Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

Ifosfamide: la tossicità ematologica e delle mucose

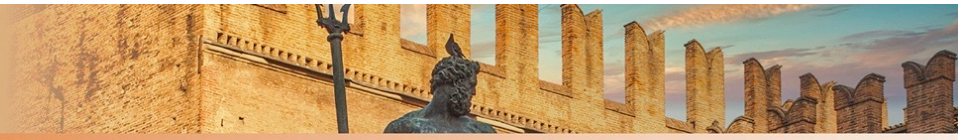
Silvia Cammelli

Radioterapia Oncologica, IRCCS Azienda Ospedaliero-Universitaria di Bologna;

Università di Bologna

Associazione Italiana Radioterapia e Oncologia clinica

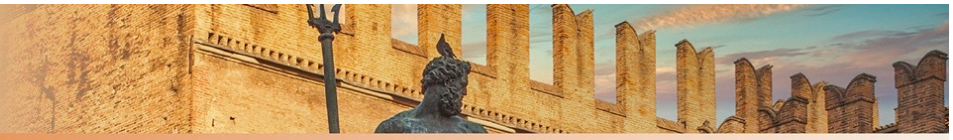
Società Italiana di Radiobiologia



DICHIARAZIONE

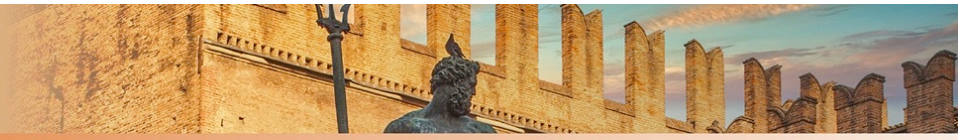
Relatore: Silvia Cammelli

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**



IFOSFAMIDE

- Alkylating drug
- Cyclophosphamide analogue with lower haematological toxicity, better therapeutic index
- Commonly used as first-line treatment for soft tissue and bone sarcomas, concomitant with other drugs (anthracycline, etoposide, vincristine)
- In testicular cancer, lung cancer and head-neck cancer can be used as a second or third line drug
- Always administered in association with MESNA (uroprotector)



IFOSFAMIDE

toxicity

- **Myelosuppression**
- Nausea and vomiting
- Hemorrhagic cystitis
- Alopecia
- Renal toxicity with tubular damage and even severe renal failure
- Neurological toxicity (convulsions , impairment of consciousness or capacity of thought)
- Sterility

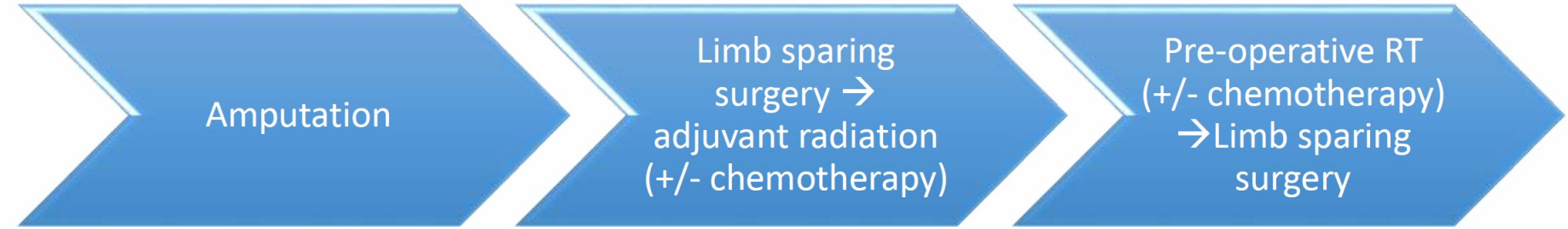
SOFT TISSUE SARCOMAS

GUIDELINES

NCCN National Comprehensive Cancer Network®

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Treatment evolution:



ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 4, pp. 1117–1127, 2003

0360-3016/03/$–see front matter

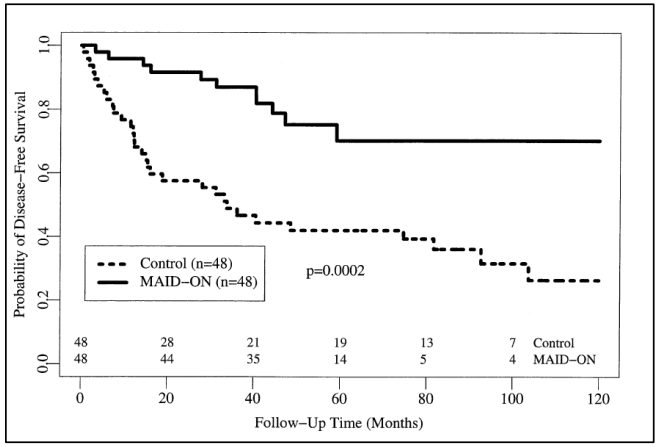
doi:10.1016/S0360-3016(03)00186-X

CLINICAL INVESTIGATION **Soft Tissues**

NEOADJUVANT CHEMOTHERAPY AND RADIOTHERAPY FOR LARGE EXTREMITY SOFT-TISSUE SARCOMAS

Thomas F. DeLaney, M.D.,* Ira J. Spiro, M.D., Ph.D.,* Herman D. Suit, M.D., D. Phil.,* Mark C. Gebhardt, M.D.,† Francis J. Hornicek, M.D., Ph.D.,† Henry J. Mankin, M.D.,† Andrew L. Rosenberg, M.D.,‡ Daniel I. Rosenthal, M.D.,§ Fariba Miryousefi, M.D.,* Marcus Ancukiewicz, Ph.D.,* and David C. Harmon, M.D.¶

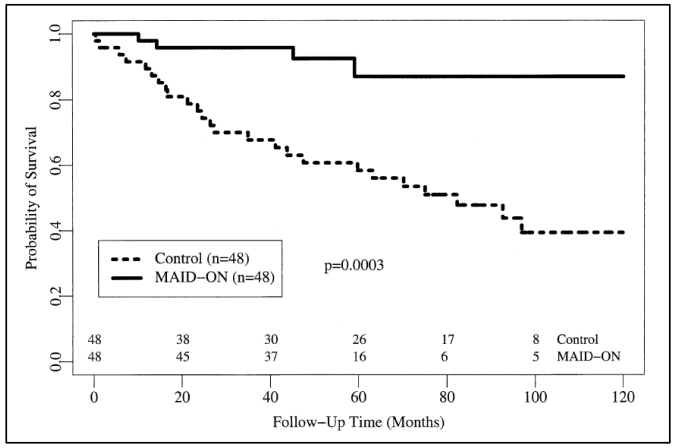
Departments of *Radiation Oncology, †Orthopedic Surgery, ‡Pathology, §Diagnostic Radiology, and ¶Hematology/Oncology, Massachusetts General Hospital, Boston, MA

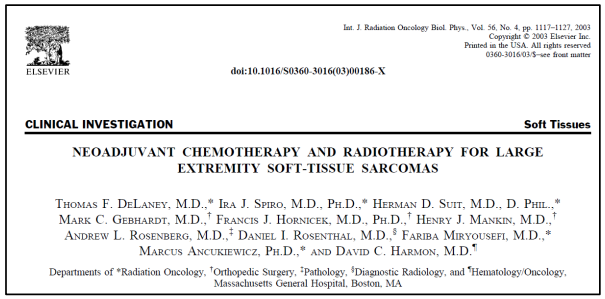


Pilot study
(48 vs 48 patients)

CHT: Ifosfamide (2000mg/m^2/day, days 1-3) + Doxorubicin (20mg/m^2/day, days 1-3)+ Dacarbazine (250mg/m^2/day, days 1-4)
+ RT (split course, 44 Gy)

Only RT (44 Gy)





Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 4, pp. 1117–1127, 2003

0360-3016/03/$–see front matter
ELSEVIER
doi:10.1016/S0360-3016(03)00186-X

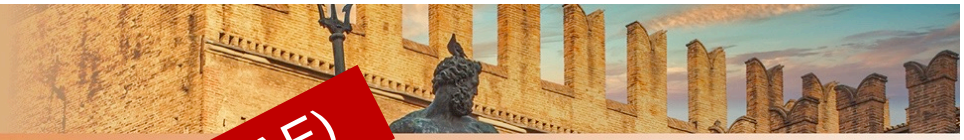
CLINICAL INVESTIGATION **Soft Tissues**

NEOADJUVANT CHEMOTHERAPY AND RADIOTHERAPY FOR LARGE EXTREMITY SOFT-TISSUE SARCOMAS

Thomas F. DeLaney, M.D.,* Ira J. Spiro, M.D., Ph.D.,* Herman D. Suit, M.D., D. Phil.,* Mark C. Gebhardt, M.D.,† Francis J. Hornicek, M.D., Ph.D.,† Henry J. Mankin, M.D.,† Andrew L. Rosenberg, M.D.,‡ Daniel I. Rosenthal, M.D.,§ Fariba Miryousefi, M.D.,* Marcus Ancukiewicz, Ph.D.,* and David C. Harmon, M.D.¶

Departments of *Radiation Oncology, †Orthopedic Surgery, ‡Pathology, §Diagnostic Radiology, and ¶Hematology/Oncology, Massachusetts General Hospital, Boston, MA

- Febrile neutropenia requiring hospital admission and antibiotics occurred in 12 patients **(25%)** at some point in their chemoradiation
- G-CSF was given to 39 patients (81.3%)
- Grade 1 (microscopic) hematuria was seen in 28 patients (58.3%)
- No data about the possible interruption of radiotherapy due to febrile neutropenia



VOLUME 24 · NUMBER 4 · FEBRUARY 1 2006
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Phase II Study of Neoadjuvant Chemotherapy
Radiation Therapy in the Management
High-Grade, Soft Tissue Sarcomas
Body Wall: Radiation Therap
oup Trial 9514

William G. Kraybill, Jonathon Harris, Ira
Thomas F. DeLaney, Ronald H. Bl
David R. Lucas, David C. Harmon,
on Eisenberg

Cancer
16(19): 4613–4621. doi:10.1

g-Term Results of
Chemotherapy
Risk, High
Bod
eoadjuvant
e Management of High-
arcomas of the Extre
and

Jonathan Harris, MS[2], Ira J.
vid S. Ettinger, MD[4],
y, MD[3], Ronald H. Blum, MD[5]
MD[6], David C. Harmon,
las Letson, MD[8], and Burton

Common Terminology Criteria for Adverse Events (CTCAE)

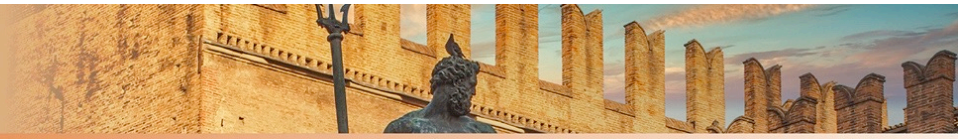
Grade 3: severe or medically significant but not immediatly life threating; hospitalization or prolongation of hospitalization indicates

Grade 4: Life-threatening consequences; urgent intervention indicated

64 Pati

- 59%
- d all planned
- notherapy cicles
- nematologi
- icity
- Gr 4 hemat
- gic toxicity (mainly leukopenia)

No data
the possible interruption of radiotherapy due t
ile neutropenia



Clinical Trial > Am J Clin Oncol. 2019 Jan;42(1):1-5. doi: 10.1097/COC.0000000000000467.

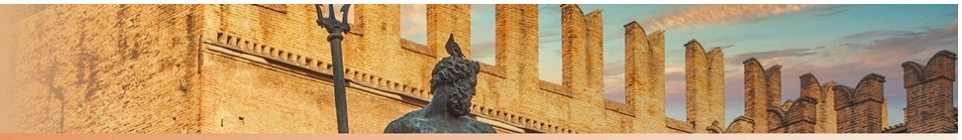
Neoadjuvant Interdigitated Chemoradiotherapy Using Mesna, Doxorubicin, and Ifosfamide for Large, High-grade, Soft Tissue Sarcomas of the Extremity: Improved Efficacy and Reduced Toxicity

Mudit Chowdhary [1], Neilayan Sen [1], Elizabeth B Jeans [1], Luke Miller [1], Marta Batus [2], Steven Gitelis [3], Dian Wang [1], Ross A Abrams [1]

26 adults with large G3 extremity STS between 2008 to 2016 underwent neoadjuvant chemoradiotherapy with 3 cycles of mesna, doxorubicin, and ifosfamide (MAI) and 44 Gy (22 Gy in 11 fractions between cycles of MAI)+ surgery+ 3 additional adjuvant cycles of MAI. Ifosfamide: 2000 to 2500 mg/m^2 on days 1 to 3, Doxorubicina: 30 to 37.75 mg/m^2 on days 1 and 2

Results: At a median follow-up of 47.3 months, no therapy-related deaths or secondary malignancies. 69.2% of patients experienced acute grade 4 hematologic toxicity. The nonhematologic G 4 toxicity rate was 7.7%

Conclusions: Neoadjuvant interdigitated MAI RT followed by resection and 3 cycles of adjuvant MAI has resulted in acceptable and manageable toxicity.



VOLUME 33 · NUMBER 31 · NOVEMBER 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Feasibility of Preoperative Chemotherapy With or Without Radiation Therapy in Localized Soft Tissue Sarcomas of Limbs and Superficial Trunk in the Italian Sarcoma Group/ Grupo Español de Investigación en Sarcomas Randomized Clinical Trial: Three Versus Five Cycles of Full-Dose Epirubicin Plus Ifosfamide

Elena Palassini, Stefano Ferrari, Paolo Verderio, Antonino De Paoli, Javier Martin Broto, Vittorio Quagliuolo, Alessandro Comandone, Claudia Sangalli, Emanuela Palmerini, Antonio Lopez-Pousa, Rita De Sanctis, Stefano Bottelli, Michela Libertini, Piero Picci, Paolo G. Casali, and Alessandro Gronchi

303 patients included in this analysis.

All received pre-op CHT (epirubicina + Ifosfamide)

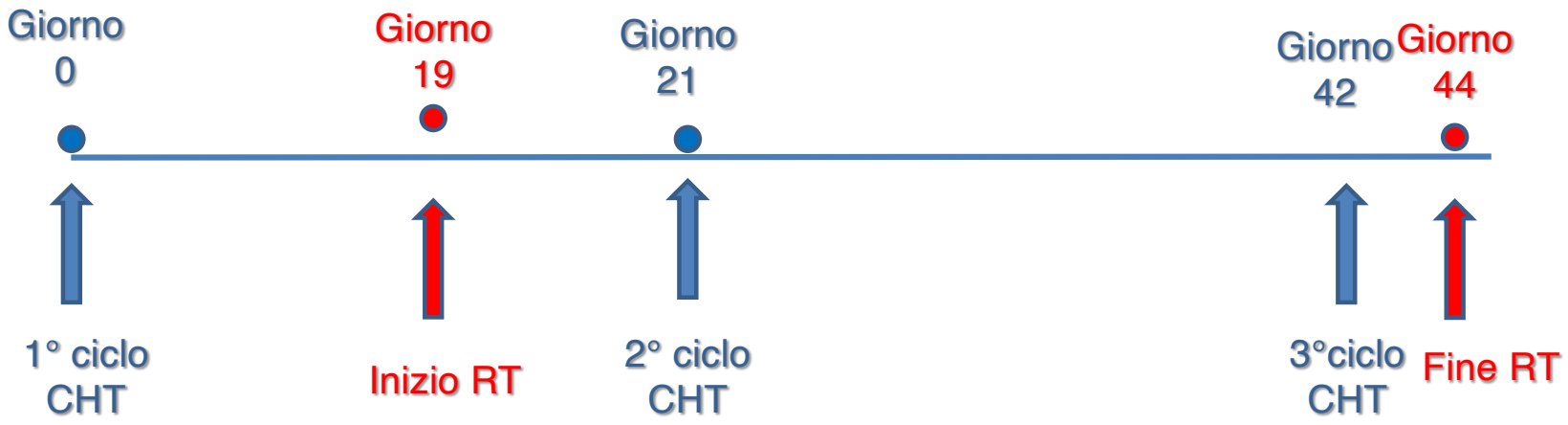
152 pt: concurrent RT preoperatively at a total dose of 44 to 50 Gy.

VOLUME 33 · NUMBER 31 · NOVEMBER 1 2015
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Feasibility of Preoperative Chemotherapy With or Without Radiation Therapy in Localized Soft Tissue Sarcomas of Limbs and Superficial Trunk in the Italian Sarcoma Group/ Grupo Español de Investigación en Sarcomas Randomized Clinical Trial: Three Versus Five Cycles of Full-Dose Epirubicin Plus Ifosfamide

Elena Palassini, Stefano Ferrari, Paolo Verderio, Antonino De Paoli, Javier Martin Broto, Vittorio Quagliuolo, Alessandro Comandone, Claudia Sangalli, Emanuela Palmerini, Antonio Lopez-Pousa, Rita De Sanctis, Stefano Bottelli, Michela Libertini, Piero Picci, Paolo G. Casali, and Alessandro Gronchi

Ifosfamide: 3000 mg/m2/day, days 1-3
Epirubicina: 60 mg/m2/day, days 1-2
Granulocyte stimulating factors: from day 7 to day 14

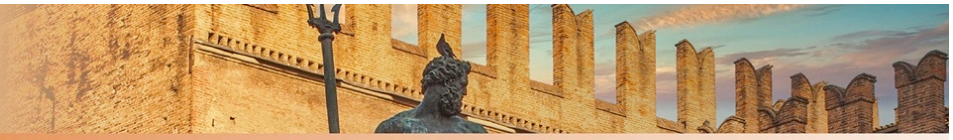


	Neutropenia Gr.3-4	Anemia Gr.3-4	Thrombo cytopenia Gr.3-4
TOT	61,4 %	22,4 %	23,8 %
CHT+ RT	*66,4 %*	*24,3 %*	*31,6 %*
CHT only	*56,4 %*	*20,5 %*	*15.9 %*

VOLUME 33 · NUMBER 31 · NOVEMBER 1 2015
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Feasibility of Preoperative Chemotherapy With or Without Radiation Therapy in Localized Soft Tissue Sarcomas of Limbs and Superficial Trunk in the Italian Sarcoma Group/ Grupo Español de Investigación en Sarcomas Randomized Clinical Trial: Three Versus Five Cycles of Full-Dose Epirubicin Plus Ifosfamide

Elena Palassini, Stefano Ferrari, Paolo Verderio, Antonino De Paoli, Javier Martin Broto, Vittorio Quagliuolo, Alessandro Comandone, Claudia Sangalli, Emanuela Palmerini, Antonio Lopez-Pousa, Rita De Sanctis, Stefano Bottelli, Michela Libertini, Piero Picci, Paolo G. Casali, and Alessandro Gronchi

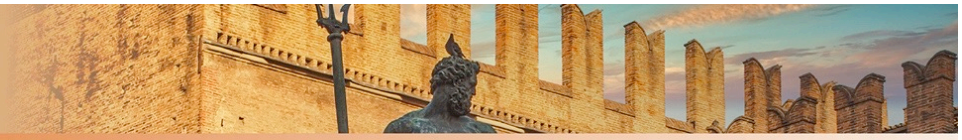


VOLUME 33 · NUMBER 31 · NOVEMBER 1 2015
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Feasibility of Preoperative Chemotherapy With or Without Radiation Therapy in Localized Soft Tissue Sarcomas of Limbs and Superficial Trunk in the Italian Sarcoma Group/ Grupo Español de Investigación en Sarcomas Randomized Clinical Trial: Three Versus Five Cycles of Full-Dose Epirubicin Plus Ifosfamide

Elena Palassini, Stefano Ferrari, Paolo Verderio, Antonino De Paoli, Javier Martin Broto, Vittorio Quagliuolo, Alessandro Comandone, Claudia Sangalli, Emanuela Palmerini, Antonio Lopez-Pousa, Rita De Sanctis, Stefano Bottelli, Michela Libertini, Piero Picci, Paolo G. Casali, and Alessandro Gronchi

- ✓ Results:... Chemotherapeutic Dose Intensity (DI) was greater than 90%, even in patients receiving preoperative RT and in patients age 65 years or older
- ✓ 15.2 % CHT dose reduction (41% pz. older than 65y had CHT dose reduction or interruption)

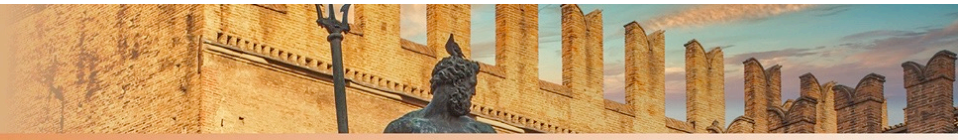


VOLUME 33 · NUMBER 31 · NOVEMBER 1 2015
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Feasibility of Preoperative Chemotherapy With or Without Radiation Therapy in Localized Soft Tissue Sarcomas of Limbs and Superficial Trunk in the Italian Sarcoma Group/ Grupo Español de Investigación en Sarcomas Randomized Clinical Trial: Three Versus Five Cycles of Full-Dose Epirubicin Plus Ifosfamide

Elena Palassini, Stefano Ferrari, Paolo Verderio, Antonino De Paoli, Javier Martin Broto, Vittorio Quagliuolo, Alessandro Comandone, Claudia Sangalli, Emanuela Palmerini, Antonio Lopez-Pousa, Rita De Sanctis, Stefano Bottelli, Michela Libertini, Piero Picci, Paolo G. Casali, and Alessandro Gronchi

✓…how many Patients had to stop radiotherapy?

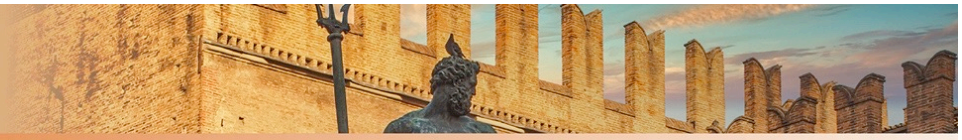


VOLUME 33 · NUMBER 31 · NOVEMBER 1 2015
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Feasibility of Preoperative Chemotherapy With or Without Radiation Therapy in Localized Soft Tissue Sarcomas of Limbs and Superficial Trunk in the Italian Sarcoma Group/ Grupo Español de Investigación en Sarcomas Randomized Clinical Trial: Three Versus Five Cycles of Full-Dose Epirubicin Plus Ifosfamide

Elena Palassini, Stefano Ferrari, Paolo Verderio, Antonino De Paoli, Javier Martin Broto, Vittorio Quagliuolo, Alessandro Comandone, Claudia Sangalli, Emanuela Palmerini, Antonio Lopez-Pousa, Rita De Sanctis, Stefano Bottelli, Michela Libertini, Piero Picci, Paolo G. Casali, and Alessandro Gronchi

- ✓simultaneous use of granulocyte stimulating factors and radiotherapy?



Contemp Oncol (Pozn). 2017;21(1):60-65. doi: 10.5114/wo.2017.66658. Epub 2017 Mar 22.

Neoadjuvant sequential chemoradiotherapy versus radiotherapy alone for treatment of high-risk extremity soft tissue sarcoma: a single-institution experience

Leyla Kılıç [1], Meltem Ekenel [1], Senem Karabulut [1], Fulya Ağaoğlu [2], Emin Darendeliler [2]

67 Patients:

34: neoadjuvant sequential chemoradiotherapy (2-3 cycles of doxorubicin and ifosfamide followed by **RT of 28 Gy administered as 8 fractions of 3,5 Gy** and 33 patients only RT.

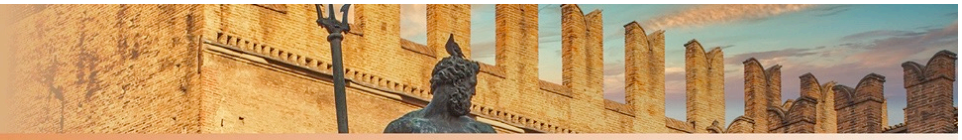
33 : Radiotherapy alone

Toxicity results:

- Leucopenia in 55% in the sequential treatment arm
- G4 toxicity in 26% of the patients.
- The most common non-haematological adverse events were nausea and/or vomiting (all patients).
- Dose reductions in 35% (n = 12) of the cases, mostly due to febrile neutropenia and G4 thrombocytopenia.
- In each arm, no RT interruptions

Conclusion:

Acceptable toxicity in both arms

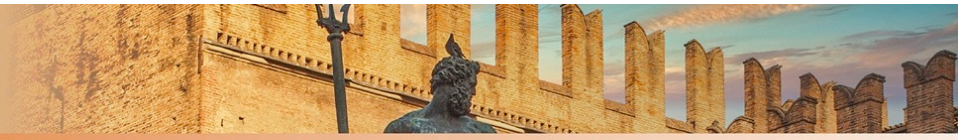


Conclusions:

- High toxicity with concomitant CHT + RT regimen (doxirubicin and ifosfamide)
- Possible concomitance but only within Clinical Trials and in Reference Centres

Open questions:

- Possible role of hypofractionated RT ? Better toxicity management?
- New drugs with lower toxicity profile?



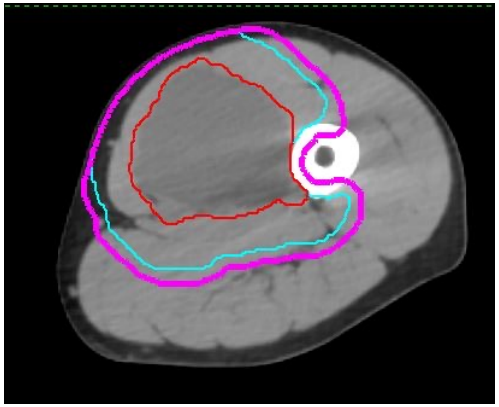
CLINICAL CASE

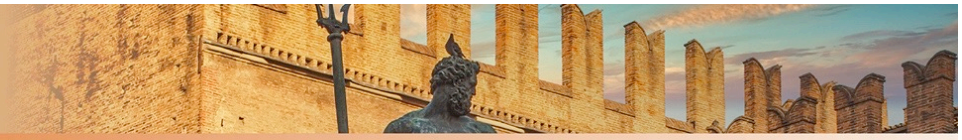
48 aa

Liposarcoma mixoide ad alto grado del terzo mediale della coscia dx (14X6X8 cm)

Stadiazione negativa per secondarismi

<u>Stadio: cT3N0M0 (IIIB)</u>





Meeting Multidisciplinare sarcomi: indicazione a trattamento chemio-radioterapico pre-operatorio

Prescrizione: **50 Gy in 25 frazioni + 3 cicli di CHT neoadiuvante**

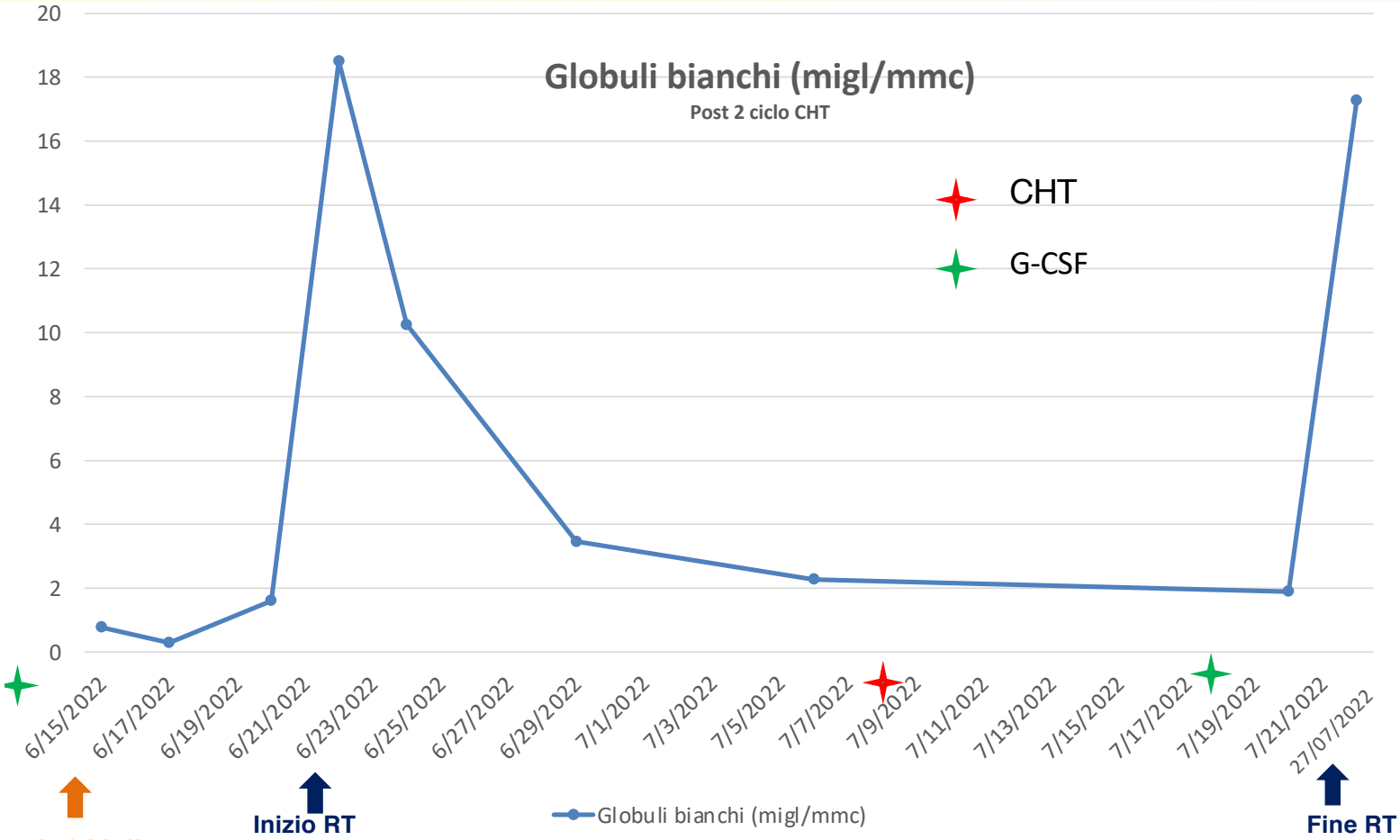
17/05/2022: 1° ciclo CHT (**ifosfamide 3 g/m2/die, gg 1,2,3+ doxorubicina 37.5 mg/m2/die, gg 1-2**)

06/06/22 visita radioterapica + TC centratura

07/06/2022 : 2° ciclo CHT (ifosfamide 3 g/m2/die, gg 1,2,3+ doxorubincina 37.5 mg/m2/die, gg 1-2)

08/07/22 3° ciclo (solo ifosfamide)

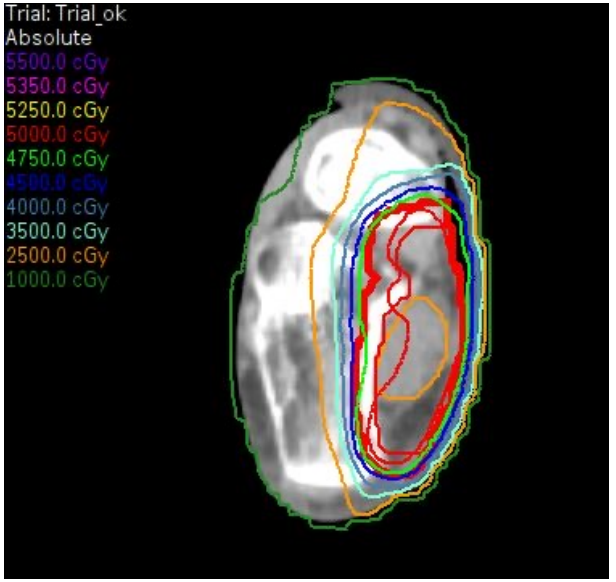
01/08 4 ciclo CHT solo doxorubicina


Globuli bianchi (migl/mmc)
Post 2 ciclo CHT
CHT
G-CSF
20
18
16
14
12
10
8
6
4
2
0
6/15/2022
6/17/2022
6/19/2022
6/21/2022
6/23/2022
6/25/2022
6/27/2022
6/29/2022
7/1/2022
7/3/2022
7/5/2022
7/7/2022
7/9/2022
7/11/2022
7/13/2022
7/15/2022
7/17/2022
7/19/2022
7/21/2022
27/07/2022
Neutropenia febbrile
Inizio RT
Globuli bianchi (migl/mmc)
Fine RT

Caso clinico 2

54 aa
Sarcoma sinoviale bifasico della regione mediale del piede sn (3.7 cm)
Stadiazione negativa per secondarismi
Discussa al MDT sarcomi con indicazione a radio-chemioterapia neoadiuvante.
22/06/22: 1 ciclo CHT (IFO + adria)
08/08/22: 3 ciclo CHT
08/08/22 Visita + TC di centratura
19/08/22 contattata la Paziente, fattori di crescita in corso
Fino al 24/08/22: ricovero per leucopenia febbrile
Emocromo del 27/08/22: GB 1970, Neutr 1020, Hb 9.6, PLT 321 000

29/08/22: inizio RT (prescrizione: 5000 cGy in 25 fx)
06/09/22: 7 seduta (1400 cGy)→ GB 1650, Neutr 900, Hb 10.1, PLT 346 000



Ritardo dell'inizio della RT in attesa di stabilità ematologica