ONCOLOGY DOSAGE TOOLS BASED ON THE STATISTICAL MODELS PROJECT (SMp) MODELS

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ABSTRACT
Purposes: 1) To establish a new methodology for evaluating efficacy and toxicity in chemotherapy (CTX) following the same probabilistic principles that have been used in the radiation oncology therapies (ROTs) in the tumor control/normal tissue complication probability (TCP/NTCP). In CTX, the sickness control probability (SCP) and a NTCP1 (NTCP for CTX) function of a dose of reference are proposed; 2) To establish a new methodology of dosage in CTX using optimal values of these proposed indices; 3) To provide SMp models for the stochastic processes (SPs) involved into the CTX; and 4) To develop simple computer tools using TCP, NTCP, SCP and NTCP1.
The following results were obtained: 1) Two Excel calculation sheets that determine the TCP and NTCP for the ROT using the SMp models; and evaluating until three organs at risk, as well as indices for a real CTX treatment, the SCP and NTCP1; and 2) SMp models for SPs involved in CTX.

KEYWORDS: TCP; NTCP; efficacy; toxicity; body surface area

MSC: 62P10

RESUMEN
Propósitos: 1) Establecer una nueva metodología para evaluar la eficacia y la toxicidad en la quimioterapia (CTX en inglés) siguiendo los mismos principios probabilísticos que se han utilizado en las terapias oncológicas con radiaciones (ROTs en inglés) en la probabilidad del control de tumores /complicación del tejido normal (TCP/NTCP en inglés). En CTX se proponen la probabilidad de control de la enfermedad (SCP en inglés) y NTCP1 (NTCP parar la CTX) función de una dosis de referencia; 2) Establecer una nueva metodología de dosificación en CTX utilizando valores óptimos de estos índices propuestos; 3) Proporcionar modelos SMp para los procesos estocásticos (PEs) involucrados en el CTX; y 4) Desarrollar herramientas informáticas sencillas que usan el TCP, NTCP, SCP y NTCP1.
Se obtuvieron los siguientes resultados: 1) Dos hojas de cálculo en Excel que determinan el TCP y NTCP para las ROTs utilizando los modelos SMp; y evalúa hasta tres órganos en riesgo, así como índices para un tratamiento real de CTX, el SCP y la NTCP1; y 2) modelos SMp para PEs involucrados en CTX.

PALABRAS CLAVES: TCP; NTCP; eficacia; toxicidad; área superficial del cuerpo

1. BACKGROUND

The statistical models project (SMp) is a modeling and simulation project based on the most appropriate treatment and modeling of many stochastic processes/effects (SP/Es) of fields, like the radiotherapy where the SMp has been initially applied.
The tumor control probability (TCP) and normal tissue complication probability (NTCP) are probabilistic metrics associated respectively with the efficacies and toxicities in the radiation oncology therapies (ROTs).
In whatever therapy, getting the major possible efficacy with the lees possible adversity effects are the most important objectives. Generally these are stochastic processes, which are uniquely measured in the ROTs through TCP and NTCP.
The ROTs are treatments involving use of high-energy radiation, while the chemotherapy (CTX) is a category of cancer treatment that uses chemical substances, especially one or more anti-cancer drugs that are given as part of a standardized CTX regimen. This therapy may be given with a curative intent, or it may aim to prolong life or to reduce symptoms (palliative CTX).
"Dosage of chemotherapy can be difficult: If the dose is too low, it will be ineffective against the tumor, whereas, at excessive doses, the toxicity (side-effects) will be lethal to the patient" [1]. "The standard method of determining chemotherapy dosage is based on calculated body surface area (BSA). This formula was originally derived in a 1916

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study and attempted to translate medicinal doses established with laboratory animals to equivalent doses for humans" [2]. "When chemotherapy was introduced in the 1950s, the BSA formula was adopted as the official standard for chemotherapy dosing for lack of a better option" [3]. "Several clinical studies have demonstrated that when chemotherapy dosing is individualized to achieve optimal systemic drug exposure, treatment outcomes are improved and toxic side effects are reduced" [4] and [5]. In the CTX, as in whatever clinical therapy, there are several clinical and technological factors, but one should consider the most important and interesting among them for planning the treatment.

Generally, the ROT treatments are regionally localized, while in CTX are systemic, for this reason the type of stochastic process associated with efficacy of these treatments are different. There are several similarities between ROT and CTX according to the following aspects: (a) there are malign cells that should be eliminated or treated before/after other clinical therapies, using aggressive factors directly into the target or administered to the patients; and (b) biological metrics can be used for measuring adversity effects and efficacy of the treatments.

In ROT and CTX treatments there are stochastic processes given the independent variables and their parameters are uncertain quantities, and they should be treated and evaluated by means of probability concepts. The final interests in the RT are the tumor control (TC) and normal tissue complications (NTCs), while in CTX they are mainly sickness control, NTCs and intolerable effects. This latter defines the free-lethal region where the treatments must be given. Although the TC and SC are associated with efficacy of the treatments, they have different probabilistic behaviors in function of their independent variables.

The SMp TCP and NTCP models in the ROT represent new models for the well-known radiobiological indices, while SMp SCP and NTCP1 will represent new models and new chemo-biological indices in CTX. The SCP is the sickness control probability, and NTCP1 is NTCP in CTX.

The recently SMp formulations in ROT, like in [6], have models and parameters mathematically simples and with strong macro-probabilistic foundations, which will allow extending to CTX.

The radiobiological indices TCP and NTCP can be used in ROT for evaluating and/or optimizing treatment planning how is described in [7]. The NTCP is associated with an organ at risk (OAR) or with a disease.

In this work we expect to extend TCP/NTCP-similar indices to CTX, encourage the use of methodologies that provide criteria about quantitative evaluations of sickness control and adverse effects or side effects in the CTX, and establishing a methodology for the dosage.

2. METHODS

2.1. The statistical models project.

The SMp has classified in three types (P1, P2 and P3) the behaviours of the mean values of the following SP/Es. P1: For values of the independent variable –In radiotherapy, the dose that is translated to absorbed energy- < a threshold value (TV) the process is 0%-deterministic, i.e. it will never occur. For values ≥ this threshold, the process is increased when the independent variable (IV) increases, from 0% to 100%, and is stochastic until a determined value of IV where the process becomes 100%-deterministic, i.e. it certainly occurs; P2: For values of IV < a TV, the process is 0%-deterministic; for values ≥ this threshold, the process is increased when IV increases, from 0% to a maximum value, and later it begins to decrease until 0%, at this point the process is 0%-deterministic when IV increases; and P3: For values of IV < a TV, the process is 100%-deterministic; with an increase of IV, it is stochastic and decreases from 100% to 0%, at this point the process is 0%-deterministic when IV increases.

An example of application of the SMp P1, P2 and P3 is: The mean behaviors for several homogeneous populations Vs. Different levels of alcohol in blood follow these three SP/Es, for respectively death alcohol poisoning, sub-lethal damage, and without effects.

Let us do the following physic-probabilistic analysis: "The dosage in the ROTs is limited in the small values by the ineffective treatments or tumor control, while in the major ones by the normal tissue complications. The dosage in the CTX is limited by the ineffective treatments or sickness control, while in the major ones by the normal tissue complications and ineffective treatments too". Just the previously said represents typical or similar descriptions of stochastic processes SMp type P1 in the ROT, and type P2 in the CTX.

3. RESULTS

3.1. Applied statistics in the radiotherapy.

The SMp proposes a TCP and NTCP model based on the SP/Es SMp type P1 as

For TCP:

$$SMp\ TCP(Dmin) = \left(\frac{Dmin-TTDmin}{TTDmax-TTDmin}\right)^{pT} \qquad TTDmin \le Dmin \le TTDmax \tag{1}$$

where,

TTDmin: Threshold value for TCP

TTDmax: Minimum Dmin for TCP=100%

pT: Power of the SMp TCP model (*pT>0*)

Dmin: Total minimum dose in the tumor region

SMp TCP is respectively 0% and 100%-deterministic in *Dmin< TTDmin* and *Dmin>TTDmax*. For multiple tumors, *TCP= min (TCP$_i$)*, where TCP$_i$ is TCP for each individual tumor. The SMp TCP(*Dmin*) is a probabilistic function,

where TCP increases when *Dmin* increases, and takes values in the interval [0%;100%].

In [6] the NTCP model was formulated for the most critic End-Points, i.e. Grade *Xmax* (*Xmax*: maximum of x) or global complication, i.e. Grade ≥ x of an organ at risk (OAR)

$$SMp\ NTCP(Dref) = \left(\frac{Dref-TDmin}{TDmax-TDmin}\right)^{pN} \qquad TDmin \le Dref \le TDmax \tag{2}$$

where, *TDmin*: Threshold value of *Dref* for an End-Point with Grade ≥ x

TDmax: Minimum *Dref* for NTCP=100%;

pN: Power of this model *(pN>0)*

Dref: Dose of reference, like maximum dose in the normal tissue.

SMp NTCP is respectively 0% and 100%-deterministic in *Dref< TDmin* and *Dref>TDmax*. For multiple OARs, NTCP= max (NTCP$_i$), where NTCP$_i$ is NTCP for each individual OAR.

The SMp will provides pure probabilistic functions suitable of describing and predicting many SP/Es in order for simplifying, doing more precise, and unifying the treatments and models for these SP/Es through calculation methodologies using mechanistic-probabilistic models or simulation tools.

3.2 The SMp in Chemotherapy

Contrary to ROTs, where the tumor control is a SP/E type P1, in CTX the process of sickness control is generally a stochastic process type P2; and the same kind type P1 for both concerning the normal tissue complications.

The stochastic processes related to CTX treatments are: lethal effect (LE), cured patient (CP), ineffective treatment (IT) where there are toxicities, but the patient is not completely cured; and undamaged patient (UP) here the dose-response is null. These processes depend of the dose employed, and are probabilistically related as

$$LE + CP + IT + UP = 100\% \tag{3}$$

From the Eq. (3), the *CP* is always ≤ *100%-LE-IT-UP*

Due to CTX treatments can be given with one or more drugs, the mathematical relationship between dose-response and dose of reference (Dref) should be established with the dose of one of them as the Dref.

3.2.1. The SMp normal tissue complication in CTX, SMp NTCP1 (Dref)

The normal tissue complication can be considered generally as a stochastic processes type P1, therefore the new proposed NTCP1 model is ~~are~~ defined for End-Points associated with the total complication, i.e. Grade Xmax (Xmax: maximum value of x) or global complication, i.e. Grade ≥ x of an OAR or disease as

$$SMp\ NTCP1 = \left(\frac{Dref-CDmin}{CDmax-CDmin}\right)^{pN1} \quad CDmin \le Dref \le CDmax \tag{4}$$

where, *CDmin*: Threshold value of *Dref,* which produces an End-Point Grade ≥ x

CDmax: Minimum value of *Dref* for NTCP1=100%.

pN1: Power in the SMp NTCP1 model (pN1>0)

Dref: Dose of reference.

SMp NTCP1 is respectively 0% and 100%-deterministic in *Dref< CDmin* and *Dref>CDmax*.

3.2.2. The SMp lethal effect in CTX, SMp LE(Dref)

While NTCP1 is associated with complication for a specific OAR or disease, the lethal effect (LE) is associated with lethal damages, and if it is considered as a SP/E type P1 its SMp expression is

$$SMp\ LEP = \left(\frac{Dref - LDmin}{LDmax - LDmin}\right)^{pL} \quad LDmin \leq Dref \leq LDmax \tag{5}$$

where LDmin: Threshold value of *Dref,* which produces a lethal effect (LE)
LDmax: Minimum value of *Dref for* LE=100%.
pL: Power in this model (*pL*>0)
Dref: Dose of reference.
LEP: Lethal effect probability
SMp LE is respectively 0% and 100%-deterministic in *Dref*< *LDmin* and *Dref*>*LDmax*.

3.2.3. The SMp undamaged patient in CTX, SMp UP(Dref)

The undamaged patient (UP) of a CTX treatment can be considered as a SP/E type P3, so its SMp model is expressed as

$$SMp\ UPP = \left(\frac{UDmax - Dref}{UDmax - UDmin}\right)^{pU} \qquad UDmin \leq Dref \leq UDmax \tag{6}$$

where, *UDmin:* Maximum value of *Dref* for UP=100%
UDmax: Minimum value of *Dref* for UP=0%.
pU: Power in this model (*pU*>0)
Dref: Dose of reference.
UPP: Uncured patient probability

SMp UP is respectively 100% and 0%-deterministic in *Dref*< *UDmin* and *Dref*>*UDmax*.

3.2.4. The SMp ineffective treatment probability in CTX, SMp IT(Dref)

The cell sub-lethal damage has been modeled based on SP/E type P2 in [8]. The formulation of ineffective treatment (IT) model has the same foundation, so this is defined as

$$SMp\ ITP = \begin{cases} \left(\frac{Dref - ITDmin}{MLIT - ITDmin}\right)^{p1IT} MIT & ITDmin \leq Dref \leq MLIT \\ \left(\frac{ITDmax - Dref}{ITDmax - MLIT}\right)^{p2IT} MIT & MLIT \leq Dref \leq ITDmax \end{cases} \tag{7}$$

where, *ITDmin*: Threshold value of *Dref* for an IT. *ITDmin=UDmin*
MLIT: Dref with the most likelihood of occurrence of an IT
ITDmax: Upper limit value of *Dref* for which an IT **is** produced. *ITDmax=LDmax*
MIT: Maximum probabilistic of IT
p1IT and *p2IT*: Powers in this model (*p1IT*>0 and *p1IT*>0)
Dref: Dose of reference.
ITP: Ineffective treatment probability
SMp IT is 0%-deterministic in *Dref*< *ITDmin* and *Dref*>*ITDmax*.

3.2.5. The SMp sickness control probability in CTX, SMp SCP(Dref)

The SCP model is equivalent to TCP one in the ROT. This new proposed model is determined according to the stochastic process type P2, and defined as

$$SMp\ SCP = \begin{cases} \left(\frac{Dref - SDmin}{MLS - SDmin}\right)^{p1S} MET & SDmin \leq Dref \leq MLS \\ \left(\frac{SDmax - Dref}{SDmax - MLS}\right)^{p2S} MET & MLS \leq Dref \leq SDmax \end{cases} \tag{8}$$

where, *SDmin*: Threshold value of *Dref* for a SC. *SDmin* ≥ *ITDmin*
MLS: Dref with the most likelihood of occurrence of a SC
SDmax: Upper limit value of *Dref* for which a SC is produced. *SDmax* ≤ *ITDmax*
MET: Maximum efficacy of the treatment
p1S and *p2S*: Powers in this model (*p1S*>0 and *p2S*>0)
Dref: Dose of reference.
SCP: Sickness control probability
SMp SCP is 0%-deterministic in *Dref*< *SDmin* and *Dref*>*SDmax*.

The CTX treatments must be given in regimens for 0% of lethal effects; and where the efficacy increases; i.e. *Dref*< *LDmin* and *Dref* ≤ *MLS*, i.e. *Dref* ≤ *min (LDmin, MLS)*. For this reason, the practical importance for these treatments is only at the first step of the function in Eq. (8) .

3.3. Oncology dosage tools

Two Excel calculation sheets were developed by this study, which are available in https://gitlab.com/tfrometa/ODtools.git. The example of a CTX treatment taken from [9] was used for showing the new methodology of dosage in the CTX using SMp models.

3.3.1. Reproducibility

a) For dosage in ROTs based on the SMp TCP and NTCP models

The Code uses the Eq. (1) and Eq. (2) for respectively TCP and NTCP calculations. The input cells appear in yellow for these calculations; and in orange for treatment information; and the outcomes in green. For SMp TCP calculations, one should enter values of its parameters, while for the NTCP one can introduce information of until three OARs and End-points, as well as their respective SMp parameters. The reported values of TCP and NTCP allow evaluations/optimizations of real ROTs.

b) For dosage in CTX based on the SMp models, and assuming pN1=1 and p1S=p2S=1

This uses the Eq. (4) and (8) for respectively NTCP1 and SCP calculations. Given the practical importance for CTX treatment is where efficacy increases, the Eq. (8) is used only its first step. At the sheet, the input cells appear in yellow for SCP and NTCP1 calculations; in orange for patient and treatment information; and in light blue for BSA. The outcome cells appear in green for SCP and NTCP1, while in blue for BSA, which is a reference in the current CTX dosages. For SMp SCP calculations, one should enter values of its parameters, while for NTCP1 one can introduce information of until three OARs and End-points, as well as their respective SMp parameters. The reported values of SCP and NTCP1 allow quantitative evaluations/optimizations of real CTX treatments.

4. DISCUSSION

The similarities between ROT and CTX allow applying the same SMp methodologies in the latter. New probabilistic-mechanistic models for chemo-biological indices: Sickness control/normal tissue complication probabilities 1 (SCP/NTCP1) are formulated for evaluating respectively efficacy and toxicity in CTX.
Contrary to ROT where the tumor control is a stochastic process SMp type P1, in CTX the processes of sickness control is generally a SMp type P2.
The new SMp models can be used for dosage based on quantitative-probabilistic values of efficacy and toxicity in CTX.
The SMp can be extended to other CTX-similar clinical therapies, like the treatments using antibiotics. It is very important identifying the type of stochastic process for the sickness control in whatever therapy.

5. CONCLUSIONS

The proposed indices in CTX will represent an extension of good ROT-practices, where its stochastic processes efficacy and toxicity will be appropriately evaluated using probabilistic metrics. These evaluations will let establishing a new methodology of dosage that will use optimal values of the new indices.
This work developed a macro-probabilistic study on stochastic processes involved in the CTX treatments, and simple computer tools for evaluating and optimizing treatment in ROT and CTX.
The new SMp model parameters in CTX have a high level of familiarization, and many of them are associated with chemo-biological concepts.
The SMp NTCP1 and SCP models were formulated under assumptions that they were SP/Es P1 and P2 respectively. For this reason, it is recommended using real data of CTX, which will allow corroborating these assumptions or defining precise forms of the quoted formulations.

RECEIVED: AUGUST, 2018.
REVISED: DECEMBER, 2018.

REFERENCES

[1] CORRIE, P.G. and PIPPA, G. (2008): Cytotoxic chemotherapy: clinical aspects. **Medicine**. 36, 24–28.

[2] DU BOIS, D. and DU BOIS, E.F. (1916): A formula to estimate the approximate surface area if height and weight be known. **Archives Internal Medicine**; 5, 303–131.

[3] KAESTNER, S.A. and SEWELL, G.J. (2007): Chemotherapy dosing part I: scientific basis for current practice and use of body surface area. **Clinical Oncology***;* 19, 23–37.

[4] GAMELIN, E.C., DELVA R., JACOB J., et al. (2008): Individual fluorouracil dose adjustment based on pharmacokinetic follow-up compared with conventional dosage: Results of a multicenter randomized trial of patients with metastatic colorectal cancer. **J ClinOncol**, 26, 2099–2105.

[5] CAPITAIN, O., ASEVOAIA A., BOISDRON-CELLE M., ET AL. (2012): Individual Fluorouracil Dose Adjustment in FOLFOX Based on Pharmacokinetic Follow-Up Compared With Conventional Body-Area-Surface Dosing: A Phase II, Proof-of-Concept Study. **ClinColorectalCancer**, 11. 263–267.

[6] FROMETA-CASTILLO, T. (2017): The Statistical Models Project (SMp) Normal Tissue Complication Probability (NTCP) Model and Parameters. **American Journal of Applied Mathematics and Statistics**; 5, 115-118.

[7] FROMETA-CASTILLO, T. and FROMETA-LEON, E. (2017): The statistical models project (SMp) in optimization of radiotherapy treatments. **International Journal of Radiology & Radiation Therapy**; Available in http://medcraveonline.com/IJRRT/IJRRT-04-00089.pdf

[8] FROMETA-CASTILLO, T. (2017) The Statistical Models Project (SMp) for evaluation of biological radiation effects. **American Journal of Applied Mathematics and Statistics**. 5, 119-124.

[9] GURNEY, H. (2002): How to calculate the dose of chemotherapy. **British Journal of Cancer**; 86, 1297–1302.