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Serum Tumor Markers: Comparison between Guidelines and the Clinical Practice in a University Hospital Center

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Abstract

Background: Among the different existing serum tumor markers (TM), none fulfills criteria for a clinical practice in screening, diagnosis, prognosis, targeted therapy and follow-up, due to a weak sensitivity and specificity. Guidelines from different national and international expert groups in cancer have been edited relating to the best use of those serums TM for a given cancer.

The goal of our study was to evaluate the pattern of serum TM used in our University Hospital Center and to determine whether their prescriptions were appropriate related to those guidelines.

Methods: We analyzed all the prescriptions including at least one serum TM among CEA (carcino-embryonic antigen), CA (carbohydrate antigen or cancer antigen) 125, CA15-3, CA19-9, NSE (neuron-specific enolase) and Cyfra 21-1 recorded in our biochemistry department between June 2012 and June 2013. For each prescription, we determined the clinical department, the use of the serum TM (diagnostic phase or follow-up), the serum TM and their number.

Results: We analyzed 1682 serum TM among 778 prescriptions. Whatever the medical or surgical department, CEA and CA19-9 were the two most prescribed TM corresponding to 29.8% and 25.4% of all assays, respectively. However, we noticed a more targeted prescription of TM for departments with an oncology activity. We also observed that serum TM was mainly used for diagnosis in about 2/3 of cases, which isn't consistent with national and international guidelines.

Conclusion: Oncologists have a targeted use of serum TM which enables a better rationalization of prescriptions while non-oncologists are less experienced resulting in multiple TM prescriptions for unrelated cancers. Discrepancies regarding the use of serum TM among national and international guidelines still exist; this requires a harmonization for a better clinical care of cancer patients with a lower medical expenditure.

Keywords: Serum tumor marker; Guidelines; Cancer diagnosis; Cancer follow-up

Abbreviations:

TM: Tumor marker; CEA: Carcinoembryonic Antigen; PSA: Prostate-Specific Antigen; AFP: Alpha-Fetoprotein; NSE: Neuron-Specific Enolase; NACB: National Academy Of Clinical Biochemistry; ASCO: American Society of Clinical Oncology; EGTM: European Group on Tumor Markers; HAS: Haute Autorité de Santé.

Introduction

According to the World Health Organization, cancers figure among the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012 and it is expected that annual cancer cases will rise from 14 million to 22 within the next 2 decades [1]. In this context, early diagnosis, targeted therapy and efficient follow-up are critical to reduce cancer deaths. Among the available tools for oncologists, biological markers are of great interest. They consist in molecules (proteins, glycolipids, glycoproteins, nucleic acids) that are produced by cancer cells and can be detected or quantified on biopsy materials or in body fluids (blood, urine, ascite etc.). As they do not require invasive procedure (i.e. biopsy) and they have been broadly used, we will focus our attention only on serum tumor markers (TM). The ideal serum TM must fulfill the following criteria: a) to be highly specific for a given tumor type b) to be sensitive enough to enable an early detection of the tumor development before clinical signs c) its level should be correlated with the tumor burden. In this case, it could be used for several applications including screening, diagnosis, staging, monitoring the treatment and relapse [2]. Unfortunately, this kind of serum TM doesn't exist since those molecules are also produced by non-tumor cells (but to a lower level than tumor cells), in cancerous conditions their level may not be increased, and conversely in healthy people or in other non-cancerous conditions (tobacco for carcinoembryonic antigen(CEA), ascites for CA125 (CA: carbohydrate

antigen or cancer antigen), pregnancy for alpha-fetoprotein (AFP)) their level can be measured above the upper reference level [3].

However, despite those limitations, the serum TM has been widely used by physicians to help them in their clinical setting. To enable a better practice and data interpretation, several guidelines have been published for the different serum TM from different scientific societies or governmental agencies; The National Academy of Clinical Biochemistry (NACB) published the laboratory medicine practice guidelines for the use of tumor markers in the clinic [4], the american society of clinical oncology (ASCO) and the european group on tumor markers (EGTM) published several guidelines for different cancers (see their web sites, http://www.instituteforquality.org/practice-guidelines and http://www.egtm.eu/, respectively). In France, the « haute autorité de santé » (HAS), which is a governmental agency, also proposed recommendations for using serum TM (see the web site, http://www.has-sante.fr/portail/jcms/fc_1249601/fr/evaluation-recommandation). However, national and international guidelines, whose roles are to provide clear advices to physicians for a better care of patients, are sometimes heterogeneous (Table 1). Furthermore, those recommendations should also contribute to control costs in a responsible public policy [5].

Cancer type		EGTM	ASCO	HAS
Breast	CA 15-3	D : + ; F : + (NI)	D : + ; F : - (2007)	D : - ; F : - (2010)
	CEA	D : + ; F : + (NI)	D : + ; F : - (2007)	D : - ; F : - (2010)
Ovarian	CA 125	D : + ; F : + (2012)	NC	D : + ; F : + (2010)
Colorectal	CEA	D : + ; F : + (2012)	D : + ; F : + (2008)	D : + ; F : + (2012)
	CA 19-9	D : - ; F : - (2012)	D : - ; F : - (2008)	D : - ; F : - (2012)
Gastric	CEA	D : - ; F : - (2012)	NC	D : - ; F : - (2014)
	CA 19-9	D : - ; F : - (2012)	NC	D : - ; F : - (2014)
Pancreatic	CA 19-9	D : + ; F : + (2012)	D : + ; F : + (2008)	D : - ; F : + (2010)
Lungs	NSE	D : + ; F : + (2012)	NC	D : - ; F : - (2013)
	Cyfra 21-1	D : + ; F : + (2012)	NC	D : - ; F : - (2013)
	CEA	D : + ; F : + (2012)	NC	D : - ; F : - (2013)
Liver	AFP	NC	NC	D : + ; F : + (2010)
Prostate	PSA	D : + ; F : - (2012)	D : +* ; F : + (2015)	D : + ; F : - (2012)

D: diagnostic phase; F: follow-up; +: recommended; -: not recommended; NC: no recommendation; NI: not indicated; *recommendation from the American Cancer Society. EGTM: European Group on Tumor Markers; ASCO: American Society of Clinical Oncology; HAS: Haute autorité de santé. In bracket, the year of the guideline publication is indicated.

Table 1: Summary of selected guidelines for the use of tumor markers in cancers.

Nowadays, public hospitals undergo more and more pressure to reduce health expenditures especially in biology. Furthermore, biologists are asked to provide advices about biological marker prescriptions including serum TM in order to reduce financial costs. So, in the present study we addressed the question about the serum TM prescriptions in our tertiary hospital and which recommendations for that serum TM were followed by physicians.

Materials and Methods

In order to rationalize the prescriptions of serum TM, we designed an observational and retrospective study at the university hospital center of Caen (Normandy, France). Our tertiary hospital is composed of medical and surgical specialized units. Using the biochemistry laboratory database, we analyzed all the prescriptions including one marker among CA 15-3, CA125, CA 19-9, CEA, NSE (neuron-specific enolase), Cyfra 21-1 (cytokeratin-19 fragments) between June 2012 and June 2013 except from the pediatric and the occupational medicine departments. All serum TM was analyzed on a Cobas e411 (Roche).

For each prescription, we determined the serum TM requested by clinicians, the clinical context (diagnosis or follow-up) and the clinical department.

In order to calculate the cost of such biological assays, we used the classification of the French health care system (nomenclature des actes de biologie médicale, ww.codage.ext.cnamts.fr/codif/nabm//chapitre/index_chap.php?p_ref_menu_code=28&p_site=AMELI).

Results

Over a period of one year, we listed 778 prescriptions with a total of 1682 assays of serum TM. Among the eight serums TM that we analyzed, CEA and CA19-9 were the most ordered with a frequency of about 30 and 25%, respectively (Table 2). When considering the main reason for TM prescription, we found that in most of the cases they were ordered for diagnosis when clinicians were suspicious of cancer; this was true for CA125, AFP, Cyfra 21-1 and PSA (prostate-specific antigen) with a frequency of more than 90% (Table 2). Regarding CA15-3, CA19-9, CEA and NSE, they were also prescribed for the

follow-up of cancer patients with a frequency ranging from 19.4 to 30.5% (Table 2). Then, we examined the major prescriber for each serum TM among 31 medical and surgical departments including the prison centre and the establishment of accommodation for dependent old persons (EADOP). As expected, hepatogastro-enterology department was the major prescriber of CEA, CA19-9 and AFP while the department of pneumology selectively ordered NSE and Cyfra 21-1 (Table 2). Surprisingly, internal medicine was the most important prescriber of CA15-3 and PSA.

	CA125	CA15-3	CA19-9	CEA	AFP	NSE	Cyfra 21-1	PSA
Number of assays (%)	115 (6.8%)	140 (8.3%)	428 (25.4%)	501 (29.8 %)	169 (10.0 %)	199 (11.8 %)	32 (1.9%)	98 (5.8%)
Cost (euros)	1863	2079	6934	7440	2875	4245	778	1085
Diagnosis (% of total)	93	76.4	80.6	78.9	94.7	69.5	97	91.8
Follow-up (% of total)	7	23.6	19.4	21.1	5.3	30.5	3	8.2
Major prescriber	Visceral surgery	Internal medicine	Hepatogastro enterology	Hepatogastro enterology	Hepatogastro enterology	pneumology	pneumology	Internal medicine

Table 2: Summary of the serum TM prescribed, their frequency, their use, their cost and the major prescriber.

As the health expenditures are rising and represent a major issue for the health system, we evaluated the global costs of all serum TM assays, based on the nomenclature of the health insurance, by 27297 Euros/year with CEA and CA19-9 representing about half of those expenditures (Table 2).

In the second part of this work, we examined the prescriptions from the different departments of our hospital. Clearly, we can distinguish frequent from occasional prescribers. Hepatogastro-enterology, pneumology, visceral surgery, internal medicine and neurology departments were the 5 most important prescribers with a prescription number ranging from 36 to 164 (Table 3). They represent 66% of the total prescriptions (514/778) and 63% of the total number of TM assays (1055/1682). Similarly, we identified the 5 departments with the lowest prescription number (1-2/year): addictology, hematology, EADOP, ENT (ear, nose and throat) and prison centre (Table 3).

Department	Prescription (No.)	Serum TM (No.)	Department	Prescription (No.)	Serum TM (No.)
Hepatogastro-enterology	164	353	Addictology	2	5
Pneumology	129	163	Hematology	2	8
Visceral surgery	103	240	EADOP	2	2
Internal medicine	82	197	ENT	1	1
Neurology	36	102	Prison centre	1	1
EADOP : Establishment of accommodation for Dependent Old Persons; ENT : Ear, Nose and Throat department					

Table 3: Identification of medical and surgical departments with the highest and the lowest prescription number/year.

Finally, we listed the different departments using the ratio serum TM number/prescription as an index of targeted prescription (Table 4); this index ranges from 1.3 to 4. As depicted in the Table 4, the majority of prescriptions from the pneumology department correspond to the NSE assay only. In contrast, more the index increases lesser is the prescription targeted (i.e. hematology department with a TM/P index of 4) ; in this case, CA19-9 and CEA represent the most prescribed TM in association with AFP or CA15-3 (Table 4).

Discussion

The goal of our study was to determine how serum TM were used by both oncologists and other medical and surgical specialists in our tertiary hospital since we had observed that some prescriptions included several TM for unrelated cancers (sometimes more than 4 TM per prescription). We showed that CEA and CA19-9, corresponding to about 55% of the total request, were the major serum TM prescribed for cancer diagnosis and mainly by the hepatogastro-enterology department as expected. When looking both at national (HAS) and international guidelines (ASCO and EGTM) (Table 1),

CEA but not CA19-9 is recommended for both diagnosis and follow-up of colorectal cancer. So, our data suggest that CA19-9 prescriptions are probably inappropriate in regards to the French and international guidelines. When regarding the two other digestive system cancers (Table 1), those guidelines are less homogeneous. For instance, for the gastric cancer the ASCO don't propose any recommendation while the EGTM and the HAS don't recommend the use of either CEA or CA19-9 for diagnosis and follow-up. Regarding the pancreas cancer, we noticed discrepancies between national and international guidelines: CA19-9 is not recommended by the French agency HAS for diagnosis contrasting with the american (ASCO) and the european (EGTM) guidelines (Table 1). Such heterogeneity among guidelines about the use of serum TM, which was previously reported [6], may explain their inappropriate prescriptions by physicians. Differences between guidelines also exist for other TM such as PSA. While ASCO, EGTM and HAS recommend using the PSA for diagnosis (Table 1), there are contradictory data about using this serum TM for screening [7,8]. In the present paper, we deliberately did not mention other scientific societies who also published clinical practice guidelines for cancers including serum TM (National Institute for Health and Clinical Excellence in United Kingdom and The European Society for Medical Oncology, see web sites https://www.nice.org.uk/ and http://www.esmo.org/, respectively). Such different and sometimes discordant guidelines between scientific societies may cause some confusion for physicians and may contribute to erroneous prescription of TM. It's surprising that such different guidelines for the use of serum TM exist between scientific societies and therefore harmonization would be necessary.

In our tertiary hospital, we also observed that oncologists had a targeted prescription of serum TM evidenced by a low TM/prescription ratio (TM/P) (Table 4). For instance, the pneumology department prescribes mainly NSE with a TM/P of 1.3. For two other departments with a strong activity in oncology, hepatogastro-enterology and visceral surgery, we also noticed an appropriate prescription, revealed by a high level of CEA and CA19-9, with a TM/P ratio of 2.2-2.3. When considering other departments less familiar with oncology, such as neurosurgery or surgical intensive care, we observed prescriptions of the different TM with almost similar level (between 10-20%) and a higher TM/P ratio. This probably reflects a different use of TM; those biological markers are notably used in patients with a loss of body weight and condition or metastasis to find the primary tumor. However, a critical interpretation of those data should be made since it's highly difficult to compare departments with such a different activity (i.e., 2 and 7 prescriptions for hematology and surgical intensive care vs. 129 and 164 for pneumology and hepatogastro-enterology) (Tables 3 and 4).

Department	Presc No.	TM/P	CA125	CA153	CA19-9	CEA	AFP	NSE	Cyfra 21-1	PSA
Pneumology	129	1.3	3.1%	8.6%	1.8%	3.1%	4.9%	**70.5%**	1.9%	6.1%
Hepatogastro-enterology	164	2.2	2.6%	1.4%	**40.5%**	**39.1%**	10.2%	2.5%	0.6%	3.1%
Visceral surgery	103	2.3	7.9%	4.6%	**37.5%**	**37.5%**	8.7%	1.7%	0.4%	1.7%
Internal medicine	82	2.4	7.6%	12.7%	**20.8%**	**30%**	7.6%	7.1%	4.1%	10.1%
Cardiology	15	2.7	12.2%	14.6%	**19.5%**	**31.7%**	14.6%	2.5%	2.4%	2.5%
Neurology	36	2.8	4.9%	7.8%	**16.7%**	**25.5%**	13.7%	12.8%	4.9%	13.7%
Dermatology	19	2.9	0%	16.4%	**25.4%**	**29.1%**	14.6	3.6%	0%	10.9%
Surgical intensive care	7	3	4.8%	9.5%	**23.8%**	**33.3%**	**23.8%**	0%	0%	4.8%
Neurosurgery	21	3	14.1%	**17.2%**	**23.4%**	**17.2**	7.8%	10.9%	3.1%	6.3%
Hematology	2	4	12.5%	12.5%	**25%**	**25%**	**25%**	0%	0%	0%

Presc No: Prescription Number; TM/P: Ratio of Serum Tumor Marker/Prescription; In bold, the most frequent TM requested are indicated.

Table 4: A detailled prescription of serum TM by departments.

There are some limitations in our study. First, we only consider prescriptions including at least one serum TM among CEA, CA125, CA15-3, CA19-9, NSE and Cyfra 21-1 since our goal was to evaluate inappropriate use of TM. For instance, we did not include single prescriptions of PSA or AFP either for screening or follow-up whereas they represented a high activity in our laboratory (1260 and 1127 assays/year, respectively). We considered prescriptions for diagnosis when no further requests were found in biochemistry laboratory database. However, we cannot totally rule out that further serum TM assays for the follow-up were realized in other laboratories even if this practice is not recommended. While the majority of serum TM has a low sensitivity and specificity limiting their use in screening and diagnosis [9-11], we found out that they were mainly prescribed for diagnosis. However, we did not distinguish the use of TM in screening, diagnosis, monitoring the treatment and prognosis. All those situations were grouped under the term diagnosis. Data suggest that serum TM have a great prognostic value [12-14] and they were probably used in this context. Finally, the presence of a private health institution, with an important activity in gynecological cancers, near our hospital may have induced a little bias in our study as evidenced by low CA125 and 15-3 requests.

In conclusion, serum TM are valuable tools for cancer management but due to numerous and sometimes contradictory guidelines, they are not always used in appropriate situations. In order to reduce health

expenditure, biologists should therefore propose an advice for a better use of TM, notably for non-oncologists physicians.

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