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SYMPOSIUM-IN-WRITING PAPER

IgE and chemotherapy

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Abstract The nexus of chemotherapeutic intervention and the immunomodulation of IgE-related phenomena are not well understood. The relationship bears importance in better understanding the causal and/or resultant effects of one on the other and their collective role in the management and sequelae of the cancer patient. This review discusses the relationship of chemotherapy on immunoglobulins with a focus on IgE and other related biological processes including hypersensitivity reactions and proposes models toward effective management of the cancer patient in this regard.

Keywords IgE · Allergy · Chemotherapy · Cancer · Antibody · AllergoOncology Symposium-in-Writing

Introduction

It was almost 40 years ago when Mclaughlan and Stanworth refuted claims that cancer patients had increased levels of circulating IgE [1]. The focus was not on the relationship with allergy but the rather possibility that tumor-related IgE may interfere with certain assays. Although since then the disease spaces of atopy and malignancy have infrequently crossed paths, recent data suggest that there is in fact a rapport. For example, Merrill et al. [2] have described that there is a favorable relationship between allergies and cancer and others have suggested that allergic status correlated with beneficial cancer prognosis and survival—such that patients with allergic diseases had a decreased risk for pancreatic and other cancers [2–5]. There are limitations in these reports which stem from the fact that many of these studies are derived from patient questionnaires which can be subject to patient interpretation of allergic/atopic disease, disease organ site (respiratory, skin etc.), allergen type and exposure, tissue influence, symptom severity and event recall [6]. Objective IgE classification (hi vs low IgE serum levels), timing of patient sample procurement, and types of treatment can also present a concern in data accumulation, comparison, and analysis [7]. For example, studies by Toren et al. [8] have shown that patients suffering from mild asthma were less prone to report their disease, demonstrating one form of collection bias. Furthermore, recent meta analysis found varied relationships between IgE and cancer when different tumor origin (mesenchymal, nervous system, lymphatic or hematopoietic tissue, and epithelium) cell types were analyzed [6]. In those studies, cancers with origin in epithelium demonstrated a positive association, whereas overall meta-analysis and cohort studies showed a weak negative association between IgE and cancer [6]. Although the mechanisms involved in these responses have been postulated to depend on Th1/Th2 cytokine responses, Fcε binding [9] or possibly affected by therapeutic regimens, the pathobiology remains ill defined.

Despite these limitations, it remains plausible that the relationship between atopy and cancer may also be induced or affected by the therapeutic regimens employed as treatments for patients, atopic or otherwise, with malignancies. This review serves to highlight what is known with respect to the relationship of IgE and related biology as they relate to chemotherapeutic agents and the cancer patient. Hypersensitivity reactions, treatment options, and clinical application models are presented where applicable for effective patient management.

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IgE responses in chemotherapy

Although total serum IgE or antigen-specific IgE levels in malignancy have been reported either as a diagnostic, prognostic, or functional response [9–14], serum IgE levels or antigen-specific IgE in response to *chemotherapy* in cancer patients are not well described. A prevailing thought could be that cancer patients are immunosuppressed and as such may maintain a blunted allergic or immune response [15], and therefore, immunotherapeutic intervention should have no consequence on IgE levels. To this end, studies by Weimels et al. [7] reported that, among glioma patients, IgE levels were associated with gender, age, smoking status, and ethnicity. However, IgE levels were not associated with therapy including radiation, chemotherapy, or tumor resection in those studied. Furthermore, recent studies by Fu et al. [13] have shown that total serum IgE and its low-affinity receptor FcεRII (CD23) are significantly elevated in patients with pancreatic cancer compared with healthy controls. Serum was obtained from these patients before any treatment thereby obviating and chemotherapeutic effects.

Alkylating agents

The relationship between chemotherapy and IgE may be regimen dependent. A subsequent study by Weimels et al. [16] reported that their observed decrease in IgE among glioma patients was only apparent among cases receiving temozolomide. Among patients receiving temozolomide, IgE levels, in patients whose blood samples were obtained within 30 days of diagnosis, were slightly higher than that of controls, whereas IgE levels in patients whose blood sample was obtained >60 days after diagnosis were significantly lower than controls [16]. Temozolomide (Temodar® and Temodal®) is an oral alkylating agent for use in a variety of brain and skin tumors. It is possible that temozolamide reverses the normal suppression of allergic responses and potentiates selective IgE production either in general or to specific antigens as has been reported with other alkylating agents such as cyclophosphamide [17–19]. It is thought that these alkylating agents eliminate suppressor T cells in addition to potentiating the IgE antibody response [18]. It is also likely that alkylating agents such as cyclophosphamide affects IgE responses depending on the state (atopic/allergic, inflammatory) of the individual. Animal studies have demonstrated recovery of IgE anti-antigen (OVA) responses in certain infected murine models of disease [20]; however, there were no differences in IgE responses pre- vs post-vaccination in healthy animals (beagles) treated with cyclophosphamide [21]; these responses also differed among animal models and immunization protocols [22]. IgE responses to alkylating agents are likely dependent on the type of disease insult, in addition to drug dosing and timing of responses [23].

Hormone-based chemotherapy

Hormonal analogs have also been reported to affect IgE production. Pan et al. [24] have shown that patients with hepatocellular carcinoma who were treated with tamoxifen and octreotide had elevated IgG and IgE levels after treatment, whereas treatment with 5-fluorouracil and mitomycin-C did not affect immunoglobulin levels. Of interest is that tamoxifen- and octreotide-treated patients increased their IgE almost six fold post-treatment (205 vs. 1,121, $P < 0.01$); twice that of IgG (9 vs. 29, <0.01). Although the mechanism for the increased IgE is unclear, it could be that octreotide stimulate immune cells within the reticuloendothelial system [25] which may facilitate IgE production. Interestingly, tamoxifen treatment alone has been shown to improve allergen-induced dermatitis and inhibit allergic responses in an animal model of allergic disease by reducing allergen-specific serum IgE levels [26]. In those studies, interleukin-4 was decreased in the tamoxifen treatment group, providing a mechanism for IgE reduction since IgE is potentiated by IL-4 along with other cytokines [27]. The relationship of tamoxifen treatment alone on IgE in malignancy remains unknown. However, some studies report selective increases in IgE levels compared with other immunoglobulins and their isotypes, suggesting unique mechanisms for IgE regulation which are distinct from those of IgM, IgG and IgA [13, 28]. The dissociation between IgE and other immunoglobulin isotypes has been shown in malignancies such as multiple myeloma [11, 29], pancreatic cancer [13], and other diseases [19].

Hypersensitivity

Chemotherapeutic intervention may also provoke deleterious IgE responses. Although IgE-related hypersensitivity reactions have been reported for various agents in non-malignant disease [30–33], data on such reactions in cancer therapy vary. A recent report by Mariotte et al. [34] demonstrated that certain patients with head and neck cancer receiving cetuximab, a chimeric mouse-human IgG1 monoclonal antibody against the epidermal growth factor receptor, are at increased risk for type I hypersensitivity responses and anaphylaxis. In those studies, similar levels of anti-cetuximab IgE were detected in pre-treatment patient sera and sera from healthy blood donors (26.1% vs 28.2%). Of the 92 patients treated, type 1 hypersensitivity reactions (HSR) were observed in 14 of them (15.2%). Of those patients experiencing HSR, approximately half presented with severe reactions and

also contained IgE anti cetuximab antibodies (ELISA). The authors further proposed the application of an anti-cetuximab IgE ELISA test as a means to help the physician anticipate an anaphylaxis episode following cetuximab infusion and opt for suitable treatment alternatives in patients who test positive. In addition, monoclonal antibodies such as rituximab and cetuximab have a unique side-effect profile that includes the potential for non-allergic infusion reactions caused by cytokine release [35]. IgE-mediated anaphylactic reactions subsequent to administration of other chemotherapeutic agents have also been reported including the 5-HT3 antagonists, palonosetron, for the treatment of ovarian cancer [36], thiol-containing agents in neuroectodermal cancer [37] and methotrexate [38] among others [39].

In general, platinum agents (cisplatin, carboplatin, and oxaliplatin) and in certain cases asparaginase have been reported to be associated with IgE-mediated hypersensitivity reactions, whereas taxanes (paclitaxel, docetaxel)-related reactions are generally non-IgE mediated [40]. Certain agents such as procarbazine can be IgE mediated but are also associated with a type III reaction manifested by pulmonary toxicity and cutaneous reactions. Asparginase may be related to complement activation in addition to IgE, and others such as epipodophyllotoxins may involve both immunologic and nonimmunologic factors. Identification of IgE-related responses may be resolved through skin testing, where available, prior to treatment selection. Furthermore, the ability to identify the offending agent can be challenging in the patient receiving multiple regimens to treat their malignancy. Management of these responses includes premedication with corticosteroids and antihistamines or may be mitigated or avoided with a slow infusion [40].

Cancer patients who develop reactions to chemotherapeutic agents may need to discontinue the offending agent. However, desensitization protocols have been established to allow cancer patients to continue therapy in certain cases. Patients with non-small-cell lung cancer who developed hypersensitivity to the taxane, docetaxel, were subjected to a desensitization protocol, thus providing a reliable alternative to permanent discontinuation [41]. Non-IgE-related anaphylactoid reactions to small molecular therapeutics and immune-based therapies with symptoms including pruritus, flushing, urticaria, angioedema, respiratory and gastrointestinal distress, changes in blood pressure including hypotension, and shock have also been successfully treated with desensitization regimens [42]. Other options include liposomal encapsulation, pegylation, and nanoparticle-based delivery systems of offending chemotherapeutic agents including doxorubicin, carboplatin and paclitaxel [43] which have shown decreased adverse sensitivity reactions.

Synbiotics

Probiotics, live cultures such as those found in yogurt and the lactic acid–producing bacteria (lactobacillus, bifidobacterium) in addition to certain yeast species and prebiotics which refer to certain fibers, resistant starches and non-digestible oligosaccarides such as inulin, have been promoted as effective anti-cancer agents either alone or in conjunction with conventional chemotherapy to treat malignancy [44]. The understanding that synbiotics provide a tempering of the gut flora and immunomodolatory function of the body to provide physiologic balance has been well described as a means for both preventing and treating cancer and other diseases [45, 46].

Probiotics have also been shown to be beneficial in suppressing or decreasing hapten-specific IgE responses by modulating expression of Th1/Th2 cytokine responses such as IL4 [47, 48]. Although studies on the role of symbiotic effects of chemotherapy-related hypersensitivity reactions are lacking, they are likely to provide benefit. For example, gut-based immune responses result from intestinal immune cells (GALT, PP, M cells) facilitating interface and transport of antigens, macromolecules, microorganisms, and inert particles from the lumen into lymphoid tissue through adsorptive endocytosis and/or active transepithelial vesicular transport in enterocytes [49]; many ingestible chemotherapeutic agents traverse these pathways to reach systemic effect. Further, many cancer drugs exert their effect by decreasing malignant cell growth or provide cellular arrest in G0 phase. A well-known consequence of this mechanism results in non-malignant cells (i.e., gut, hair) succumbing to this fate, facilitating disarray in the gut flora. Since enterobacteriaceae within the alimentary canal have been reported to maintain the body in a commensurate immunosuppressive state with respect to the generation of allergic responses [50] and malignancy [51], it remains plausible that repletion of the gut with probiotics would obviate chemotherapy-related IgE and/or non-IgE-mediated hypersensitivity reactions. Additional studies are warranted to determine the efficacy, scope, utility and application of synbiotics with respect to chemotherapy and IgE.

Direction for patient management

The relationship of IgE and cancer treatment is in its infancy. It therefore remains laudable to further investigate these responses in clinical trials as a means of better understanding chemotherapeutic mechanisms and if drug-related IgE responses potentiate or hinder tumor eradication and/or forecast patients who are at risk for hypersensitivity reactions. Pharmaceutical companies should include basic IgE-related interrogation algorithms

into their clinical trial plans and designs—at a minimum serum IgE, soluble CD23(FcεRII) and agent specific IgE where available. Addition of other biomarkers (IgG1, IgG4, cell surface leukocyte expression of FcεRI, FcεRII, CD16, CD8/CD60, IL4, etc.) which are involved in IgE responses is also valuable. Generation of specific IgE anti-drug antibodies, when possible, to serve as a biomarker to detect hypersensitivity responses, would be advantageous. These approaches are prudent since in some studies, an estimated 40% of the general population has some form of allergic/atopic condition [52] and cancer patients contain a subset of this population in addition to having other responses which are not linked to atopy.

In certain instances, it may be challenging to dissect out specific IgE-related physiology in malignancy. For example, although IgE levels have classically been found to be increased in Hodgkin's lymphoma [53], recent reports by Biggar et al. [54] have shown that although general serum immunoglobulin levels were lower than controls, both homocytotropic antibodies IgE and IgG4 were disproportionately *decreased* in non-Hodgkin's lymphoma, with the most extreme decrease in IgE in chronic lymphocytic leukemia/small lymphocytic lymphoma variety [54]. In contrast, recent reports by Kural et al. [55] have found *increased* IgE levels in cutaneous T-cell lymphoma irrespective of patients' atopic status. The ability to tease out a functional relationship between IgE, atopy and lymphoma may prove difficult due to the fact the low-affinity receptor for IgE (CD23) serves as an independent marker for lymphoma classification [56, 57] and as such its role in causation or response both pre and post chemotherapy may be difficult to interpret.

Furthermore, in the current era of personalized medicine, the establishment of data sets that highlight patients who potentiate IgE responses, their atopic and malignant status and their ability to augment or facilitate agent-specific survival in addition to the ability to identify those who mount a deleterious IgE anti-drug response, would prove valuable in the design, maturation, and utility of which agents to administer to which patients.

Improved understanding of IgE/chemotherapy relationships would also provide more effective treatment and cost savings to the healthcare industry by means of avoiding trial and error of treatment and doctor office visits/hospital stays associated with IgE-related reactions to specific therapies. To this end, Foley et al. [58] reported on the adverse events of cancer patients receiving cetuximab treatment for colorectal cancer. In those studies, of 1,122 patients followed, 8.4% of those who experienced infusion reactions (hypersensitivity and allergic reactions, such as anaphylactic shock, angioneurotic edema, bronchospasm, cardiac arrest, dyspnea, and hypotension with treatments including epinephrine, inhaled bronchodilators, antihistamines, corticosteroids, fluid administrations, glucagons, oxygen, and vasopressors) required medical intervention. Sixty-eight percent of the patients had treatment disruptions and 34% discontinued cetuximab treatment. The adjusted costs were $13,863 for cetuximab administrations with an infusion reaction requiring ER visit or hospitalization and $6,280 for those with an infusion reaction requiring outpatient treatment, compared with $4,555 for those without an infusion reaction for an approximate increased cost of $9,308 and $1,725, respectively. Although the relationship of patient history of atopy on experiencing an infusion reaction did not correlate, residence in a pollen state and initial therapeutic administration were associated with a statistically higher likelihood of a response requiring medical intervention.

More recently, Overbeek et al. [59] reported the cost of adverse events in the treatment of colorectal cancer with monoclonal antibodies. In those studies, 271 hospital events occurred in 210 patients among approximately 3,000 metastatic colorectal cancer patients which were followed over 34 months. The longest hospital length-of-stay per admission was for stroke, arterial thromboembolism, wound-healing complications, acute myocardial infarction, congestive heart failure, and neutropenia. The highest mean costs per admission were for stroke ($19,170), arterial thromboembolism ($18,886), and wound-healing complications ($15,336). These studies did not identify a causal relationship between any specific event or treatment. However, although these studies only targeted monoclonal antibody therapy, one can surmise that the availability of biomarkers which can effectively identify the appropriateness or more importantly avoidance of chemotherapeutic treatment candidates of various classes would likely, in conjunction with or as an alternative to test dosing [60], decrease the morbidity and costs associated with such adverse events.

Conclusion

The relationship between IgE and chemotherapeutic regimens warrants consideration. Although there is a paucity of data on this subject, there is precedent for such interface from other related disciplines. A better understanding of the interaction of IgE in cancer patients subjected to a variety of chemotherapeutic agents (small molecule, immunotherapy) will provide more effective treatment with respect to choice of drug, combination therapy, and elucidation of potential hypersensitivity reactions as a means to provide personalized medicine, cost containment, and patient safety.

Conflict of interest The author declares that he has no conflict of interest.

References

1. McLaughlan P, Stanworth DR (1975) A critical search for evidence of changes in levels of circulating IgE in patients with cancer. Lancet 1:64–65
2. Merrill RM, Isakson RT, Beck RE (2007) The association between allergies and cancer: what is currently known? Ann Allergy Asthma Immunol 99:102–116
3. Eppel A, Cotterchio M, Gallinger S (2007) Allergies are associated with reduced pancreas cancer risk: a population-based case–control study in Ontario, Canada. Int J Cancer 121:2241–2245
4. Turner MC, Chen Y, Krewski D, Ghadirian P (2006) An overview of the association between allergy and cancer. Int J Cancer 118:3124–3132
5. Gandini S, Lowenfels AB, Jaffee EM, Armstrong TD, Maisonneuve P (2005) Allergies and the risk of pancreatic cancer: a meta-analysis with review of epidemiology and biological mechanisms. Cancer Epidemiol Biomarkers Prev 14:1908–1916
6. Van Hemelrijck M, Garmo H, Binda E, Hayday A, Karagiannis SN, Hammar N, Walldius G, Lambe M, Jungner I, Holmberg L (2010) Immunoglobulin E and cancer: a meta-analysis and a large Swedish cohort study. Cancer Causes Control 21:1657–1667
7. Wiemels JL, Wiencke JK, Patoka J, Moghadassi M, Chew T, McMillan A, Miike R, Barger G, Wrensch M (2004) Reduced immunoglobulin E and allergy among adults with glioma compared with controls. Cancer Res 64:8468–8473
8. Toren K, Palmqvist M, Lowhagen O, Balder B, Tunsater A (2006) Self-reported asthma was biased in relation to disease severity while reported year of asthma onset was accurate. J Clin Epidemiol 59:90–93
9. Karagiannis SN, Wang Q, East N, Burke F, Riffard S, Bracher MG, Thompson RG, Durham SR, Schwartz LB, Balkwill FR, Gould HJ (2003) Activity of human monocytes in IgE antibody-dependent surveillance, killing of ovarian tumor cells. Eur J Immunol 33:1030–1040
10. Karagiannis SN, Bracher MG, Hunt J, McCloskey N, Beavil RL, Beavil AJ, Fear DJ, Thompson RG, East N, Burke F, Moore RJ, Dombrowicz DD, Balkwill FR, Gould HJ (2007) IgE-antibody-dependent immunotherapy of solid tumors: cytotoxic and phagocytic mechanisms of eradication of ovarian cancer cells. J Immunol 179:2832–2843
11. Matta GM, Battaglio S, Dibello C, Napoli P, Baldi C, Ciccone G, Coscia M, Boccadoro M, Massaia M (2007) Polyclonal immunoglobulin E levels are correlated with hemoglobin values and overall survival in patients with multiple myeloma. Clin Cancer Res 13:5348–5354
12. Tsavaris N, Tsigalacis D, Kosmas C, Koufos C, Vaiopoulos G, Tzivras M, Kouraklis G, Papadimas V, Georgoulis V, Archimandritis A, Sechas M (1998) Preliminary evaluation of the potential prognostic value of serum levels of immunoglobulins (IgA, IgM, IgG, IgE) in patients with gastric cancer. Int J Biol Markers 13:87–91
13. Fu SL, Pierre J, Smith-Norowitz TA, Hagler M, Bowne W, Pincus MR, Mueller CM, Zenilman ME, Bluth MH (2008) Immunoglobulin E antibodies from pancreatic cancer patients mediate antibody-dependent cell-mediated cytotoxicity against pancreatic cancer cells. Clin Exp Immunol 153:401–409
14. Wrensch M, Wiencke JK, Wiemels J, Miike R, Patoka J, Moghadassi M, McMillan A, Kelsey KT, Aldape K, Lamborn KR, Parsa AT, Sison JD, Prados MD (2006) Serum IgE, tumor epidermal growth factor receptor expression, and inherited polymorphisms associated with glioma survival. Cancer Res 66:4531–4541
15. Kim R, Emi M, Tanabe K, Arihiro K (2006) Tumor-driven evolution of immunosuppressive networks during malignant progression. Cancer Res 66:5527–5536
16. Wiemels JL, Wilson D, Patil C, Patoka J, McCoy L, Rice T, Schwartzbaum J, Heimberger A, Sampson JH, Chang S, Prados M, Wiencke JK, Wrensch M (2009) IgE, allergy, and risk of glioma: update from the San Francisco Bay Area Adult Glioma Study in the temozolomide era. Int J Cancer 125:680–687
17. Su YC, Rolph MS, Cooley MA, Sewell WA (2006) Cyclophosphamide augments inflammation by reducing immunosuppression in a mouse model of allergic airway disease. J Allergy Clin Immunol 117:635–641
18. Akasaki M, Ishizaka K (1987) Effects of cyclophosphamide treatment and gamma irradiation of SJL mice on the IgE antibody response and the nature of IgE-binding factors. Int Arch Allergy Appl Immunol 82:417–418
19. Turk JL, Parker D, Cameron AE (1984) The effect of cyclophosphamide on immunological control mechanisms. Int J Tissue React 6:205–211
20. Amarante-Mendes JG, Ferreira AP, Macedo MS (1991) Suppression of antibody response to an unrelated antigen in experimental murine paracoccidioidomycosis: effect of cyclophosphamide and indomethacin. J Investig Allergol Clin Immunol 1:185–193
21. Jones RD, Offutt DM, Longmoor (2000) Capture ELISA and flow cytometry methods for toxicologic assessment following immunization and cyclophosphamide challenges in beagles. Toxicol Lett 115:33–44
22. Graziano F, Haley C, Gundersen L, Askenase PW (1981) IgE antibody production in guinea pigs treated with cyclophosphamide. J Immunol 127:1067–1070
23. de Macedo MS, Mota I (1982) Antigenic competition in IgE antibody production. II. Effect of cyclophosphamide. Immunology 47:67–74
24. Pan DY, Qiao JG, Chen JW, Huo YC, Zhou YK, Shi HA (2003) Tamoxifen combined with octreotide or regular chemotherapeutic agents in treatment of primary liver cancer: a randomized controlled trial. Hepatobiliary Pancreat Dis Int 2:211–215
25. Davies N, Kynaston H, Yates J, Taylor BA, Jenkins SA (1995) Octreotide, the reticuloendothelial system, and experimental liver tumour. Gut 36:610–614
26. Babina M, Kirn F, Hoser D, Ernst D, Rohde W, Zuberbier T, Worm M (2010) Tamoxifen counteracts the allergic immune response and improves allergen-induced dermatitis in mice. Clin Exp Allergy 40:1256–1265
27. Ishizaka K (1984) Regulation of IgE synthesis. Ann Rev Immunol 2:159–182
28. Ferrazzi M, De Rinaldis ML, Salotti A, Cirelli A (1993) Serum IgE levels in human immunodeficiency virus (HIV)-1 infected patients: correlation between IgE and CD4 + T cells. Riv Eur Sci Med Farmacol 15:67–70
29. Tamir R, Barchat I, Weiss H, Pick AI (1993) IgE response in multiple myeloma. Ann Allergy 70:214–217
30. Bluth MH, Beleza P, Hajee F, Jose-Jordao M, Figueiredo J, Almeida F, Smith-Norowitz TA (2007) IgE mediated hypersensitivity after ibuprofen administration. Ann Clin Lab Sci 37:362–365
31. Cornejo-Garcia JA, Blanca-López N, Doña I, Andreu I, Agúndez JA, Carballo M, Blanca M, Canto MG (2009) Hypersensitivity reactions to non-steroidal anti-inflammatory drugs. Curr Drug Metab 10:971–980
32. Blanca M, Romano A, Torres MJ, Férnandez J, Mayorga C, Rodriguez J, Demoly P, Bousquet PJ, Merk HF, Sanz ML, Ott H, Atanasković-Marković M (2009) Update on the evaluation of hypersensitivity reactions to betalactams. Allergy 64:183–193
33. Mertes PM, Aimone-Gastin I, Guéant-Rodriguez RM, Mouton-Faivre C, Audibert G, O'Brien J, Frendt D, Brezeanu M, Bouaziz H, Guéant JL (2008) Hypersensitivity reactions to neuromuscular blocking agents. Curr Pharm Des 14:2809–2825

34. Mariotte D, Dupont B, Gervais R, Galais MP, Laroche D, Tranchant A, Comby E, Bouhier-Leporrier K, Reimund JM, Le Mauff B (2011) Anti-cetuximab IgE ELISA for identification of patients at a high risk of cetuximab-induced anaphylaxis. MAbs 3:396–401
35. Vogel WH (2010) Infusion reactions: diagnosis, assessment, and management. Clin J Oncol Nurs 14:E10–E21
36. Pietkiewicz JM (2011) Possible anaphylaxis to palonoestron. J Oncol Pharm Pract. 22 Aug [Epub ahead of print]
37. Dorris K, Fouladi M, Davies SM, Perentesis JP, Lawrence JM, Chow LM, Assa'ad A, Uygungil B, Jodele S (2011) Severe allergic reactions to thiol-based cytoprotective agents Mesna and Amifostine in a child with a supratentorial primitive neuroectodermal tumor. J Pediatr Hematol Oncol 33:e250–e252
38. Pugi A, Benemei S, Vietri M, Tondo A, Calvani AM, Mugelli A, Vannacci A, Lapi F (2011) Anaphylaxis during the first course of high-dose methotrexate: a case report and literature review. J Clin Pharm Ther. May 13. doi:10.1111/j.1365-2710.2011.01275.x [Epub ahead of print]
39. Bautista MA, Stevens WT, Chen CS, Curtis BR, Aster RH, Hsueh CT (2010) Hypersensitivity reaction and acute immune-mediated thrombocytopenia from oxaliplatin: two case reports and a review of the literature. J Hematol Oncol 3:12
40. Lee C, Gianos M, Klaustermeyer WB (2009) Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents. Ann Allergy Asthma Immunol 102:179–187
41. Syrigou E, Dannos I, Kotteas E, Makrilia N, Tourkantonis I, Dilana K, Gkiozos I, Saif MW, Syrigos KN (2011) Hypersensitivity reactions to docetaxel: retrospective evaluation and development of a desensitization protocol. Int Arch Allergy Immunol 156:320–324
42. Castells M (2006) Rapid desensitization of hypersensitivity reactions to chemotherapy agents. Curr Drug Saf 1:243–251
43. Joly F, Ray-Coquard I, Fabbro M, Donoghoe M, Boman K, Sugimoto A, Vaughan M, Reinthaller A, Vergote I, Ferrandina G, Dell'anna T, Huober J, Pujade-Lauraine E (2011) Decreased hypersensitivity reactions with carboplatin-pegylated liposomal doxorubicin compared to carboplatin-paclitaxel combination: analysis from the GCIG CALYPSO relapsing ovarian cancer trial. Gynecol Oncol 122:226–232
44. Fotiadis CI, Stoidis CN, Spyropoulos BG, Zografos ED (2008) Role of probiotics, prebiotics and synbiotics in chemoprevention for colorectal cancer. World J Gastroenterol 14:6453–6457
45. Dennis T, Fanous M, Mousa S (2009) Natural products for chemopreventive and adjunctive therapy in oncologic disease. Nutr Cancer 61:587–597
46. Iannitti T, Palmieri B (2010) Therapeutical use of probiotic formulations in clinical practice. Clin Nutr 29:701–725
47. Yoshida A, Aoki R, Kimoto-Nira H, Kobayashi M, Kawasumi T, Mizumachi K, Suzuki C (2011) Oral administration of live Lactococcus lactis C59 suppresses IgE antibody production in ovalbumin-sensitized mice via the regulation of interleukin-4 production. FEMS Immunol Med Microbiol 61:315–322
48. Segawa S, Nakakita Y, Takata Y, Wakita Y, Kaneko T, Kaneda H, Watari J, Yasui H (2008) Effect of oral administration of heat-killed *Lactobacillus* brevis SBC8803 on total and ovalbumin-specific immunoglobulin E production through the improvement of Th1/Th2 balance. Int J Food Microbiol 121:1–10
49. Gourbeyre P, Denery S, Bodinier M (2011) Probiotics, prebiotics, and synbiotics: impact on the gut immune system and allergic reactions. J Leukoc Biol 89:685–695
50. Kaplan JL, Shi HN, Walker WA (2011) The role of microbes in developmental immunologic programming. Pediatr Res 69:465–472
51. Rook GA, Dalgleish A (2011) Infection, immunoregulation, and cancer. Immunol Rev 240:141–159
52. Juliá-Serdá G, Cabrera-Navarro P, Acosta-Fernández O, Martín-Pérez P, Losada-Cabrera P, García-Bello MA, Carrillo-Díaz T, Antó-Boqué J (2011) High prevalence of asthma and atopy in the Canary Islands, Spain. Int J Tuberc Lung Dis 15:536–541
53. Davies MG (1978) Serum IgE, lymphomas, and atopy. Br Med J 1:580–581
54. Biggar RJ, Christiansen M, Rostgaard K, Smedby KE, Adami HO, Glimelius B, Hjalgrim H, Melbye M (2009) Immunoglobulin subclass levels in patients with non-Hodgkin lymphoma. Int J Cancer 124:2616–2620
55. Kural YB, Su O, Onsun N, Uras AR (2010) Atopy, IgE and eosinophilic cationic protein concentration, specific IgE positivity, eosinophil count in cutaneous T Cell lymphoma. Int J Dermatol 49:390–395
56. DiGiuseppe JA, Borowitz MJ (1998) Clinical utility of flow cytometry in the chronic lymphoid leukemias. Semin Oncol 25:6–10
57. Pangalis GA, Angelopoulou MK, Vassilakopoulos TP, Siakantaris MP, Kittas C (1999) B-chronic lymphocytic leukemia, small lymphocytic lymphoma, and lymphoplasmacytic lymphoma, including Waldenström's macroglobulinemia: a clinical, morphologic, and biologic spectrum of similar disorders. Semin Hematol 36:104–114
58. Foley KA, Wang PF, Barber BL, Long SR, Bagalman JE, Wagner V, Song X, Zhao Z (2010) Clinical and economic impact of infusion reactions in patients with colorectal cancer treated with cetuximab. Ann Oncol 21:1455–1461
59. Overbeek JA, Zhao Z, van Herk-Sukel MP, Barber BL, Gao S, Herings RM (2011) Costs of hospital events in patients with metastatic colorectal cancer. J Med Econ 14:656–661
60. George TJ Jr, Laplant KD, Walden EO, Davis AB, Riggs CE, Close JL, George SN, Lynch JW (2010) Managing cetuximab hypersensitivity-infusion reactions: incidence, risk factors, prevention, and retreatment. J Support Oncol 8:72–77