UNIVERSITATEA DE MEDICINĂ ŞI FARMACIE
"IULIU HAȚIEGANU" CLUJ-NAPOCA

STRATEGIA TERAPEUTICĂ ADAPTATĂ GRUPELOR DE RISC ÎN TUMORILE GERMINALE

TEZĂ DE DOCTORAT
REZUMAT

Coordonator Ştiinţific

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CUPRINS

CUVINTE CHEIE: tumori cu celule germinale, factori de prognostic, regimuri de chimioterapie standard si originale, celule tumorale circulante, rezultate pe termen lung

PARTEA INTAI
CAPITOL 1. INTRODUCERE

Tumorile germinale sunt cele mai frecvente cancere la barbatii tineri, cu varsta intre 20 si 40 de ani. In Uniunea Europeana exista o variatie de cca 5 ori in incidenta intre diverse tari. In Romania, incidenta cancerului testicular s-a dublat din anul 1985 pina in anul 2005, cu un varf in 1995. Romania se numara printre tarile cu cele mai joase rate, putin sub nivelul mediei Europei Centrale si Estice, estimate la 2.6/100,000 in 2002. Mortalitatea cauzata de cancerul testicular in Romania a variat de la 54 decese in anul 1985 la 76 in anul 2005. Mortalitatea cauzata de cancerul testicular a scazut dramatic din anul 1970 datorita progreselor inregistrate in tratament in tarile dezvoltate, dar inegal, datorita distributiei inechitabile a resurselor economice. In Europa de Est, mortalitatea a inceput sa scada doar la sfarsitul anilor 1980.

Actualul standard de chimioterapie se bazeaza pe o lunga serie de trialuri randomizate controlate, in ciuda faptului ca tumorile germinale sunt destul de rare. Peste 90% din pacienti sunt actualmente vindecati, chiar in stadii avansate si tratamentul tumorilor germinale reprezinta unul dintre cele mai mari succese medicale. Este obligatoriu sa se faca toate eforturile in vederea vindecarii pacientilor, cu limitarea efectelor adverse.

CAPITOL 2. STADIUL ACTUAL AL CUNOASTERII

Tumorile germinale sunt extrem de curabile si apar la barbati tineri. In prezent sansa de vindecare completa este de 70-100% pentru toate stadiile, chiar metastatice. Tumorile extragonadale, histopatologic se impart in seminoame si tumori nonseminomatoase. Tumorile extragonadale trebuie tratate similar cu cele testiculare, in functie de factorii de prognostic.

In acest capitol sunt dezvoltate urmatoarele aspecte:

a). Conduita in cancerul testicular stadiul I
b).Tratamentul tumorilor germinale din grupa cu prognostic favorabil (extensie minima-moderata)
c). Tratamentul tumorilor germinale din grupele cu prognostic rezervat si intermediar
d). Tratamentul bolii reziduale
e). Conduita in resuta postchimioterapie

PARTEA A DOUA
CAPITOL 3: CONTRIBUTII ORIGINALE

Aceasta lucrare a urmat patru trepte successive de cercetare, fiecare reprezentand cate un studio distinct:

- Primele doua sunt studii retrospective efectuate pe cazuistica pacientilor cu tumori cu cellule germinale tratati la Institutul Oncologic `Prof Dr Ion Chiricuta` din Cluj-Napoca, in perioada 1982-2004, cu scopul de a determina factorii de prognostic (studiul 1) si efectele adverse ale chimioterapiei (studiul 2);
- Un studiu prospectiv de faza II cu o combinatie originala de citostatice pentru pacientii cu risc crecut (studiul 3);
- Un studiu pilot, inca in derulare, pentru evaluarea unui posibil factor predictiv, celulele tumorale circulante (studiul 4).

CAPITOL 4: STUDIUL NUMARUL 1: CHIMIOTERAPIA ADAPTATA GRUPELOR DE RISC LA PACIENTII CU TUMORI GERMINALE TRATATI IN INSTITUTUL ONCOLOGIC CLUJ

Introducere

Supravietuirea la 5 ani pentru pacientii cu tumori germinale cu prognostic bun, intermediar si rezervat este de 94%, 83%, si 71%. S-au depus eforturi pentru a reduce toxicitatea tratamentului fara a scadea eficacitatea. In ciuda ratelor inalte de vindecare pentru pacienti cu boala avansata, la 20% - 30% dintre acestia nu se ajunge sa se obtina un raspuns complet durabil la cisplatin plus etopozid. Selectia pacientilor in functie de factorii de prognostic este extrem de importanta.

Designul studiului

Este un studiu retrospectiv efectuat pe cazuistica institutiei noastre la pacientii cu TCG confirmate tratati in perioada ianuarie 1982 si ianuarie 2004. Scopul a fost de a urmari evolutia acestor pacienti si de a selecta factori prognostici viabili in aceasta boala extrem de curabila.

Analiza statistica

Variabilele au fost evaluate cu testul hi patrat cu corectii Yates. Pentru a calcula curbe de supravietuire au fost folosite metode iar pentru estimarea diferentelor statistice intre curbele de supravietuire s-a folosit testul log rank.

Rezultate

Studiul demonstreaza ca aplicarea tratamentului sistemic chimioterapic adaptat grupelor de risc la pacientii cu tumori germinale duce la rezultate excelente. Doar 97 din cei 570 pacienti au decedat din cause legate de tumora germinala. Trei sute nouazeci din cei 570 pacienti au avut un raspuns favorabil la chimioterapie, iar optiunea de supraveghere `adjuvanta` la pacientii cu stadiul I de risc scazut a constituit o metoda viabila. Supravietuirea generala la 8 ani a fost de 82%. Rezultatele noastre confirma necesitatea adaptarii terapiei la grupa de risc, totusi, este necesara selectarea unor noi si moderni factori de prognostic pentru a ameliora rezultatele fara a creste toxicitatea.

CAPITOL 5: STUDIUL NUMARUL 2: EFECTE SECUNDARE ACUTE SI SUBACUTE ALE CHIMIOTERAPIEI IN TUMORI GERMINALE: ANALIZA RETROSPECTIVA PE CAZUISTICA INSTITUTULUI ONCOLOGIC ION CHIRICUTA

Introducere

In aceasta neoplazie atat de curabila, trebuie facute toate eforturile pentru administrarea unui tratament eficace de linia I si II cu minime efecte secundare. Trebuie dezvoltata , dar fara a cauza efecte secundare inutile.o strategie de tratament adaptata grupelor de risc astfel incat terapia adjuvanta sa previna recidivele, cu evitarea toxicitatii inutile. Scopul acestui studiu retrospectiv a fost de a examina toxicitatile pe termen scurt induse de chimioterapie la pacientii cu tumori germinale testiculare si extragonadale tratati in institutia noastra in perioada 1982-2004.

Designul studiului

Au fost colectate date privind regimul de chimioterapie, toxicitatile acute si subacute stratificate in functie de grad. Informatiile au provenit din dosarele medicale ale institutiei noastre.

Resultate

La pacientii cu tumori germinale testiculare si extragonadale tratati in Institutul nostrum, toxicitatile acute si subacute au fost preponderant gastrointestinale, hematologice, si, mai putin frecvent, cutanate, renale si neurologice. Efectele secundare au fost de grad redus sau moderat, tratabile si reversibile.

CAPITOL 6: STUDIUL NUMARUL 3: REZULTATE PE TERMEN LUNG ALE CHIMIOTERAPIEI IN TUMORI GERMINALE CU PROGNOSTIC NEFAVORABIL. TRIAL PROSPECTIV DE FAZA II EVALUAND IN PRIMA LINIE COMBINATIA TAXOL, IFOSFAMIDA SI CISPLATIN (TIP) LA PACIENTII CU RISC CRESCUT

Introducere

Sunt raportate rezultatele pe termen lung ale combinatiei Taxol, Ifosfamida si Cisplatin (TIP) ca tratament chimioterapic in doze standard de prima linie la pacientii cu tumori germinale cu prognostic nefavorabil, in cadrul unui trial uniinstitutional prospectiv de faza II.

Designul studiului

In perioada octombrie 1997- septembrie 2000, in acest trial au fost inrolati 28 pacienti de sex masculin, corespunzand criteriilor IGCCCG de incadrare in grupa cu risc crescut.

Analiza statistica
Nivelul de semnificatie statistica a fost ales la 0.05 pentru toate tipurile de teste utilizate si pentru estimarea intervalelor. In ceea ce priveste diferentele dintre distributia factorilor de prognostic s-a folosit testul hi patrat cu corectia Yates de cate ori a fost necesar pentru numarul mic de cazuri. Supravietuirea globala si cea fara semen de boala au fost evaluate prin metoda Kaplan-Meier iar diferentele dintre curbe au fost stabilite prin testul log rank.
Rezultate
Regimul de chimioterapie TIP (paclitaxel, ifosfamide, cisplatin) s-a demonstrat a fi un tratament eficace administrat in prima linie la pacientii cu tumori germinale cu risc crescut in ceea ce priveste rata de rapuns, supravietuirea fara semne de boala si supravietuirea generala, iar efectele secundare au fost moderate.

CAPITOL 7: STUDIUL NUMARUL 4: CORELATIA DINTRE DETECTIA CELULELOR TUMORALE CIRCULANTE SI RASPUNSUL SEROLOGIC SI IMAGISTIC LA TRATAMENT LA PACIENTII CU TUMORI GERMINALE: STUDIU PILOT. UN NOU FACTOR DE PROGNOSTIC INTR-O NOUA ERA?

Introducere
In cazul unui cancer atat de curabil, este important sa se identifice orice influenta care confera un risc crescut de mortalitate specifica. Sunt necesare studii aditionale pentru a descoperi factori prognostici complementari.
Designul studiului
Este un studiu pilot condus prospectiv in institutia noastra la doi pacienti cu tumori germinale cu risc crescut pentru a evalua fezabilitatea izolarii si numararii CTC, precum si potentialul rol in corelarea reapunsului radiologic si serologic al markerilor tumorali cu dinamica scaderii CTC.
Rezultate
Acest studiu pilot a demonstrat abilitatea de a detecta prezenta celulelor tumorale circulante la pacientii cu celule germinale cu risc crescut si corelatia dintre numarul CTC si nivelul seric al markerilor tumorali impreuna cu raspunsul radiologic pre- si post-chimioterapie, dar sunt necesare studii suplimentare pentru investigarea acestui domeniu pentru a gasi posibili noi factori prognostici.

CAPITOL 8: DISCUTII GENERALE

Cancerul testicular constituie un exemplu de ce se poate invata din trialuri bine conduse. Chimioterapia standard in tumorile cu celule germinale se bazeaza pe o lunga serie de trialuri randomizate si controlate. Peste 90% din pacienti sunt vindecati, chiar in stadii avansate si tratamentul tumorilor germinale reprezinta unul din marile succese ale oncologiei medicale. Trebuie depuse toate eforturile pentru a vindeca pacientii si a limita toxicitatea tratamentului, iar pentru pacientii incadrati in grupa cu risc crescut, este nevoie sa se valideze noi factori de prognostic si algoritmi pentru a imbunatati rezultatele prin adaptarea individuala a tratamentului, deoarece ultimul scor prognostic validat dateaza dintr-un larg consens din 1997. In acest capitol se compara rezultatele obtinute in centrul nostrum cu cele din literature.

CAPITOL 9: CONCLUZII

1. Pentru toti pacientii cu tumori germinale, scopul trebuie sa fie vindecarea, cu concentrarea eforturilor de cercetare a unor tratamente mai eficace in linia I pentru cei cu risc crescut si in linia II pentru pacientii cu boala platinum-refractara. Este necesara aplicarea unui tratament adaptat grupelor de risc, astfel incat terapia sa tinteasca eficient metastazele primare si oculte, si a se evita crearea chimiorezistentei si a unei toxicitati inutile.
2. Primul studiu reprezinta o analiza exhaustiva a factorilor de risc si a rezultatelor pe termen lung pe o cazuistica bogata de pacienti cu tumori germinale tratati si urmariti la Institutul Oncologic Ion Chiricuta Cluj-Napoca in perioada 1980 pana in 2010. Este primul si unicul studiu de aceasta magnitudine publicat in literatura medicala din Romania.
3. In al doilea studiu s-au analizat toxicitatile tratamentului conform criteriilor NCIC CTC, principalele efecte adverse fiind: gastrointestinale, hematologice, neurologice, cutanate, renale, alergice, pulmonare si alopecia. Toate toxicitatile acute si subacute constatate la pacientii nostri au fost de magnitudine scazuta sau moderata, controlabile si reversibile, fara a se inregistra decese toxice.
4. In al treilea studiu, un studiu de faza 2, a fost investigat un nou regim citostatic in linia I cu taxol, ifosfamida si cisplatin la pacientii cu celule germinale cu risc crescut. Scopul studiului a fost gasirea unei noi combinatii mai eficace, deoarece aproape 50% din pacientii cu risc crescut prezinta resuta dupa protocolul standard BEP. Efectele adverse ale protocolului TIP

au fost moderate si controlabile, fara decese toxice, si comparabile cu cele ale regimului BEP, dar mult mai putin agresive decat in chimioterapia de linia I cu doze mari.
5. In al patrulea studiu am demonstrat ca utilitatea celulelor tumorale circulante in stratificarea ca factor de pronostic ar putea fi de interes in tumorile germinale, aceste noi date facand ca folosirea acestora in practica sa constituie un instrument cu adevarat fascinant.
6. Treatmentul tumorilor cu celule germinale reprezinta o adevarata poveste de succes a oncologiei moderne si este rezultatul multor eforturi de colaborare de-a lungul timpului intre numeroase centre oncologice de renume din intreaga lume.

Bibliografia: 174 citatii

CURRICULUM VITAE

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- Doctorand al Universitatii de Medicina si Farmacie „Iuliu Hațieganu” Cluj-Napoca, Romania

Educatie

- Liceul de Stiinte Naturale, Cluj-Napoca, absolvit in 1984;
- Universitatea de Medicina si Farmacie „Iuliu Hatieganu” Cluj-Napoca, medic, absolvita cu diploma de merit in 1990;
- Stagiatura: Spitalul Clinic Judetean Cluj: 1990-1991;
- Rezidentiat in Oncologie Medicala: Institutul Oncologic „Prof. Dr. Ion Chiricuță” Cluj-Napoca, 1992-1994;
- Specialitate: medic specialist Oncologie Medicala, confirmata in Decembrie 1994;
- Specializare aprofundata in oncologie/hematologie si cancerologie: Universitatea de Medicina Paris XIII, Paris, Franta, si Universitatea de Medicina Rouen, Franta, Mai 1999-Noiembrie 2001;
- Medic primar oncologie medicala in Mai 1999;
- Certificare in Oncologie Medicala de catre ESMO - Vienna, 2004 (European Society of Medical Oncology Certification).

Experiente relevante:

- Bursier Tempus in Oncologie, Centre de Lutte Contre le Cancer Henri Bequerel, Dept Oncologie Medicala, Rouen, France, June-Sept 1996
- Stagiu de pregatire in Oncologie/Hematologie, Institut Gustave Roussy, Dept of Hematologie/ Chimioterapie in doze mari cu transplant de celule stem, Villejuif, Franta, Mai 1999- Noiembrie 1999, si Mai 2000-Noiembrie 2000.
- Medic Asistent al Serviciului, Spital Universitar `Charles Nicole`, Dept Tumori Digestive, Noiembrie 1999- Aprilie 2000.
- Educatie Medicala Continua prin participare la mai multe cursuri avansate de Oncologie Medicala&Hematologie organizate de ESMO/ASCO

Afilieri la Societati Medicale Profesionale:

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- Membru activ certificat ESMO (2004) din Decembrie 1998
- Membru activ BUON din 1997
- Membru activ SRROM din 1994

Cooperari internationale:

- Membru al comitetului consultant ESMO din 2011

- Membru al Comitetului International de experti pentru NSCLC Pfizer
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Domenii de interes: carcinoame genitourinare, limfoaes, carcinoame pulmonare, digestivs, ginecologice, cap si gat, neuroendocrine, melanoame,trialuri clinice de faza I, II, III, IV
Investigator principal in peste 25 trialuri clinice trials in ultimii 8 ani
Participant la raportul colectiv: Publication and Education, Investigator Incentives for Trial Participation (I-Incent) Report, Clinical Trial Magnifier Vol 3:6, December 2010, page 397-398, Clinical Investigator Incentives for Participation in Industry-Sponsored Clinical Trials, Kota Kinabalu, Malaysia, November 24-26, 2010
Acreditare in Masterclass de Comunicare (Berlin, 2009)
Lucrari stiintifice:

- 73 lucrari, 14 ca prim autor
- 32 articole publicate (8 in strainatate, una ca prim autor, 24 nationale, 8 ca prim autor)
- Lector invitat: 8

Lucrari publicate:

- In strainatate:
  - 1 articol ca prim autor in jurnal peer-reviewed
  - 7 articlole ca si co-autor injurnale peer-reviewed
  - 24 comunicari stiintifice presentate la congrese internationale (2 ca prim autor, 22 ca si co-autor)
  - 1 prezentare (lector invitat) la cursuri internationale
- In tara:
  - 9 articole ca prim autor in jurnale peer-reviewed
  - 15 articole ca si co-autor in jurnale peer-reviewed
  - 9 comunicari stiintifice la congrese nationale (2 ca prim autor, 7 ca si co-autor)
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PROGNOSTIC FACTORS AND LONG TERM RESULTS IN GERM CELL TUMORS

DOCTORAL THESIS

Abstract

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2011

CONTENTS

Key words: germ cell tumors, pronostic factors, standard and original chemotherapy regimens, circulating tumor cells, long term results

PART ONE
CHAPTER1. INTRODUCTION

Germ cell tumors are the most frequent cancers in young men, aged between 20 and 40 years. Within the European Union, there is an approximately five-fold variation in incidence between countries with highest and lowest incidence rates. In Romania, the incidence of testicular cancer more than doubled from 1985 to 2005, with a peak in 1995. Romania is among the countries with the lowest rates, slightly under the Central and Eastern European average estimated at 2.6 per 100,000 in 2002. In our country, mortality caused by testicular cancer varied from 54 deaths in 1985 to 76 in 2005. Mortality from testicular cancer has declined dramatically since 1970, because of the advances in treatment in most developed countries, but not at all at the same time, due to inequitable distribution of resources and expertise between countries. In Eastern Europe, mortality did not begin to decline until the late 1980s.

The current standard chemotherapy in Germ Cell Tumors is based on a long series of randomized controlled clinical trials, despite the fact that this is a relatively rare tumor. More than 90% of patients are now cured, even in advanced stages and the treatment of Germ Cell Tumors represents one of the great successes of medical science. All attempts should be made to cure patients and to limit toxicity.

CHAPTER 2. PRESENT STATUS OF KNOWLEDGE

Testicular Germ Cell Tumors (GCT) are highly curable and usually develop in young and middle-aged men. Currently the chance of a complete cure is 70-100% for all stages, even metastatic. Testicular testis tumors are broadly divided into seminoma and nonseminoma types. Extragonadal germ cell tumors should be treated like gonadal tumors, according to the prognostic factors.

In this chapter, the following issues are treated:

a). Management of Stage I Testicular Cancer
b). Management of Good Risk Germ Cell Tumors (Minimal-Moderate Disease)
c). Management of Poor- and Intermediate- Risk Germ Cell Tumors
d). Management of Residual Disease
e). Management of Relapse after chemotherapy

PART TWO
CHAPTER 3: ORIGINAL CONTRIBUTIONS

This research has followed four sequencing steps, each one representing a distinct study:

- The first two are retrospectives studies on germ cell tumors patients treated at the Cancer Center „Prof. Dr. Ion Chiricuță" of Cluj-Napoca, during 1982-2004 period, to assess prognostic factors (study 1) and the adverse effects of chemotherapy (study 2);
- A prospective phase II study with an original combination of drugs for high-risk patients (study 3);
- A pilot study, still ongoing, for real-time assessing a possible predictive factor, the circulating tumor cells (study 4).

CHAPTER 4: STUDY NUMBER 1: RISK-ADAPTED CHEMOTHERAPY IN GERM CELL TUMORS IN A SINGLE INSTITUTION SERIES.

Introduction

The 5-year survival rates for good-, intermediate- and high-risk germ cell tumors (GCT) are 94%, 83%, and 71%, respectively. Efforts have been made to reduce treatment toxicity while maintaining efficacy.

Despite high cure rates for patients with advanced GCT, between 20% and 30% of patients do not achieve a durable complete response to cisplatin plus etoposide. Patient selection according to prognostic factors is important.

Study design

This is a retrospective study of confirmed GCT patients treated at our institution between January 1982 and January 2004. The goal was to assess the outcome of these patients and to select viable prognostic factors in order to improve the outcome of this highly curable disease.

Statistical Analysis

Categorial variable were evaluated with the squared chi test and if appropriate Yates corrections were used. Kaplan Meier methods were used to plot survival curves and the long rank test was used for the estimation of statistical differences between survival curves.

Results

The study demonstrates that risk-adapted systemic chemotherapy for patients with germ cell tumors results in excellent outcomes. Only 97 of 570 patients died with causes related to germ cell tumor. Three hundred and ninety of 570 patients experienced favorable response to chemotherapy, and the option of "adjuvant" surveillance was a viable method in low-risk stage I patients. The overall 8-years survival was 82%. Our results strongly support the risk-adapted strategies, still, new modern prognostic factors have to be selected in order to optimize the results without increasing toxicities.

CHAPTER 5: STUDY NUMBER 2: ACUTE AND SUB-ACUTE SIDE EFFECTS OF GERM CELL TUMORS CHEMOTHERAPY: A RETROSPECTIVE ANALYSIS OF ION CHIRICUTA CANCER CENTER SERIES

Introduction

In this highly curable disease, efforts focusing on effective first-line and second-line treatments with fewer side effects should be done. A risk-adapted treatment policy should be developed so that adjuvant therapy is targeted to prevent relapses, but also to avoid unnecessary toxic effects.

The purpose of this retrospective study was to examine short term chemotherapy induced toxicities in a uni-institutional series of germ cell testicular and extragonadal patients treated between 1982 and 2004.

Study design

Data were collected on cytostatic schedule and setting, acute and subacute toxicities induced by chemotherapy stratified by grading. Data were collected from our Institution medical records.

Results

In our Cancer Center, for the germ cell testicular and extragonadal treated patients, acute and subacute toxicities were mainly gastrointestinal, hematologic, and, less important, cutaneous, renal and neurological. Toxicities were mild/moderate, manageable and reversible.

CHAPTER 6: STUDY NUMBER 3: LONG TERM RESULTS OF CHEMOTHERAPY IN HIGH RISK GERM CELL TUMORS. A PHASE II SINGLE INSTITUTION PROSPECTIVE TRIAL WITH PACLITAXEL, IFOSFAMIDE AND CISPLATIN (TIP) REGIMEN AS FIRST-LINE TREATMENT IN PATIENTS WITH HIGH-RISK GERM CELL TUMORS

Introduction

This study reports the long-term results of a combination of Paclitaxel, Ifosfamide, and Cisplatin (TIP) as first-line standard – dose chemotherapy in patients with poor-prognosis germ cell tumors, treated prospectively in a phase II, single-institution trial.

Study design

Twenty-eight male patients were enrolled onto this trial between October 1997 and September 2000, on the basis of poor-risk classifications according to the IGCCCG criteria.

Statistical Design and Analysis

The level of significance was chosen 0.05 for all types of tests used and for the interval estimates. For the differences concerning the distribution of prognostic factors between chemotherapy regimens we used chi squared test with Yates correction for small number of cases whenever it was necessary. Overall survival and progressive free survival were

evaluated by Kaplan-Meier method and differences between curves were established by log rank test.

Results

TIP (paclitaxel, ifosfamide, cisplatin) regimen was effective as first-line in poor-risk GCTs in terms of response rate, DFS, and OS, and the toxicity was mild.

CHAPTER 7: STUDY NUMBER 4: RELATIONSHIP OF CIRCULATING TUMOR CELLS DETECTION TO SEROLOGIC AND IMAGING RESPONSE IN GERM CELL TUMORS: A PILOT STUDY. IS IT A NEW PROGNOSTIC FACTOR IN A NEW ERA?

Introduction

In a cancer that is so curable, it is important to identify any influence that confers an increased risk of specific mortality. Additional research is needed, enabling the development of additional prognostic factors.

Study Design

This is a pilot study conducted prospectively in our institution in two germ cell high-risk patients to evaluate the feasibility of CTC isolation and enumeration and the potential role in correlating response in term of radiologic and serologic tumor markers decrease with CTC profile.

Results

This pilot study has demonstrated the ability to detect the presence of circulating tumor cells in patients with high-risk germ cell patients, and a correlation between the number of CTC and the serum markers levels all together with the radiologic response before and after chemotherapy, but further studies are required to fully investigate this line of inquiry for possible prognostic values.

CHAPTER 8: GENERAL DISCUSSIONS

Testicular cancer is an example of what can be learned from well conducted clinical trials. The current standard chemotherapy in germ cell tumors is based on a long series of randomized controlled trials. More than 90% of patients are cured, even in advanced stages and the treatment of germ cell tumors represents one of the great successes of medical oncology. All attempts should be made to cure patients and to limit toxicity, and, for poor-prognosis patients, new prognostic factors and algorithms are needed to improve results and by tailoring individual treatments, because the latest validated prognostic factors was from a large consensus made in 1997. In this chapter we compared results from literature with our results.

CHAPTER 9: CONCLUSIONS

1. The goal for all germ cell patients must be cure, with research efforts focusing on more effective first-line treatments for high-risk patients and effective second-line therapy for platinum-resistant patients. A risk-adapted treatment policy should be developed so that therapy is better targeted on the primary and occult metastases, to avoid chemoresistance or unnecessary toxicity.
2. The first study represents an exhaustive analysis on risk factors and long term results on a large series of germ cell tumors treated at the Cancer Institute Ion Chiricuta Cluj-Napoca from 1980 through 2010. It is the first and the unique study of this magnitude to be published in Romanian medical literature.
3. In the second study, toxicities were analysed according to NCIC CTC criteria, with the main adverse events related to gastrointestinal, hematological, neurological, cutaneous, renal, allergic and pulmonary, and alopecia. All acute and subacute toxicities of our patients were mild-moderate and manageable and reversible, with no toxic deaths.
4. In the third study, a phase 2 study, a new regimen of chemotherapy with paclitaxel, ifosfamide and cisplatin was investigated in first-line for high-risk germ cell patients. The rationale for the study was that almost 50% of patients in our setting relapsed after standard BEP therapy. Toxicities of TIP regimen were mild and manageable, without toxic deaths, comparable with those described in the BEP regimen, but much less aggressive than in first-line high-dose chemotherapy.
5. In the fourth study we demonstrated that CTC could have utility in stratifying prognostic factors in germ cell tumors, these new data making the story of circulating tumor cells truly fascinating.
6. The treatment of germ cells tumors represents a true success story for modern oncology and is the result of many cooperative efforts that extends over time and many cancer centers all over the world.

Refferences list: 174 titles

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Education

- High School for Natural Sciences, Cluj-Napoca, graduated 1984;
- University of Medicine and Pharmacy, Cluj-Napoca, licensed medical doctor (MD) , graduated cum laudae 1990;
- Internship: County Hospital of Cluj-Napoca: 1990-1991;
- Residency in Medical Oncology: „Prof. Dr. Ion Chiricuță" Cancer Center, Cluj-Napoca, 1992-1994;
- Specialty: confirmed as medical doctor specialist in Medical Oncology, Cluj-Napoca, December 1994;
- Postgraduate Training in Oncology/Hematology and Cancerology: Medical University Paris XIII, Paris, France, Attestation de Formation Specialisee Approfondie (AFSA) in Oncology and Medical University of Rouen, France, AFSA in Cancerology, May 1999-November 2001; Romanian recertification in Medical Oncology (Senior Medical Oncologist): Cluj Napoca, May 1999;
- Certification in Medical Oncology by ESMO - Vienna, 2004 (European Society of Medical Oncology Certification).

Other Relevant Experience

- Foreign Resident in Oncology (Tempus fellow) Centre de Lutte Contre le Cancer Henri Bequerel, Dept Oncologie Medicale, Rouen, France, June-Sept 1996
- Postgraduate Training in Oncology/Hematology, Institut Gustave Roussy, Dept of Hematology/ High-Dose Chemotherapy with Stem Cell rescue, Villejuif, France, May 1999- November 1999, and May 2000-November 2000.
- Assistant Physician `Charles Nicole` University Hospital, Dept of Digestive Tumors, November 1999- April 2000.
- Continuing Medical Education by many advanced courses in Medical Oncology&Hematology provided by ESMO/ASCO

Scientific Medical Societies Affiliation

- Full ASCO member since 2001
- Full ESMO-certified member (2004) since December 1998
- Full BUON member since 1997
- Full SRROM member since 1994

International cooperation

- Member of ESMO panel since 2011
- Member of International NSCLC Pfizer Steering Committee
- Member of Amgen Advisory Board
- Amgen CEDAR program co-author

National Steering Committee

- Member of National Renal Carcinoma Pfizer Steering Committee

Domain of interest: genitourinary cancers, lymphomas, lung carcinomas, digestive carcinomas, gynecological cancers, head and neck cancers, neuroendocrine carcinomas, melanoma, phase I, II, III, IV clinical trials

Principal investigator in more than 25 clinical trials in the past 8 years

Participant to the Group Report: Publication and Education, Investigator Incentives for Trial Participation (I-Incent) Report, Clinical Trial Magnifier Vol 3:6, December 2010, page 397-

398, a report from the Clinical Investigator Incentives for Participation in Industry-Sponsored Clinical Trials, Kota Kinabalu, Malaysia, November 24-26, 2010
Accreditation in Masterclass of Communication (Berlin, 2009)
Scientific work:

- 73 works, 14 as first author
- 32 published articles (8 abroad, one first author, 24 national, 8 first-author)
- Invited speaker: 8

Published papers

- Abroad
  - 1 article as first author in peer-reviewed journals
  - 7 articles as co-author in peer-reviewed journals
  - 24 scientific communications presented at international meetings (2 as first author, 22 as co-author)
  - 1 invited presentations (lecturer) at international courses
- National
  - 9 articles as first author in peer-reviewed journals
  - 15 articles as co-author in peer-reviewed journals
  - 9 scientific communications presented at national meetings (2 as first author, 7 as co-author)
  - 7 invited presentations (lecturer) at national courses

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Invited presentations

1. Cristina Cebotaru: Chimioterapie de linia II in cancerele ovariene. Al XIV Congres al SRROM, Arad, 23-25 Sept 2004.
2. Cristina Cebotaru: Tendinte novatoare in managementul tumorilor digestiveterapia moleculara tintita. Simpozionul `Intre Consens si Realitate in tratamentul cancerelor digestive`. Cluj-Napoca, 2006
3. Cristina Cebotaru: Tendinte novatoare in managementul tumorilor digestiveterapia moleculara tintita. Simpozionul `Intre Consens si Realitate in tratamentul cancerelor digestive`. Cluj-Napoca, 2006
4. Cristina Cebotaru: Optimization Cancer Outcomes Managing Neutropenia. Course: `Improving Cancer Outcomes Through Optimal Anemia&Neutropenia Management`. 30 Sept 2010, Cluj-Napoca.
5. Cristina Cebotaru: EMEND- added benefit to the standard therapy for prevention of CINV. Sept 2010. MSD Symposium, Cluj-Napoca.
6. Cristina Cebotaru: Gestational Trophoblastic Disease: General Considerations and Management of Nonmetastatic and Metastatic Disease.The 20th Congress of the SRROM. A Continuous Challenge: The Gynecologic Cancers. Cluj-Napoca, 2010.
7. Cristina Cebotaru: Casodex 150. Calitatea vietii la pacientul cu cancer de prostata local avansat. Simpozion Astra Zeneca, Cheile Gradistei, 28 mai, 2011
8. Cristina Cebotaru: Monitorizarea pacientului cu cancer de prostata: valoarea adaugata a ingrijirii multidisciplinare. Simpozion Astra Zeneca. Cheile Gradistei 28 mai, 2011.

Coomunications at international scientific meetings

1. Cristina Cebotaru: Quality of life measurements in cancer patients. Oral presentation at The 7th European Interuniversity symposium at `Aristoteles` Institute, 1997, Thessaloniki, Greece
2. Cebotaru CL, Todor N, Iancu D, Ghilezan N, Ciuleanu TE: Phase II Paclitaxel, Ifosfamide and Cisplatin as First-Line Chemotherapy in High Risk Germ Cell Tumors. Poster. Proc Am Soc Clin Oncol 20:2001, 194 a (Abstr 775), ASCO Conference 2001, San Francisco.
3. Ciuleanu TE, Ghilezan N, Todor N, Cvitkovic E, De Cremoux H, Armand JP, Ruffie P, Azli N, Saltiel JC, Monnet I, Voisin S, Ioan A, Cernea D, Rusu P, Radulescu I, Cebotaru C, Albiter M: A multivariate regression analysis for advanced non-small cell lung cancer patients treated with multidisciplinary approach including chemotherapy. Proc 4th Central European Conference on Lung Cancer, Gdansk, 1996.
4. TE Ciuleanu, N Ghilezan, N Todor, I Ciurdariu, I Radulescu, C Cebotaru: VAB-6 Chemotherapy (CT) for Testicular Tumors (TT). Revisited a 12 Years Experience at the Oncological Institute of Cluj. 273P, p 58 Ann Oncol 1996. ESMO Congress.
5. Ciuleanu TE, Cebotaru C, Radulescu I, Todor N, Ghilezan N: Taxol and cisplatin (TP) versus etoposide cisplatin (EP) in advanced non-small cell lung cancer (NSCLC). European Journal of Cancer ISSN 09598049, Vol:35, Sept 1999, pp S251-S252.
6. Floares AG, Floares CE, Lazar L, Cebotaru C: Artificial aintelligence systems for maximizing information extractions from oncological data bases: Ovarian cancer survival. Proc Am Soc Clin Oncol 22: 2003 (abstr 1923). Oral presentation, 2003 ASCO Annual Meeting.
7. Marian M, Ciuleanu TE, Todor N, Cebotaru CL, Iancu D, Ghilezan N: Comparison of two cisplatin based doublets (Gemcitabine/Cisplatin, Etoposide/Cisplatin) in advanced non-small cell lung cancer. EJC Supplements (abstr 772), ISSN 13596349, Vol 1, Issue 5, Sept 2003, pp S232-S232.
8. Ciuleanu Tudor E, Marian Marisca, Todor Nicolae, Cebotaru Cristina, Iancu Dana, Ghilezan Nicolae: Comparison of three cisplatin (P) doublets- Gemcitabine/P (GP), paclitaxel/P (TP), etoposide/P (EP) in advanced (stage IIIB and IV) non-small cell lung cancer (NSCLC). Lung cancer (Amsterdam, abstr P-209), ISSN 01695002, Vol;41, Aug 2003, pp S144-S144.
9. Tudor Eliade Ciuleanu, Cristina Cebotaru, Nicolae Todor, Dana Iancu, Elisabeta Ciuleanu, Nicolae Ghilezan: A phase II study of bi-monthly gemcitabine with `De Gramont` 5FU/folinic acid (FOL-FU-GEM) as palliative chemotherapy (CT) for advanced pancreatic carcinoma. 718P, p 194, Ann Oncol 2002, ESMO Congress 2002 Nice.
10. Tzekova V, Cebotaru C, Ciuleanu TE, Damjanov D, Ganchev H, Kanarev V, Stella PJ, Sanders N, Pover G, Hainsworth JD: Efficacy and safety of AZD6244 (ARRY-142886) as second/third-line treatment of patients (pts) with advanced non-small cell lung cancer (NSCLC). Abstr 8029, J Clin Oncol 26:2008 (may 20 suppl; abstr 8029), 2008 ASCO Annual Meeting.

11. Von Pawel J, Harvey JH, Spigel DR, Dediu M, Reck M, Cebotaru CL, Kumm E, Gallant G, Fox NL, Camidge DR: A randomized phase II trial of mapatumumab, a TRAIL-R1 agonist monoclonal antibody, in combination with carboplatin and paclitaxel in patients with advanced NSCLC. Oral presentation. Proc Am Soc Clin Oncol Chicago 2010, abstract 50910, 2010 ASCO Annual Meeting.
12. Rusu P, Ciuleanu TE, Cernea D, Pelau D, Gaal V, Cebotaru C, Iancu D, Guttman T, Todor N, Ghilezan N: The 18th UICC International Cancer Congress 30 June-5 July 2002, Oslo. Abstract Book.
13. Rusu P, Ciuleanu TE, Cernea D, Pelau D, Gaal V, Cebotaru C, Iancu D, Guttman T, Todor N, Ghilezan N: Navelbine and Cisplatin with concurent radiotherapy for unresectable stage III NSCLC, a phase II study. EJC Supplement Abstract Book of ECCO 12, 21-25 Sept 2003, Copenhagen, S 241.
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22. Ciuleanu TE, Todor N, Radulescu I, Cebotaru C, Eniu Al, Banu E, Cainap C, Neacsu C, Mihailov A, Homokos H, Iancu D, Ghilezan N: Bi-Weekly Irinotecan plus High-Dose Infusional Folinic Acid and 5-Fluorouracil Combination as Second Line Chemotherapy for Advanced Inoperable Metastatic or Relapsed Colorectal Carcinoma Patients: a Phase II Study. Proc of BUON Congress, Radioter Oncol Med, 2000, 2:44S-55S, abst 116.
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Communications at National Scientific Meetings

1. Cristina Cebotaru: Toxicitatea indusa de chimioterapie in tumorile germinale; analiza pe cazuistica Institutului Oncologic Prof Dr Ion Chiricuta, Conferinta Nationala de Oncologie, Bucuresti, 2003.
2. Cristina Cebotaru: Rezultatele chimioterapiei in tumorile germinale cu risc crescut. Al 17-lea Congres al SRROM, Cluj Oct 2007
3. Rusu P, Ciuleanu TE, Cernea D, Cebotaru C, Iancu D, Guttman T, Ghilezan N: PCI 99-EULINT 1 – eligibility and noneligibility criteria (Trial International de iradiere craniana profilactica). Vol abstr., Conferinta Nationala de Oncologie Bucuresti, 23-24 Noi, 2001.
4. Rusu P, Ciuleanu TE, Cernea D, Cebotaru C, Iancu D, Roman D, Todor N, Ghilezan N: Vol abstr Conferinta Nationala de Oncologie, 23-24 nov 2001 Bucuresti.
5. Rusu P, Ciuleanu TE, Cernea D, Pelau D, Gaal V, Cebotaru C, Iancu D, Guttman T, Todor N, Ghilezan N: Chimio-radioterapia concomitenta urmata de chimioterapia de consolidare cu vinorelbina si cisplatin in carcinoamele bronhopulmonare non-small cell avansate locoregional. Prima Conferinta Nationala de Oncologie medicala, 11-14 aprilie, 2002, Caciulata.
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8. Rusu P, Ciuleanu TE, Cernea D, Pelau D, Gaal V, Cebotaru C, Guttman T, Todor N, Ghilezan N: Strategii chimioradioterapeutice in carcinoamele bronhopulmonare non small cell avansate locoregional - experienta Institutului Oncologic Prof Dr Ion Chiricuta. Zilele UMF `Iuliu Hatieganu` 8.12.2004.
9. Rusu P, Ciuleanu TE, Hica S, Cernea D, Cebotaru C, Guttman T, Hrab I, Grigore L, Todor N, Ghilezan N: Valoarea prognostica a invaziei limfatice ganglionare si implicatiile terapeutice la pacientii cu cancer bronho-pulmonar non-small cell. Zilele UMF Iuliuu Hatieganu, 3.12.2007 Cluj.