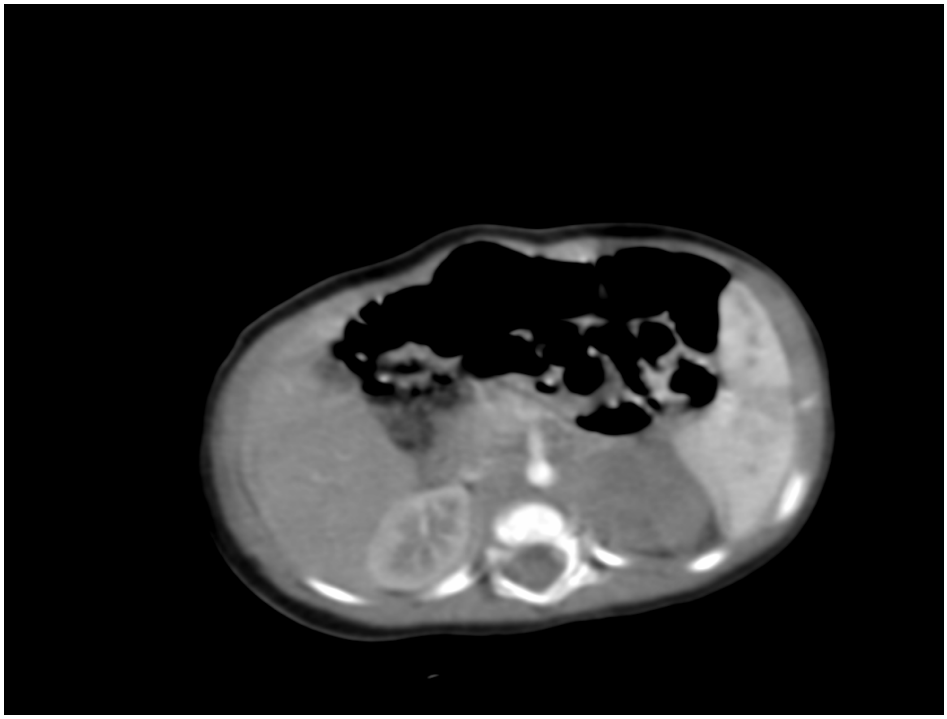
- Uso più corretto dei chemioterapici e conoscenza degli effetti collaterali
- Chemioterapia ad alte dosi
- Trapianto di cellule staminali emopoietiche
- Farmaci intelligenti
- Farmaci biologici
- Farmaci antiangiogenetici

Novità nella terapia

- **Uso più corretto dei chemioterapici e conoscenza degli effetti collaterali**
- Chemioterapia ad alte dosi
- Trapianto di cellule staminali emopoietiche
- Farmaci intelligenti
- Farmaci biologici
- Antiangiogenetici

Giulia: 5 mesi

- Massa surrenalica prenatale
- Attenta osservazione clinico-strumentale
- Aumento volumetrico dopo i 3 mesi
- Non presenta metastasi
- Intervento chirurgico



Giulia: 5 mesi

- Istologia: Neuroblastoma a prognosi favorevole
- Oncogene *MYCN* non amplificato
- Assenti alterazioni cromosomiche segmentali (delezioni – amplificazioni)

No chemioterapia

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Novità nella terapia

- **Uso più corretto dei chemioterapici e conoscenza degli effetti collaterali**
- Chemioterapia ad alte dosi
- Trapianto di cellule staminali emopoietiche
- Farmaci intelligenti
- Farmaci biologici
- Antiangiogenetici

Vittoria 26/03/2011

Protocollo RMS 2005 per rabdomiosarcoma non metastatico:
stratificazione dei pazienti in gruppi di rischio

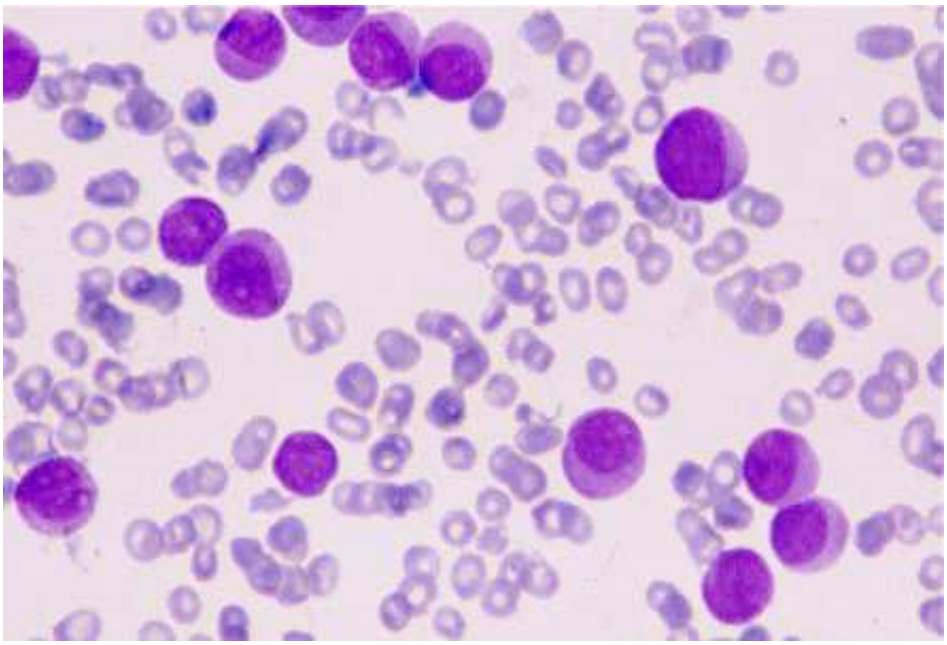
Risk Group	Subgroups	Pathology	Post surgical Stage (IRS Group)	Site	Node Stage	Size & Age
Low Risk	**A**	Favourable	I	Any	N0	Favourable
Standard Risk	***B***	Favourable	I	Any	N0	Unfavourable
	C	Favourable	II, III	Favourable	N0	Any
	D	Favourable	II, III	Unfavourable	N0	Favourable
High Risk	***E***	Favourable	II, III	Unfavourable	N0	Unfavourable
	F	Favourable	II, III	Any	N1	Any
	G	Unfavourable	I, II, III	Any	N0	Any
Very High Risk	***H***	Unfavourable	I, II, III	Any	N1	Any

Novità nella terapia

- Migliore conoscenza dei chemioterapici e dei loro effetti collaterali
- Chemioterapia ad alte dosi
- Trapianto di cellule staminali emopoietiche
- **Farmaci intelligenti**
- Farmaci biologici
- Antiangiogenetici

Nel 1992: Angela 14 anni

- Ricovero per gravi emorragie cutanee
- Hb 9 GB 3.500 PLT 5.000
- Diagnosi: Leucemia Acuta Mieloide M3 (promielocitica)
- Chemioterapia: Citarabina-Daunoblastina
- Dopo 36 ore: coma conseguente a CID
- **Rapido decesso nonostante terapia di supporto**



Dal 1994 numerosi altri bambini

- Stessa sintomatologia di Angela
- Stesso emocromo di Angela
- Stessa diagnosi di Angela

TRATTAMENTO DIVERSO
PROGNOSI BUONA

Acido transretinoico

Vittoria 26/03/2011

Acido transretinoico

- Nel promielocita neoplastico c'è la t(15;17) cui corrisponde il trascritto PML/RAR che blocca la differenziazione della cellula
- L'acido retinoico interagisce con PML/RAR
- È una "terapia differenziante" che riconverte la cellula neoplastica in cellula normale

Novità nella terapia

- Migliore conoscenza dei chemioterapici e dei loro effetti collaterali
- Chemioterapia ad alte dosi
- Trapianto di cellule staminali emopoietiche
- Farmaci intelligenti
- **Farmaci biologici**
- Antiangiogenetici

Giuseppe: 8 anni

- Massa addominale
- Tumore epatico che infiltra lo stomaco ed occupa buona parte dell'addome
- Biopsia epatica: epatocarcinoma

- Terapia: cisplatino-adriblastina + **sorafenib**

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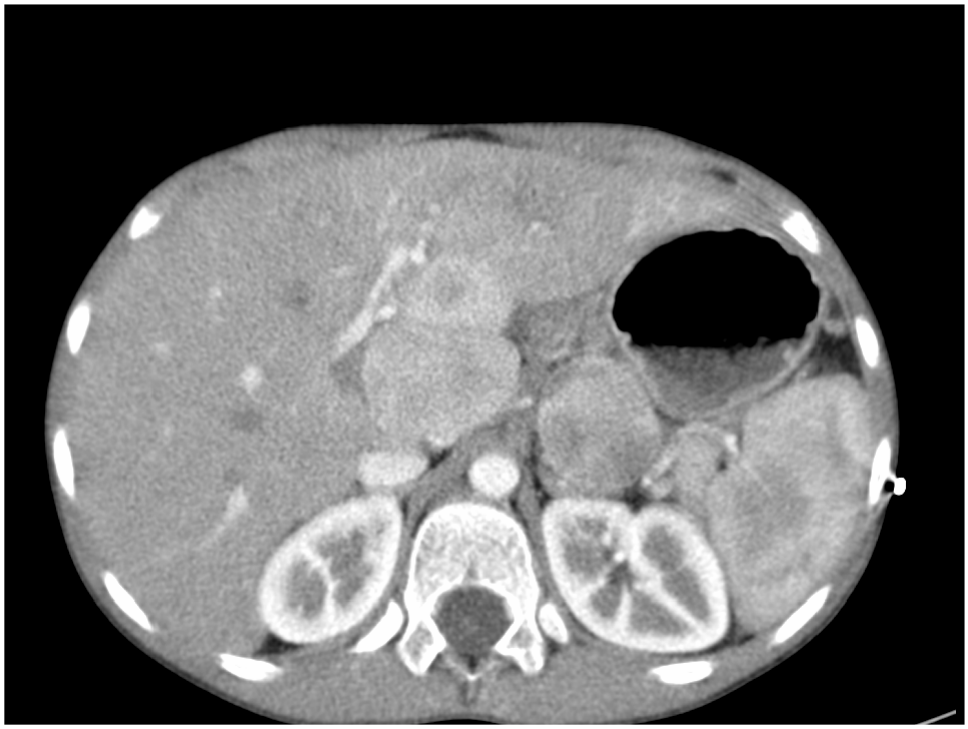

Sorafenib

- **Inibitore di alcune Tirosin-kinasi (VEGFR - PDGFR) attive in pathway moleculari della cancerogenesi**

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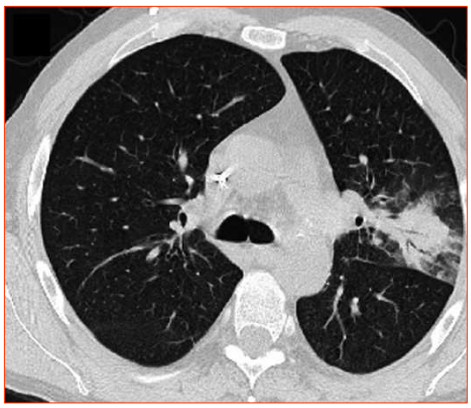
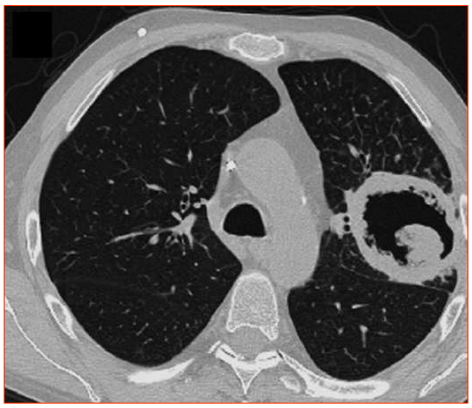
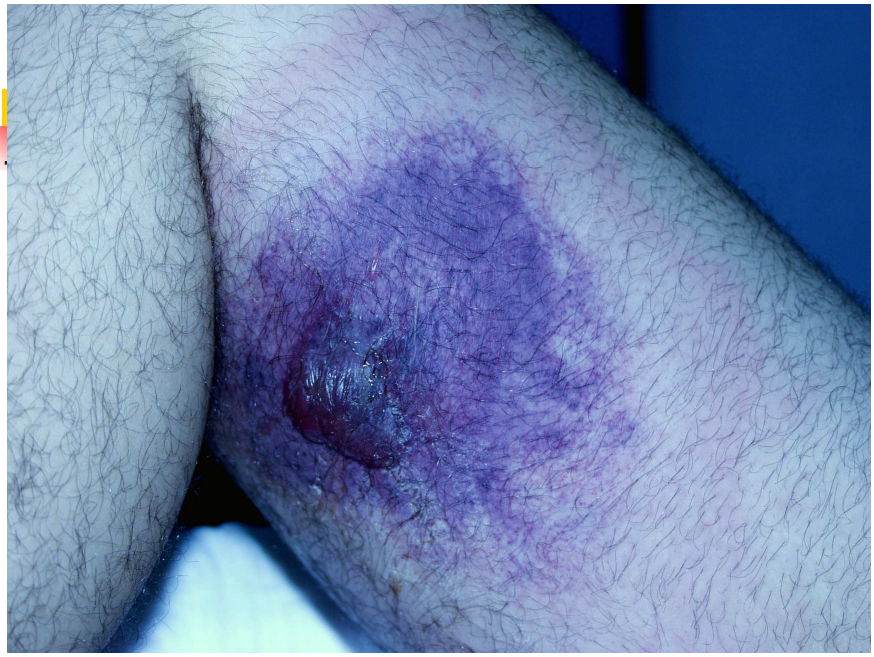
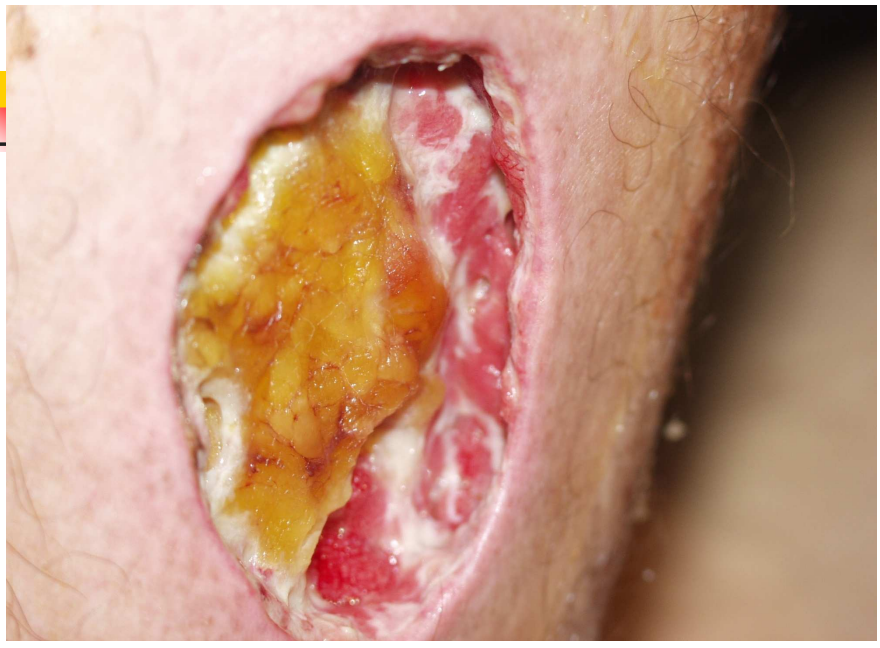
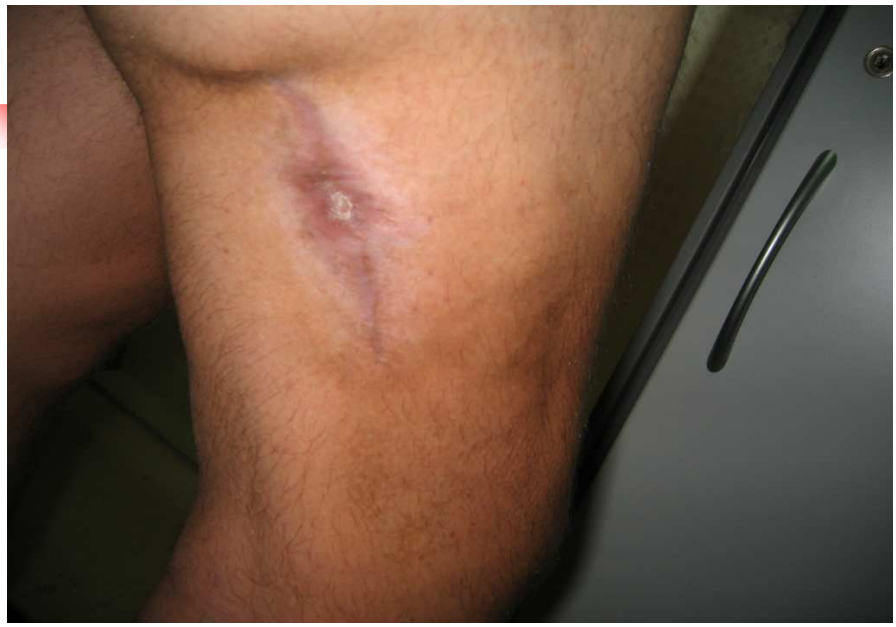
Novità nella terapia di supporto

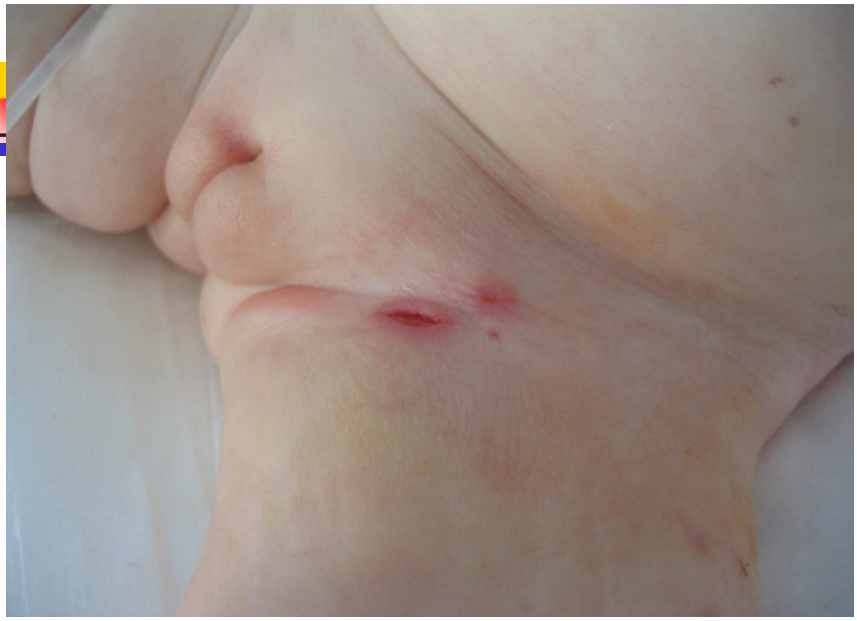


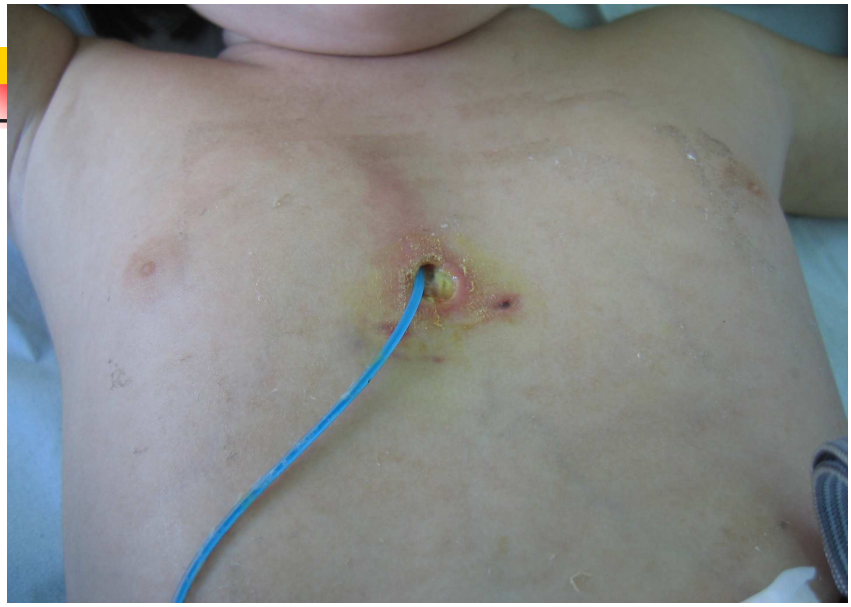












Terapia di supporto

- Accessi vascolari
- Terapia antinfettiva
- Nutrizione parenterale
- Terapia del dolore
- Psicologi
- Scuola
- Volontari

Vittoria 26/03/2011

Novità nella prognosi

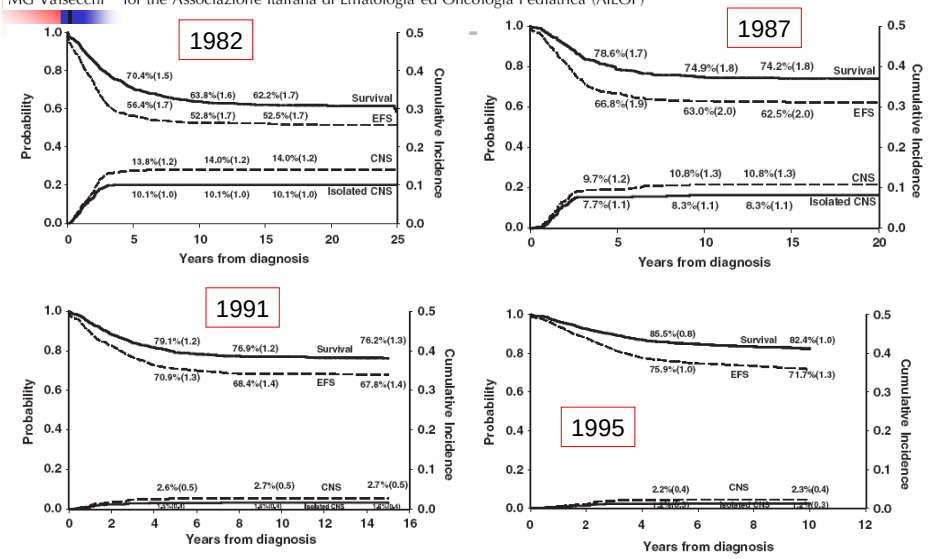
- Leucemia linfoblastica acuta
- Linfomi
- Tumore di Wilms
- Rabdomiosarcoma

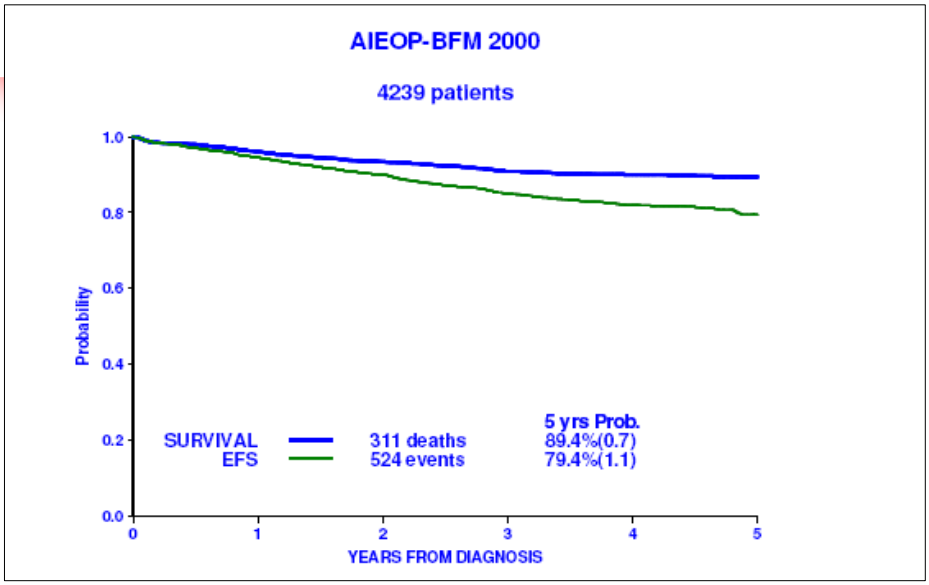
Vittoria 26/03/2011

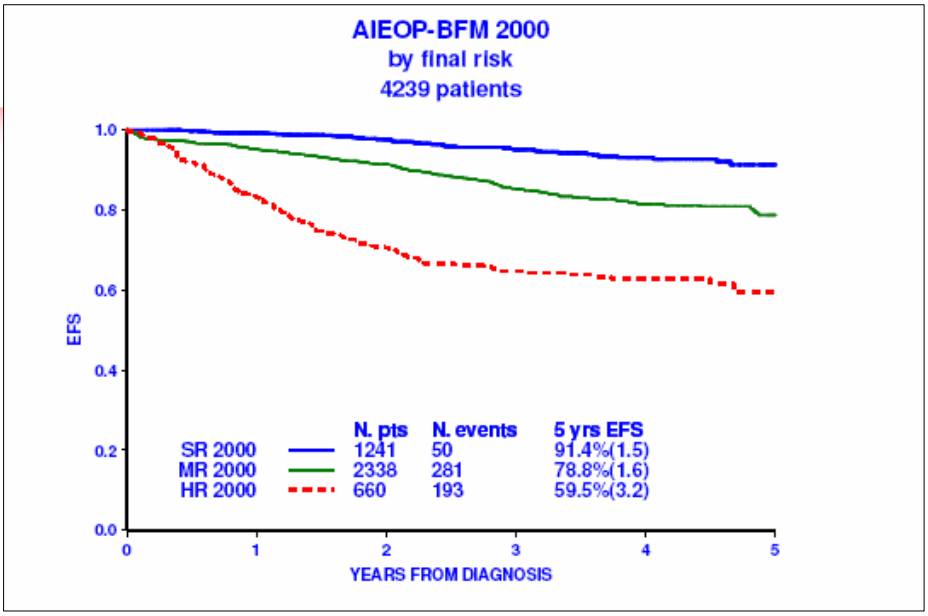
EDUCATIONAL REPORT

Long-term results of the Italian Association of Pediatric Hematology and Oncology (AIEOP) Studies 82, 87, 88, 91 and 95 for childhood acute lymphoblastic leukemia

V Conter[1,2], M Aricò[3], G Basso[4], A Biondi[1], E Barisone[5], C Messina[4], R Parasole[6], G De Rossi[7], F Locatelli[8], A Pession[9], N Santoro[10], C Micalizzi[11], M Citterio[1], C Rizzari[1], D Silvestri[1], R Rondelli[9], L Lo Nigro[12], O Ziino[13], AM Testi[14], G Masera[1], MG Valsecchi[15] for the Associazione Italiana di Ematologia ed Oncologia Pediatrica (AIEOP)




AIEOP-BFM 2000
4239 patients
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
YEARS FROM DIAGNOSIS
5 yrs Prob.
SURVIVAL
EFS
311 deaths
524 events
89.4%(0.7)
79.4%(1.1)


AIEOP-BFM 2000
by final risk
4239 patients
EFS
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
YEARS FROM DIAGNOSIS
N. pts
N. events
5 yrs EFS
SR 2000
MR 2000
HR 2000
1241
2338
660
50
281
193
91.4%(1.5)
78.8%(1.6)
59.5%(3.2)

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Successful Treatment of Childhood High-Risk Hepatoblastoma With Dose-Intensive Multiagent Chemotherapy and Surgery: Final Results of the SIOPEL-3HR Study

Josef Zsíros, Rudolf Maibach, Elizabeth Shafford, Laurence Brugieres, Penelope Brock, Piotr Czauderna, Derek Roebuck, Margaret Childs, Arthur Zimmermann, Veronique Laithier, Jean-Bernard Otte, Beatriz de Camargo, Gordon MacKinlay, Marcelo Sugimoto, Daniel Aronson, Jack Plaschkes, and Giorgio Perilongo

From the Departments of Pediatric Oncology and of Pediatric Surgery, Emma Children's Hospital/Academic Medical Centre, Amsterdam, the Netherlands; International Society Cancer Study Group, Coordinating Center, and Department of Surgical Pathology, Institute of Pathology, and Department of Surgery, University Children's Hospital, Bern, Switzerland; Children's Cancer and Leukaemia Group (CCLG) Data Centre, Leicester, and Departments of Haematology and Oncology and of Radiology, Great Ormond St Hospital for Children, London, and Department of Paediatric Surgery, Royal Hospital for Sick Children, Edinburgh, United Kingdom; Department of Paediatrics, Institut Gustave Roussy, Villejuif Cedex, and Department of Pediatric Hemato-Oncology, Centre Hospitalier Universitaire, Besançon, France; Department of Surgery and Urology for Children and Adolescents, Medical University of Gdansk, Gdansk, Poland; Department of Pediatric Surgery, Université Catholique de Louvain, Saint Luc University Clinics, Brussels, Belgium; Department of Research, Hospital do Cancer, Sao Paolo, Brazil; Department of Haemato-Oncology, Hospital Prof Dr J.P. Garrahan, Buenos Aires, Argentina; and Division of Haematology-Oncology, Department of Pediatrics, University Hospital of Padua, Padua, Italy.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Josef Zsíros, MD, PhD, Department of Pediatric Oncology, Emma Children's Hospital/Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands; e-mail: j.zsiros@amc.uva.nl.

0732-183X/10/2815-2584/$20.00

DOI: 10.1200/JCO.2009.23.4667

ABSTRACT

Purpose

The primary objective was to determine the efficacy of a newly designed preoperative chemotherapy regimen in an attempt to improve the cure rate of children with high-risk hepatoblastoma.

Patients and Methods

High risk was defined as follows: tumor in all liver sections (ie, Pretreatment Extension IV [PRETEXT-IV]), or vascular invasion (portal vein [P+], three hepatic veins [V+]), or intra-abdominal extrahepatic extension (E+), or metastatic disease, or α-fetoprotein less than 100 ng/mL at diagnosis. Patients were treated with alternating cycles of cisplatin and carboplatin plus doxorubicin (preoperatively, n = 7; postoperatively, n = 38) and delayed tumor resection.

Results

Of the 151 patients (150 evaluable for response) 118 (78.7%) achieved a partial response to chemotherapy. Complete resection of the liver tumor could be achieved in 116 patients (76.2%) either by partial hepatectomy (55.6%) or by liver transplantation (20.6%). In 106 children (70.2%), complete resection of all tumor lesions including metastases was achieved. Among the patients with initial lung metastases, 52.2% achieved complete remission of the lung lesions with chemotherapy alone. In half of the patients with initial PRETEXT-IV tumor as the only high-risk feature, the tumor could be completely resected with partial hepatectomy. Event-free (EFS) and overall survival (OS) estimates at 3 years were 65% (95% CI, 57% to 73%) and 68% (95% CI, 60% to 77%) for the whole group. EFS and OS for all patients with PRETEXT-IV tumor were 68% and 69%, respectively, and they were 56% and 62%, respectively, for patients with metastasis.

Conclusion

The applied treatment rendered a great proportion of tumors resectable, and, in comparison with previously published results, led to an improved survival in patients with high-risk hepatoblastoma.

J Clin Oncol 28:2584-2590. © 2010 by American Society of Clinical Oncology

INTRODUCTION

The first International Childhood Liver Tumours Strategy Group (SIOPEL) study, applying preoperative chemotherapy (PLADO: cisplatin plus doxorubicin) and delayed surgery to all patients, resulted in a 5-year overall survival (OS) of 75% and event-free survival (EFS) of 66%.[1] However, similarly to other studies,[2-5] the prognosis of patients with tumor involving all four liver sections or metastasis remained unsatisfactory (5-year EFS, 44% and 28%, respectively[1]).

To improve the survival of patients with bad prognosis, the SIOPEL group decided to intensify chemotherapy in the subsequent studies. Carboplatin, a platinum derivative with different activity and toxicity profile than cisplatin, had previously shown significant clinical activity in patients with advanced and relapsed hepatoblastoma and, therefore, was chosen to add to the PLADO backbone.[6,7] In the new scheme, alternating cycles of cisplatin and carboplatin plus doxorubicin were given every 14 days, in contrast to the PLADO regimen, which was given every 21 days. In addition, total hepatectomy with orthotopic liver transplantation (OLT) was recommended for patients whose primary tumors remained unresectable after chemotherapy.[8-10]

The feasibility of the new approach was tested in a pilot study (SIOPEL-2HR).[11] The SIOPEL-3HR trial was then launched to study the efficacy

Epatoblastoma ad alto rischio

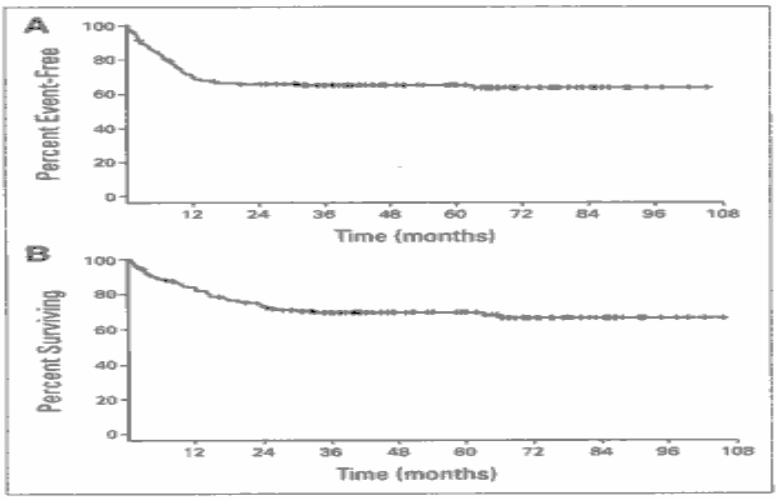
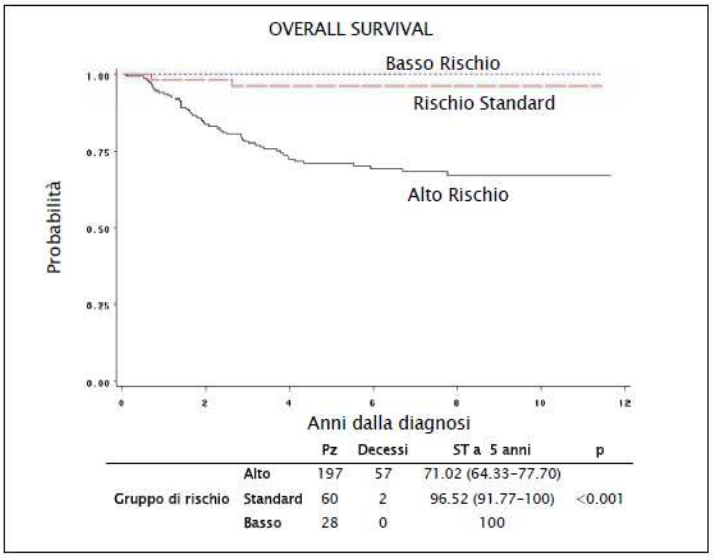


Fig 2. Kaplan-Meier estimates of (A) event-free survival and (B) overall survival.

Protocollo RABDOMIOSARCOMA 96



		Pz	Decessi	ST a 5 anni	p
Gruppo di rischio	Alto	197	57	71.02 (64.33–77.70)	
	Standard	60	2	96.52 (91.77–100)	<0.001
	Basso	28	0	100	

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Anti-GD2 Antibody with GM-CSF, Interleukin-2, and Isotretinoin for Neuroblastoma

Alice L. Yu, M.D., Ph.D., Andrew L. Gilman, M.D., M. Fevzi Ozkaynak, M.D., Wendy B. London, Ph.D., Susan G. Kreissman, M.D., Helen X. Chen, M.D., Malcolm Smith, M.D., Ph.D., Barry Anderson, M.D., Judith G. Villablanca, M.D., Katherine K. Matthay, M.D., Hiro Shimada, M.D., Stephan A. Grupp, M.D., Ph.D., Robert Seeger, M.D., C. Patrick Reynolds, M.D., Ph.D., Allen Buxton, M.S., Ralph A. Reisfeld, Ph.D., Steven D. Gillies, Ph.D., Susan L. Cohn, M.D., John M. Maris, M.D., and Paul M. Sondel, M.D., Ph.D., for the Children's Oncology Group

From the University of California, San Diego, and Moores Cancer Center — both in San Diego (A.L.Y.); Genomics Research Center, Academia Sinica, Taiwan (A.L.Y.); Levine Children's Hospital, Charlotte (A.L.G.), and Duke University Medical Center, Durham (S.G.K.) — both in North Carolina; New York Medical College, Valhalla (M.F.O.); Dana Farber Cancer Institute, Children's Hospital Boston, and the Children's Oncology Group Statistics and Data Center — all in Boston (W.B.L.); the National Cancer Institute, Bethesda, MD (H.X.C., M.S., B.A.); Children's Hospital Los Angeles, University of Southern California, Los Angeles (J.G.V., H.S., R.S.); University of California School of Medicine and University of California, San Francisco, Children's Hospital, San Francisco (K.K.M.); Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, Philadelphia (S.A.G., J.M.M.); School of Medicine, Texas Tech University Health Sciences Center, Lubbock (C.P.R.); Children's Oncology Group Statistics and Data Center, Arcadia (A.B.); and Scripps Research Institute, La Jolla (R.A.R.) — both in California; Provenance Biopharmaceuticals, Waltham, MA (S.D.G.); University of Chicago, Chicago (S.L.C.); and University of Wisconsin Carbone Cancer Center, Madison (P.M.S.). Address reprint requests to Dr. Yu at the University of California, San Diego, and Moores Cancer Center, 200 W. Arbor Dr., San Diego, CA 92103-8447, or at aliceyu@ucsd.edu.

N Engl J Med 2010;363:1324-34.

ABSTRACT

BACKGROUND

Preclinical and preliminary clinical data indicate that ch14.18, a monoclonal antibody against the tumor-associated disialoganglioside GD2, has activity against neuroblastoma and that such activity is enhanced when ch14.18 is combined with granulocyte–macrophage colony-stimulating factor (GM-CSF) or interleukin-2. We conducted a study to determine whether adding ch14.18, GM-CSF, and interleukin-2 to standard isotretinoin therapy after intensive multimodal therapy would improve outcomes in high-risk neuroblastoma.

METHODS

Patients with high-risk neuroblastoma who had a response to induction therapy and stem-cell transplantation were randomly assigned, in a 1:1 ratio, to receive standard therapy (six cycles of isotretinoin) or immunotherapy (six cycles of isotretinoin and five concomitant cycles of ch14.18 in combination with alternating GM-CSF and interleukin-2). Event-free survival and overall survival were compared between the immunotherapy group and the standard-therapy group, on an intention-to-treat basis.

RESULTS

A total of 226 eligible patients were randomly assigned to a treatment group. In the immunotherapy group, a total of 52% of patients had pain of grade 3, 4, or 5, and 23% and 25% of patients had capillary leak syndrome and hypersensitivity reactions, respectively. With 61% of the number of expected events observed, the study met the criteria for early stopping owing to efficacy. The median duration of follow-up was 2.1 years. Immunotherapy was superior to standard therapy with regard to rates of event-free survival (66±5% vs. 46±5% at 2 years, P=0.01) and overall survival (86±4% vs. 75±5% at 2 years, P=0.02 without adjustment for interim analyses).

CONCLUSIONS

Immunotherapy with ch14.18, GM-CSF, and interleukin-2 was associated with a significantly improved outcome as compared with standard therapy in patients with high-risk neuroblastoma. (Funded by the National Institutes of Health and the Food and Drug Administration; ClinicalTrials.gov number, NCT00026312.)

Novità nella incidenza

- Forse nessuna…..forse no
- Differenza con le neoplasie dell'adulto
- Ma fra qualche anno…

Vittoria 26/03/2011

GRAZIE PER LA VOSTRA GENTILE ATTENZIONE